KUCERS' THE USE OF ANTIBIOTICS

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

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59 Erythromycin

Françoise Van Bambeke

1. DESCRIPTION

Ilotycin (CAS number: 114-07-8), thereafter renamed erythromycin A, was first isolated at Eli Lilly from a strain of *Streptomyces erythreus* (McGuire *et al.*, 1952). It is the first representative of the class of macrolide antibiotics introduced for clinical use. Macrolides are characterized by a macrocyclic lactone ring substituted by two sugars, among which a desosamine confers a character of weak base responsible for their ability to accumulate inside the cells. Erythromycin is made of a 14-membered ring, substituted by a desosamine in position 5 and a cladinose in position 3. The empirical formula is $C_{37}H_{67}NO_{13}$ and the molecular weight is 733.93; the chemical structure is shown in Figure 59.1.

Erythromycin A base is very bitter, insoluble in water, and inactivated by acid (including gastric secretions) as a result of an intramolecular cyclization reaction leading to the formation of an inactive spirocetal compound (Kirst and Sides, 1989). Effort has thus been made to develop gastro-resistant formulations or ester prodrugs to improve oral absorption. Current formulations of erythromycin base include different formulations to be administered by the oral route and a powder to be reconstituted for intravenous administration. The availability of these differs from one country to another (tablets, gastro-resistant capsules with delayed release, and granules or powder for reconstitution of oral solutions). Erythromycin is also an active ingredient in several preparations for topical applications. Stearate, estolate, ethylsuccinate, lactobionate, and gluceptate are the salt and ester forms used for clinical use. Most of the oral formulations need to be administered 1 hour before a meal to ensure optimal oral absorption because food affects drug absorption.

There are four key erythromycin compounds that have been used clinically:

1. Erythromycin stearate (a salt).
2. Erythromycin ethyl succinate (an ester). These two preparations are still susceptible to acid inactivation. Despite the fact that they are marketed with a buffering agent or as film-coated or enteric-coated tablets, they should be administered at least 1 hour before a meal.
3. Propinyl erythromycin ester lauryl sulfate (erythromycin estolate) (the salt of an ester).
4. Stearate salt of 2′-acetyl ester of erythromycin (erythromycin ascitrate) (Tuominen *et al.*, 1988). These last two formulations are more resistant to inactivation by gastric acid and can be administered in the fasting state or after food.

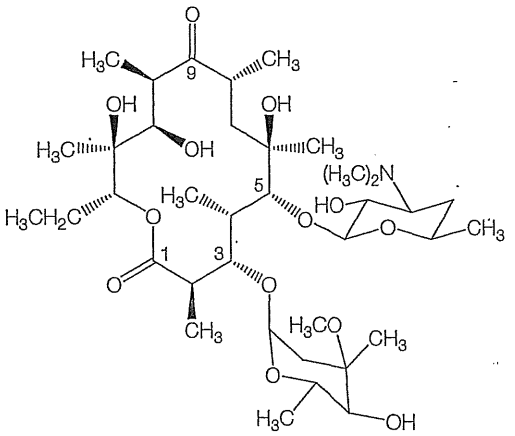

Figure 59.1 Chemical structure of erythromycin A. Chemical instability in acid medium is due to the reaction between the ketone in position 9 and the hydroxyl in position 6 to form a hemicetal, followed by the reaction of this hemicetal with the hydroxyl in position 1 to form a cetal.

Subsequent to the development of erythromycin, a series of semi-synthetic compounds with improved stability in an acidic environment and oral bioavailability, as well as markedly improved pharmacologic profiles, have been developed – these include clarithromycin, roxithromycin, and azithromycin. In addition, some older macrolides, including spiramycin, josamycin, and rosaramycin, remain available in some regions. The availability of clarithromycin, roxithromycin, and azithromycin has substantially reduced the use of erythromycin over the last decade.

Erythromycin is mainly active against Gram-positive cocci, as well as against a few Gram-negative bacteria, including *Neisseria* spp., *Haemophilus* spp., *Legionella* spp., as well as *Chlamydia* spp. and *Mycoplasma* spp.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Erythromycin, and macrolides in general, are 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., and *Legionella* spp. Erythromycin is somewhat active against some strains of *Neisseria* spp., *Coryneform* bacteria, and *Haemophilus* spp., but relatively inactive against most coliform and enteric bacteria (Haight and Finland, 1952a). Table 59.1 summarizes the susceptibility patterns observed for wild-type strains and clinical isolates of the most relevant target organisms.

Gram-positive bacteria

Erythromycin is active against organisms such as *Staphylococcus aureus* (including beta-lactamase-producing strains) and coagulase-negative staphylococci, *Streptococcus pyogenes*, Groups B, C and G streptococci, *S. pneumoniae*, *S. viridans* and *Streptococcus bovis*. *Enterococcus faecalis* is somewhat less susceptible. Nutritionally variant strains of streptococci

Table 59.1 Activity of erythromycin (MIC, μg/ml) against key target pathogens compared with susceptibility breakpoints.

Bacteria	Wild-type strains (EUCAST distributions of MIC)			Clinical isolates				Breakpoints		Resistance issues	Reference
	Range	MIC_{50}	MIC_{90}	Study period	Range	MIC_{50}	MIC_{90}	CLSI (S ≤ / R ≥)	EUCAST (S ≤/R>)		
Staphylococcus aureus (methicillin susceptible)	0.25–1	0.5	0.5	1998–2004 (North America)	≤0.06 to >8	0.5	>8	0.5/8	1/2		Jones *et al.*, 2007
Staphylococcus aureus (methicillin resistant)	0.125–1	0.5	0.5	2005 (China)	0.125 to >256	>256	>256	0.5/8	1/2	HA- MRSA frequently multiresistant	Wang *et al.*, 2008
Streptococcus pneumoniae	0.032–0.25	0.064	0.125	1998–2004 (North America)	≤0.25 to >32	0.25	32	0.25/1	0.25/0.5	High prevalence in many countries; often multiresistant strains	Jones *et al.*, 2007
Streptococcus pyogenes	0.032–0.25	0.064	0.125	1999–2000 (worlwide)	0.03–128	0.06	0.06	0.25/1	0.25/0.5		Canton *et al.*, 2002
Haemophilus influenzae	1–16	4	8	2002–2003 (UK)	0.25 to >128	4	16		0.5/16		Morrissey *et al.*, 2005
Moraxella catarrhalis	0.016–0.125	0.064	0.125	2002–2003 (UK)	0.03–0.25	0.125	0.125		0.25/0.5		Morrissey *et al.*, 2005
Legionella pneumophila	0.25–0.5	0.25	0.5	1999–2004 (Europe–USA)	≤0.25–0.5	≤0.25	0.5				Dunbar and Farrell, 2007
Neisseria gonorrhoeae	0.032-0.5	0.5	0.5	1996 (Indonesia)	0.03–2	<0.125	1				Lesmana *et al.*, 2001
Campylobacter jejuni	0.125–4	1	2	2004–2005 (Greece)		0.5	2				Papavasileiou *et al.*, 2007
Chlamydia trachomatis	0.06–1[a]			1997–1999 (Israel)	.0.06–0.25	0.125	0.25				Samra *et al.*, 2001

[a]Mulazimoglu *et al.* (2005).
CLSI: Clinical Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; R: resistance; S: susceptibility.

are usually sensitive. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of erythromycin for 90% of these organisms in one series were 0.13 and 2.0 μg/ml, respectively (Gephart and Washington, 1982). Most hospital-acquired methicillin-resistant *S. aureus* (MRSA) strains have now acquired resistance to macrolides.

Other susceptible Gram-positive organisms include *Listeria monocytogenes*, *Bacillus anthracis* (Wiggins *et al.*, 1978), *Corynebacterium diphtheriae* (Zamiri and McEntegart, 1972; Maple *et al.*, 1994), and *Rhodococcus equi* (Decre *et al.*, 1991; Verville *et al.*, 1994); whereas *Nocardia* spp. are variable in their susceptibility (Bach *et al.*, 1973; Yazawa *et al.*, 1994). As erythromycin and penicillin are antagonistic *in vitro*, the combination is not recommended for the treatment of *L. monocytogenes* infections (Winslow *et al.*, 1983).

Gram-positive anaerobic bacteria

Erythromycin shows a wide range of activity against Gram-positive anaerobes, including *Eubacterium*, *Propionibacterium*, *Bifidobacterium*, *Lactobacillus*, and *Peptostreptococcus* spp., and also against most strains of *Peptococcus* spp. (Sutter and Finegold, 1976). *Actinomyces israeli* (the causative agent of human actinomycosis) is also susceptible (Sutter and Finegold, 1976; Holmberg *et al.*, 1977). *Clostridium tetani* and *C. perfringens* are also usually susceptible (Brazier *et al.*, 1985). Some strains of *C. perfringens* are resistant owing to the presence of a gene which results in erythromycin-target site modification (Berryman *et al.*, 1994). In one study of 308 *C. difficile* isolates, almost all of the 161 isolates of serogroups A, F, G, H and X were erythromycin sensitive, but most of 32 toxigenic isolates of serogroup C were resistant. Other serogroups showed variable patterns (Delmée and Avesani, 1988). The main resistance mechanism for *C. difficile* is, again, target site modification (Hächler *et al.*, 1987; Berryman and Rood, 1989).

Gram-negative aerobic bacteria

Erythromycin is active against some Gram-negative bacteria responsible for respiratory tract infections (*Moraxella catarrhalis*, *Legionella* spp., *Bordetella pertussis*), genital infections (*Neisseria gonorrhoeae*, *Haemophilus ducreyi*, and *Gardnerella vaginalis*), digestive tract infections (*Helicobater pylori* and *Campylobacter jejuni*), and meningitis (*N. meningitidis*). However, *H. influenzae* is only moderately susceptible (McCarthy *et al.*, 1979; Vanhoof *et al.*, 1980; Brorson *et al.*, 1981; Karmali *et al.*, 1981; Ringertz *et al.*, 1981; Bannatyne and Cheung, 1982; Bilgeri *et al.*, 1982; McNulty *et al.*, 1985; Righter and Luchsinger, 1988). Although *N. gonorrhoeae* is usually susceptible, some strains with diminished sensitivity, or which are completely resistant, occur. In clinical isolates of *N. gonorrhoeae*, there is usually a correlation between the degree of susceptibility with penicillin G, tetracycline, erythromycin, and chloramphenicol (Report, 1978). In the 1970s, approximately 35% of beta-lactamase-producing strains isolated in the USA and East Asia were resistant to erythromycin (MIC 1.0 μg/ml) (CDC, 1978), and in the 1980s, Ng *et al.* (1983) found that, among strains of *N. gonorrhoeae* from various Southeast Asian countries, 80% of the beta-lactamase-producing strains and 75% of the non-beta-lactamase-producers had MICs ≥ 2 μg/ml.

Escherichia coli, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Salmonella* spp., and *Shigella* spp. are not susceptible (Arthur and Courvalin, 1986; Arthur *et al.*, 1987b). Antibacterial activity of erythromycin against Gram-negative bacilli is influenced by pH, and it increases markedly as the pH rises to 8.5. Most *E. coli* and *Klebsiella* spp. strains can be inhibited by erythromycin concentrations attained in urine with ordinary therapeutic doses, provided the urine is made alkaline (Sabath *et al.*, 1968). Some strains of *Brucella* spp. are sensitive to erythromycin (Abbott Laboratories, 1966).

Early *in vitro* and animal studies on *Legionella pneumophila* indicated that erythromycin might be effective against this organism (CDC, 1977a; CDC, 1977b). Subsequent *in vitro* and *in vivo* studies in guinea-pigs confirmed that erythromycin is one of the most active drugs against this organism (Fraser *et al.*, 1978; Thornsberry *et al.*, 1978; Edelstein and Meyer, 1980; Moffie and Mouton, 1988) and embryonated eggs (Lewis *et al.*, 1978). This agent is also active against *L. pneumophila* within human monocyte-derived macrophages (Vildé *et al.*, 1986). Other members of this genus, *L. micdadei* (the Pittsburg pneumonia agent), *L. bozemanii*, *L. gormanii*, *L. dumoffii*, *L. longbeachae*, and *L. anisa* are also sensitive to erythromycin (Pasculle *et al.*, 1981; Dowling *et al.*, 1982; Fallon and Stack, 1990; Nimmo and Bull, 1995).

Flavobacterium spp. may also be sensitive to erythromycin (Lee *et al.*, 1977). *Bartonella* (formerly *Rochalimaea*) *quintana* and *B. henselae*, the agents which cause bacillary angiomatosis and bacillary peliosis in patients with AIDS, are erythromycin sensitive (Koehler and Tappero, 1993; Maurin and Raoult, 1993; Regnery and Tappero, 1995). *Pasteurella multocida* is resistant (Goldstein *et al.*, 1988).

Gram-negative anaerobe bacteria

Erythromycin has a variable activity against anaerobic Gram-negative bacteria. Erythromycin demonstrates moderate activity against *Prevotella* and *Porphyromonas*. Most strains of *Bacteroides* spp. can be inhibited by moderately high erythromycin concentrations, but such high levels are only attained in the serum after parenteral administration (Zabransky *et al.*, 1973; Gorbach and Bartlett, 1974). Sutter and Finegold (1976) studied susceptibility of anaerobic organisms to erythromycin. Although all strains of *Prevotella melaninogenica* and some *Bacteroides* spp. were susceptible to 1.0 μg/ml, *B. fragilis* and the *Fusobacterium* spp. were usually resistant. Harvey *et al.* (1981) found that a concentration of erythromycin of 6 μg/ml was usually required to inhibit more than 90% of *B. fragilis*, other *Bacteroides* spp., and *Fusobacterium* spp., a concentration that may be difficult to achieve in routine clinical use.

Chlamydia and *Chlamydophila*

Both cell culture and clinical studies of *Chlamydia trachomatis* suggest that tetracycline (see Chapter 66, Tetracycline) and erythromycin are the most effective antibiotics against this organism before quinolones became available (Kuo *et al.*, 1977; Lee *et al.*, 1978; Schachter *et al.*, 1986). A few strains of *C. trachomatis* have been shown to be relatively resistant to erythromycin (Mourad *et al.*, 1980). *Chlamydophila pneumoniae* is also erythromycin sensitive, but clarithromycin (see Chapter 61, Clarithromycin) is some 8-fold more active *in vitro* (Chirgwin *et al.*, 1989; Fenelon *et al.*, 1990; Hammerschlag, 1994; Roblin *et al.*, 1994).

Mycoplasma spp.

Mycoplasma pneumoniae is very susceptible to erythromycin (Jao and Finland, 1967). Erythromycin-resistant *M. pneumoniae* variants can be obtained *in vitro* by serial subculture of the organism in the presence of the drug. Such erythromycin resistance is usually accompanied by resistance to other macrolides (Niitu *et al.*, 1974). In one report a strain of *M. pneumoniae* acquired resistance to erythromycin during treatment (Niitu *et al.*, 1970). Erythromycin is also active against *M. genitalium* (Renaudin *et al.*, 1992), but not against *M. hominis* (Csonka and Spitzer, 1969).

Ureaplasma urealyticum

Ureaplasma urealyticum is susceptible to erythromycin, but some strains with intermediate or complete resistance occur (Spaepen *et al.*, 1976; Waites *et al.*, 1992). Tetracycline-resistant strains of *U. urealyticum* may sometimes be susceptible to erythromycin (Ford and Smith, 1974).

Mycobacteria

Mycobacterium tuberculosis is resistant to erythromycin, but some atypical mycobacteria are erythromycin sensitive, particularly *M. chelonae* (Molavi and Weinstein, 1971). *M. avium* is sensitive, but to a lower degree (Swenson *et al.*, 1982). Generally, other macrolides such as clarithromycin (see Chapter 61, Clarithromycin) are more active against atypical mycobacteria.

Spirochetes

Treponema pallidum is erythromycin-susceptible (Brause *et al.*, 1976; Norris and Edmondson, 1988), although strains which exhibit high-level erythromycin resistance have been detected, and erythromycin is not considered an appropriate option for treating this disease (Stamm *et al.*, 1988). Erythromycin exhibits only a relatively low degree of activity against *Borrelia burgdorferi* (Johnson *et al.*, 1987).

Rickettsiae

In vitro activity of erythromycin against *Rickettsia prowazeki* has been demonstrated in cell culture, but the rate of killing of rickettsiae was slow (Wisseman *et al.*, 1974). *Rickettsia rickettsii* and *R. conorii* are erythromycin-resistant (Raoult *et al.*, 1988). In general, erythromycin is not an appropriate therapeutic option for rickettsial disease.

2b. Emerging resistance and cross-resistance

Resistance to macrolides has become a major issue for most of the species originally described as susceptible, including *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *Campylobacter* spp., *C. diphtheriae*, and *Propionibacterium* (Leclercq and Courvalin, 1991). Multiple mechanisms of resistance have been described (see below under 3. Mechanism of drug action), with the prevalence of these varying on a geographical basis. For instance, efflux-mediated resistance in pneumococci was uncommon in France (Marchandin *et al.*, 2001) and Italy (Schito *et al.*, 2004), whereas it was significantly present in Germany (Reinert *et al.*, 2003; Reinert *et al.*, 2004), The Netherlands (Neeleman *et al.*, 2005), and the USA (Doern and Brown, 2004).

Target modification

Ribosomal methylation was the first resistance mechanism described for macrolides (Lai and Weisblum, 1971) and has now become the most prevalent (Farrell *et al.*, 2003). It is mediated by the acquisition of an *erm* gene, encoding a methyltransferase, which methylates the N(6) position of adenine 2058 in 23S rRNA (Weisblum, 1995). Mono-methylation confers a high level of resistance to lincosamides and streptogramins and a lower level of resistance to macrolides, whereas dimethylation confers high levels of resistance to the three classes of drugs, conferring the MLS_B phenotype of cross-resistance (Leclercq and Courvalin, 1991). erm(A) is mostly found in staphylococci and in *S. pyogenes*, but is rare in *S. pneumoniae*. Conversely, erm(B) is the major determinant found in *S. pneumoniae* and also in other streptococci and in enterococci. Other determinants have been found in specific organisms, like erm(C) (Shivakumar and Dubnau, 1981) which is found in *S. aureus* (Lina *et al.*, 1999; Schmitz *et al.*, 2000), erm(D) and erm(G) in *Bacillus* spp. (Gryczan *et al.*, 1984; Monod *et al.*, 1987), and erm(F) in *Bacteroides fragilis* (Rasmussen *et al.*, 1986). The expression of the methylase is either constitutive or inducible. In the latter case, inducers include the 14-, 15- and 16-membered macrolides, lincosamides, and streptogramins (Leclercq and Courvalin, 1991) but not the ketolides (Bonnefoy *et al.*, 1997; Leclercq, 2001).

Mutations of 23S rRNA, with substitution of adenine 2058 by a guanine being the most common one, have also been described in bacterial pathogens (Vester and Douthwaite, 2001; Poehlsgaard and Douthwaite, 2003). This substitution defines an ML phenotype of resistance, with high MICs for erythromycin, azithromycin, the 16 membered macrolides and the lincosamides, a slightly reduced susceptibility to clarithromycin, but no influence on streptogramins and ketolides (Canu and Leclercq, 2002). This mechanism is, so far, mainly found in *Helicobacter pylori*, *Mycoplasma* spp., and *Mycobacterium* spp. (Vester and Douthwaite, 2001).

Mutations in the ribosomal proteins L4 and L22 have also been recently associated with the appearance of resistance to macrolides in clinical strains of streptococci (Tait-Kamradt *et al.*, 2000; Farrell *et al.*, 2003; Reinert *et al.*, 2003). Mutations in the L4 protein confer an MS_B resistance phenotype, with MICs remaining low (Canu and Leclercq, 2002). Mutations in the L22 protein also confer a low level of resistance to telithromycin and clindamycin (Canu *et al.*, 2002).

Antibiotic inactivation

Unlike target modification, this mechanism confers resistance to structurally related antibiotics only, which means that it affects macrolides but not lincosamides or streptogramins (Nakajima, 1999; Leclercq, 2002). At the present time, phosphorylases and esterases conferring resistance to 14-, 15-, and 16-membered macrolides have been mainly reported in Enterobacteriacae. However, the clinical significance of this resistance remains minor, since these bacteria are not the primary target of macrolides. However, a few strains of phosphotransferases producing *S. aureus* have already been reported (Wondrack *et al.*, 1996; Matsuoka *et al.*, 1998), which suggests that this mechanism may become more significant in the future.

Efflux

In Gram-positive bacteria, the expression of efflux pumps conferring resistance to macrolides is inducible. Two main types of pumps with narrow spectrum have been described so far, namely Msr(A) in staphylococci [inducible by 14- and 15-membered macrolides, conferring resistance to these macrolides and to streptogramins, but not to lincosamides (MS_B phenotype) (Ross *et al.*, 1990)], and mef(A) and mef(E) described in several species of streptococci, including *S. pneumoniae* and *S. pyogenes*, as well as in enterococci [inducible and conferring resistance only to 14- and 15-membered macrolides (M phenotype)] (Clancy *et al.*, 1996; Sutcliffe *et al.*, 1996; Tait-Kamradt *et al.*, 1997; Leclercq, 2002; Klaassen and Mouton, 2005). The mef(A) gene is located on a conjugative transposon, and can therefore easily spread between bacteria or even between streptococci species (Goldman and Capobianco, 1990; Leclercq and Courvalin, 1991; Santagati *et al.*, 2003).

3. MECHANISM OF DRUG ACTION

Macrolides are inhibitors of protein synthesis at the ribosomes (Goldman *et al.*, 1990). They impair the elongation cycle of the peptidyl chain by specifically binding to the 50S subunit of the ribosome. Specificity toward prokaryotes relies upon the absence of 50S ribosomes in eukaryotes. The main interaction site is located at the central loop of the domain V of the 23S rRNA, at the vicinity of the peptidyl transferase center. The macrolide binding site is located at the entrance of the exit tunnel used by the nascent peptide chain to escape from the ribosome, at the place where the central loop of domain V interacts with proteins L4 and L22 and with the loop of

hairpin 35 in domain II of rRNA (for a general review, see Poehlsgaard and Douthwaite, 2003).

Interaction occurs via the formation of hydrogen-bonds between the reactive groups (2′-OH) of the desosamine sugar and the lactone ring (Schlunzen *et al.*, 2001) and adenine residue 2058. This explains why mutation or methylation in position 2058 as well as mutations in proteins L4 and L22 confer resistance to macrolides. The binding site of macrolides on the ribosome overlaps that of chloramphenicol or lincosamides such as clindamycin (Schlunzen *et al.*, 2001), explaining pharmacologic antagonism between these antibiotic classes as well as cross-resistance.

4. MODE OF DRUG ADMINISTRATION AND DOSAGE

4a. Adults

Oral administration

Erythromycin is usually administered by the oral route. The dosage depends on the indication, but the maximum dose is 4 g/day (independent of its formulation) divided into four administrations. The conventional oral doses of ester forms are 250 mg every 6 hours for estolate or stearate, and 400 mg every 6 hours for ethylsuccinate (Ginsburg *et al.*, 1982).

Parenteral administration

Erythromycin can be administered i.m. as erythromycin ethylsuccinate. The adult dosage is 100–200 mg 8-hourly, but these injections are painful so this route of administration is rarely used. It is therefore rather used i.v. as erythromycin lactobionate for treatment of severe infections. The dosage is 1 g 6-hourly. Adult doses as high as 4–6 g daily have been given without toxic effects. The drug should be given as intermittent or continuous i.v. infusions. For intermittent administration, each dose should be dissolved in 100–200 ml of infusion fluid, and this should be infused relatively slowly to minimize the risk of thrombophlebitis, digestive side-effects (Marlin *et al.*, 1983; Putzi *et al.*, 1983), or ventricular arrhythmias (Schoenenberger *et al.*, 1990; Farrar *et al.*, 1993). Recommended rates of infusions are 0.5–1 hour for a dose of 500 mg and 1–2 hours for a dose of 1 g. If used by continuous infusion, compatibilities with other drugs administered by the same line should be checked carefully. Lactobionate of erythromycin is administered intravenously at a dose of 500 mg every 6 hours.

Other modes of administration

Erythromycin is also available for local applications as gels, alcoholic solutions, lotions, or ointments or eye drops/ointments. These forms are used for specific indications, such as acne in adolescents (topical formulations; Chalker *et al.*, 1983; Lesher *et al.*, 1985) or prophylaxis of trachoma (eye drops/ointments) in newborn infants.

4b. Newborn infants and children

Oral suspensions are available for children. The dosage is 30–50 mg/kg to be divided in two to four administrations. For more severe infections this dosage may be doubled. Burns and Hodgman (1963) administered 40 mg/kg/day of erythromycin estolate in four divided doses to 26 premature infants. Satisfactory serum levels, no evidence of accumulation, and no toxic effects were observed.

The pediatric dosage of erythromycin lactobionate by the intravenous route is 30–50 mg/kg/day given in four divided doses, and each dose should be infused no faster than over 60 minutes (Gouyon *et al.*, 1994; Waites *et al.*, 1994).

4c. Altered dosages

Impaired renal function

The normal serum half-life of erythromycin of 1.4 hours is prolonged to 6 hours in anuric patients, but dosage reduction is not considered necessary in patients with severe renal failure (Kunin, 1967). Erythromycin is not significantly removed by hemodialysis or peritoneal dialysis.

Impaired hepatic function

Erythromycin may accumulate in patients with severe liver disease. If large doses are administered to such patients, serum level monitoring and dosage reduction may be necessary. When 500 mg of erythromycin base was given to patients with alcoholic liver disease and to normal subjects after a 12-hour fast, the normally delayed absorption (lag time) was shorter (2 *vs* 3 hours) among liver disease patients; an earlier peak was obtained (4.6 *vs* 6.3 hours) and higher peak concentrations were also observed (2.04 *vs* 1.5 μg/ml) in this group. A slower elimination time also occurred in patients with liver disease, so that some adjustment of the dose may occasionally be required in such patients if large doses are used (Kroboth *et al.*, 1982).

Premature neonates

The drug can be safely used in the newborn. Low doses of erythromycin have been proposed to promote gastrointestinal motility in premature neonates, but conflicting data have been obtained so further evaluation is needed (Patole *et al.*, 2005).

Pregnant patients

Because of its propensity to cause hepatotoxicity (see below under 6b. Hepatotoxicity), erythromycin estolate should not be used in such patients. Other erythromycin preparations are safe in pregnancy without dosage adjustment.

The elderly

The pharmacokinetics of macrolides may be modified in elderly patients. However, dosage adjustment is usually not required with conventional dose, but closer than usual clinical monitoring of the older patient has therefore been advocated (Periti *et al.*, 1989). This is particularly the case for elderly patients who are receiving multiple other medications, because the risk of drug interactions with erythromycin is consequently increased.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

The main pharmacokinetic properties of erythromycin are summarized in Table 59.2.

Table 59.2 Pharmacokinetic parameters of erythromycin and its ester forms.

Pharmacokinetic parameter (reference)	Erythromycin (500 mg bid)	Base – 250 mg	Base – enteric coated	Stearate – 250 mg q.i.d.	Estolate – 250 mg	Ethylsuccinate – 500 mg
C_{max} (mg/l)	3	0.3–0.5	0.9–3.5	0.5–1.4	1.5	1.5 (0.5 of base)
t_{max} (h)	1.9–4.4	4	2.1–3.9	2–3	2	1–2
$t_{1/2}$ (h)	2		1.6			
V_d (l/kg)	0.64		0.78			
Bioavailability (%)	25–60		35			
Protein binding (%)	65–90		84			
Tissue–serum concentration	0.5					
AUC (mg/l h)	4.4–14					
Reference	Brogden and Peters, 1994	Chambers, 2006	Periti *et al.*, 1989; Chambers, 2006	Periti *et al.*, 1989; Chambers, 2006	Chambers, 2006	Chambers, 2006

AUC: area under the curve.

5a. Bioavailability

The oral bioavailability of erythromycin base is poor and is highly variable because of inactivation by gastric acidity (Kirst and Sides, 1989). Formulations with an acid-resistant coating have therefore been developed, as well as esters with improved oral bioavailability. Stearate is hydrolyzed in the intestine, whereas ethylsuccinate is absorbed both as the free base (55%) and the ester (45%) formulations. These are best absorbed in the fasting state. Estolate absorption is not affected by food; 20–30% of the serum concentration corresponds to the active form and 70–80% to the ester prodrug (Sivapalasingam and Steigbigel, 2005). Serum protein binding varies between 40% and 90%. Alcohol can cause a moderate reduction in the absorption of erythromycin succinate.

5b. Drug distribution

Erythromycin is distributed in the total body water, and penetrates easily into tissues where it persists longer than in the blood. Erythromycin is also able to accumulate in the cells, reaching cellular to extracellular concentrations ratios of about ten (Martin *et al.*, 1985). This property can be explained by the high diffusibility of the molecule combined with a weak basic character, allowing for the rapid diffusion through cellular membranes and the trapping of the protonated forms in the acidic compartments of the cells (lysosomes) (de Duve *et al.*, 1974; Carlier *et al.*, 1987).

Erythromycin stearate is less readily destroyed in the stomach than erythromycin base and it dissociates in the duodenum liberating active erythromycin, which is absorbed. Peak serum levels after oral administration of erythromycin base and stearate appear approximately the same, except that the absorption of the base may be slightly more delayed. Triggs and Ashley (1978) demonstrated in volunteers that, although mean serum levels were low after a single dose of erythromycin stearate, these were considerably higher after repeated doses. Doubling the dose of these compounds approximately doubles the serum concentrations. Food in stomach diminishes the absorption of both base and stearate (Disanto and Chodos, 1981). Furthermore, there is marked individual variation in the serum levels achieved after the administration of all forms of oral erythromycin (Griffith and Black, 1964; Lake and Bell, 1969).

Unlike the base and the stearate, erythromycin estolate is acid-stable and absorbed from the gastrointestinal tract more completely. It is absorbed mainly as ester, of which about 41% is hydrolyzed in serum to active erythromycin (Griffith and Black, 1962; Croteau *et al.*, 1988).

Erythromycin ethylsuccinate is another ester which is well absorbed from the gastrointestinal tract. Absorption is delayed by food, however, and the highest and earliest peak serum levels after an 800-mg dose (2.23 μg/ml) occur under fasting conditions (Thompson *et al.*, 1980). After absorption, about 69% of this ester is hydrolyzed to active erythromycin, but the estolate ester is still considered to have an advantage in pharmacokinetics as it has a longer half-life (5.47 *vs* 2.72 hours) and a larger area under the curve (AUC) (Croteau *et al.*, 1988). In another study, Bérubé *et al.* (1988) also found that after single doses of erythromycin estolate (500 mg) and erythromycin ethylsuccinate (600 mg), the bactericidal titers at 2 and 8 hours against *S. pyogenes* and *S. pneumoniae* were significantly higher with erythromycin estolate than with ethylsuccinate ester.

Eriksson *et al.* (1981) reported a decreased absorption of erythromycin suspension (both stearate and ethyl succinate) in infants less than one month old, and the stearate suspension was also poorly absorbed in infants 1–6 months old. In a pharmacokinetic study of infants younger than four months of age comparing the estolate and ethylsuccinate esters, no differences were found between peak serum concentrations or the time taken to reach them, but the elimination half-life of the estolate was longer (Patamasucon *et al.*, 1981).

Erythromycin ascitrate is an ester that is well absorbed after oral administration, provided it is given in a tablet with an acid-resistant coating. The total serum level reached is about 3.9-fold higher than that after the same dose of erythromycin base with an acid-resistant coating. In plasma, however, only about one-third of erythromycin ascitrate is hydrolyzed to active erythromycin. The absorption of this ester in some patients may be impaired by food. Concomitant administration of cimetidine does not affect the serum levels attained after erythromycin ascitrate (Männistö *et al.*, 1988; Tuominen *et al.*, 1988).

Satisfactory serum levels are achieved after parenteral erythromycin administration. After an i.m. injection of 100 mg of erythromycin ethyl succinate in adults, the mean peak level after 1 hour is 0.64 μg/ml; this level is maintained for nearly 6 hours, and measurable serum concentrations persist for at least 12 hours (Metzger *et al.*, 1959). Following a single i.v. injection of 200 mg erythromycin lactobionate, the mean serum level in adults is 3.0 μg/ml 1 hour after injection, and detectable levels persist for at least 6 hours (Abbott Laboratories, 1966). If erythromycin lactobionate is given by continuous infusion at a rate of 1.0 g every 12 hours, serum levels of about 4–6 μg/ml are maintained from 8 hours onwards (Neaverson, 1976). Peak concentrations attained after 1 hour intermittent i.v. erythromycin infusions in the usual doses are usually some 4- to 10-fold greater than those attained after oral erythromycin (Farrar *et al.*, 1993). When erythromycin lactobionate was given to preterm neonates i.v. in dosages of either 25 or 40 mg/kg/day in four divided doses 6-hourly (each dose infused over 60 min), the peak serum levels varied from 1.92 to 2.9 and 3.05 to 3.69 μg/ml, respectively (Waites *et al.*, 1994).

Overall, erythromycin is widely distributed in tissues, and is concentrated in the liver and spleen. It persists in the tissues for longer periods than in the serum. The related macrolide antibiotics, spiramycin (see Chapter 182, Spiramycin) and some newer macrolides, such as clarithromycin (see Chapter 61, Clarithromycin) and azithromycin (see Chapter 62, Azithromycin), produce even higher and better sustained tissue concentrations than erythromycin.

Adequate concentrations of erythromycin are found in pleural and ascitic fluids. The drug reaches high levels in tear fluid in infants with purulent conjunctivitis (Sandström and Ringertz, 1988). It enters middle-ear exudates in sufficient concentrations to inhibit the highly sensitive organisms *S. pyogenes* and *S. pneumoniae*, but not necessarily all strains of *H. influenzae* (Bass *et al.*, 1971). Adequate levels of erythromycin are found in tonsils after oral administration, the levels being higher after the estolate suspension than after ethylsuccinate suspension (Ginsburg *et al.*, 1976). The tonsillar concentrations are also adequate after oral erythromycin ascitrate administration and more of this ester is hydrolyzed to active erythromycin in the tonsillar tissue than in the serum (Gordin *et al.*, 1988a). In patients with lobar pneumonia treated with i.v. erythromycin lactobionate, effective concentrations were reached in the infected and uninfected lung tissue within 10 minutes and maintained for at least 1 hour (Wollmer *et al.*, 1982). Mean sputum levels of 2.6 μg/ml have been recorded when erythromycin lactobionate was given by infusion in a dose of 1 g every 12 hours (Neaverson, 1976). However, after 500 mg erythromycin stearate was given orally every 8 hours for 7 days, sputum levels in 24-hour collections did not exceed 1.0 μg/ml in five of six patients (Clarke *et al.*, 1980). After an oral dose of 500 mg erythromycin ethylsuccinate or stearate, the gastric mucosal concentration was higher than the MIC of *H. pylori* (McNulty *et al.*, 1988). However, conclusions with respect to tissue concentrations should be drawn with great caution (Mouton *et al.*, 2008).

Erythromycin does not enter the cerebrospinal fluid (CSF) in the absence of meningitis but, as with many antibiotics, the drug may be detectable in the CSF when the meninges are inflamed (Griffith and Black, 1970). Van Bambeke and Tulkens (2002) also found erythromycin concentrations in CSF to usually be low, such that i.v. administration of large doses was considered necessary to treat meningitis due to highly susceptible organisms. Overall, macrolide penetration into the central nervous system (CNS) is poor (Kearney and Aweeka, 1999). Likewise, concentrations in synovial fluid are probably too low to treat septic arthritis. The high cellular accumulation of erythromycin, however, justifies its potential use in the treatment of intracellular infections.

Peak concentrations in lymph after oral therapy were 24% of the peak serum concentrations, and the mean lymph–serum concentration ratio was 0.35 (Bergan *et al.*, 1982). After i.v. administration of erythromycin lactobionate, the concentrations in normal cancellous bone were approximately 30% of concomitant serum levels (Rosdahl *et al.*, 1979). Erythromycin crosses the placenta, but serum concentrations attained in the infant are considerably lower and less predictable than those in the mother (South *et al.*, 1964; Philipson *et al.*, 1973). Erythromycin is excreted in the milk, so its use should be avoided in pregnant or lactating women. Serum half-life is relatively short (about 1.4 h).

Erythromycin is concentrated in human polymorphonuclear leukocytes some 10–20 times the concentration in extracellular fluid (Prokesch and Hand, 1982; Ishiguro *et al.*, 1989). Phagocytosis by neutrophils appears to be unaffected by erythromycin (Naess and Solberg, 1988), but erythromycin may stimulate neutrophil migration (Anderson, 1989). In alveolar macrophages from smokers and nonsmokers, the uptake of erythromycin was lower in the cells derived from the latter group (Hand *et al.*, 1985).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Erythromycin is essentially bacteriostatic, with increased activity at alkaline pH (Haight and Finland, 1952b). The cure rate for macrolides mainly depends on the AUC/MIC ratio (Andes *et al.*, 2004), based on their time-dependent effect coupled with a postantibiotic effect, using both *in vitro* and in animal models (Rolin and Bouanchaud, 1989; Novelli *et al.*, 2002). The large diffusion of erythromycin into tissues was considered as an advantage for the treatment of several infections, including those of the respiratory tract. However, the increasing prevalence of resistance raises doubts about the drug's efficacy in some sites. As noted earlier, tissue concentrations per se do not always indicate the level of activity (Mouton *et al.*, 2008).

5d. Excretion

Erythromycin is only partly excreted in urine, and only about 2.5% of an orally administered dose and 15% of a parenterally administered dose is recoverable from the urine in the active form (Abbott Laboratories, 1966). Urinary concentrations of the active drug are usually low and variable. As renal excretion is not the main method of erythromycin elimination from the body, there is no significant accumulation of the drug in uremic patients.

The main route of excretion of erythromycin is in the bile after being metabolized. This occurs by demethylation and oxidation of the aminated sugar and implies involvement of P450 cytochrome (group 3A4) (Kirst and Sides, 1989). Some erythromycin excreted in this way is reabsorbed from the intestine.

A large proportion of administered erythromycin cannot be accounted for by combined renal and biliary excretion, and so a considerable amount appears to be inactivated in the body, probably in the liver (Osono and Umezawa, 1985).

5e. Drug interactions

Drug interactions with macrolides can be a considerable problem which seriously limits their use in some 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). Within the macrolide group, erythromycin is associated with the greatest risk. The main clinically relevant interactions are summarized in Table 59.3. In particular, ergotamin and drugs with potential to prolong the QT-interval may increase the risk

Table 59.3 Drug interactions with erythromycin.

Interaction	Drug class	Drugs
Possible pharmacologic antagonism	Lincosamides	Lincomycin
Decreased effect of macrolide	Rifamycins	Rifabutin
		rifampicin
Decreased effect		Zafirlukast
Increased serum levels	Miscellaneous	Bromocriptine
		Imatinib
Increased toxicity of both drugs	HIV protease inhibitor	Ritonavir
Increased effect	Benzodiazepines	Alprazolam
		Diazepam
		Triazolam
		Midazolam
	Anticoagulants	Acenocoumarol
		Anisindione
		Dicoumarol
		Warfarin
	Miscellaneous	Carbamazepine
		Cilostazol
		Clozapine
		Ciclosporin
		Digoxin
		Divalproex sodium
		Felodipine
		Methylprednisolone
		Repaglinide
Increased effect and toxicity	Theophylline and derivatives	Aminophylline
		Dyphylline
		Oxtriphylline
		Theophylline
	Miscellaneous	Alfentanil
		Aprepitant
		Buspirone
		Cinacalcet
		Docetaxel
		Eletriptan
		Eplerenone
		Erlotinib
		Everolimus
		Gefitinib
		Itraconazole
		Quetiapine
		Ranolazine
		Sibutramine
		Sildenafil
		Sirolimus
		Tacrolimus
		Vardenafil
Increased toxicity	Statins	Atorvastatin
		Cerivastatin
		Lovastatin
		Simvastatin
	Miscellaneous	Colchicine
		Quinupristin
		Vinblastine
Possible ergotism	Ergot derivatives	Cabergoline
		Dihydroergotamine
		Dihydroergotoxine
		Ergotamine
		Methylergonovine
		Methysergide
		Ergonovine
Increased risk of cardiotoxicity and arrhyhthmias	Fluoroquinolones	Grepafloxacin
		Levofloxacin
		Moxifloxacin
		Sparfloxacin
	Miscellaneous	Bretylium
		Astemizole
		Amiodarone
		Cisapride
		Disopyramide
		Dofetilide
		Mesoridazine
		Pimozide
		Quinidine
		Sotalol
		Terfenadine
		Thioridazine
		Verapamil
Possible serotoninergic syndrome	Miscellaneous	Citalopram
		Fluoxetine
		Sertraline

Adapted from: www.drugbank.ca/cgi-bin/getCard.cgi?CARD = APRD00953

of torsades de pointes due to the macrolides and should be avoided (Curtis *et al.*, 2003). 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 to selection of resistant strains. Co-administration of cimetidine can almost double the serum level of erythromycin by inhibiting its metabolism.

Two review articles have concluded that erythromycin can, in some individuals, inhibit the elimination of methylprednisolone, theophylline, carbamazepine, and warfarin (Descotes *et al.*, 1985; Ludden, 1985). This has been more closely studied for some of these drugs such as carbamazepine (Wroblewski *et al.*, 1986). The mean change in drug clearance was about 20–25% in most cases, with some patients having a much larger change than others. The type of erythromycin used may also be important. Concomitant erythromycin administration may cause elevation of ciclosporin serum levels by interfering with its metabolism in the liver. This can lead to acute reversible impairment of renal function (Martell *et al.*, 1986; Ben-Ari *et al.*, 1988).

6. TOXICITY

6a. Gastrointestinal adverse effects

These are the most common side-effects associated with erythromycin. Abdominal pain (16%), nausea and vomiting (14%), and diarrhea are reported with an overall incidence of 30% for erythromycin (Ellsworth *et al.*, 1990). In fact, erythromycin acts as a motilin receptor agonist in the gastrointestinal tract (Peeters *et al.*, 1989) and stimulates stomach and gut motility (Itoh *et al.*, 1984). Accordingly, it has been proposed to use erythromycin as a therapeutic agent for some motility disorders owing to this "adverse" effect. Although popular in some intensive care units, this nonantibacterial use of erythromycin may be problematic in terms of resistance emergence among routine commensal bacteria (Itoh *et al.*, 1985; Peeters, 2001) and good clinical trials are unavailable. Macrolide-induced emesis may be partially due to 5-hydroxytryptamine receptors.

6b. Hepatotoxicity

Hepatotoxicity is a rare but serious adverse effect of erythromycin. Initially, this was thought to occur after administration of erythromycin estolate, but not after other erythromycin preparations (Masel, 1962; Sherlock, 1968). It was postulated that the propionyl ester linkage at the 2′ position conferred this property on the estolate and that there was no cross-sensitivity with other erythromycin preparations (Tolman *et al.*, 1974). Jaundice usually occurs about 10–12 days after starting treatment, but it may occur within 1 or 2 days in patients who had previously experienced the drug (Robinson, 1961; Gilbert, 1962). Some patients may experience severe abdominal pain, which may lead to an erroneous diagnosis of cholelithiasis (Oliver *et al.*, 1973). Nausea and abdominal pain are initial symptoms, followed by fever (50%). Approximately 75% of patients develop eosinophilia (>500 cells/mm^3) and uniformly elevated transaminase levels. Liver function tests revert to normal within days after discontinuation of drug but may recur after rechallenge (Eichenwald, 1986). Occasionally, pruritus and a rash may recur. Jaundice may be clinical or subclinical, and hepatic enlargement is usually present. Liver function tests usually indicate cholestasis, and the mechanism of this toxicity may represent either a hypersensitivity or toxic reaction resulting from formation of nitrosoalkanes (Pessayre *et al.*, 1985). Liver histology usually reveals a picture of intrahepatic cholestasis.

The jaundice and other symptoms usually subside when the drug is stopped, but occasionally jaundice may persist for weeks, and in one case reported by Brown (1963) it persisted for about three months. There have been no deaths associated with erythromycin jaundice, and the subsequent development of chronic liver disease has not been reported. The exact frequency of this complication was not known. It is possible that this complication may be more frequent during pregnancy (McCormack *et al.*, 1977).

It now appears that similar cholestatic jaundice can arise after other erythromycin preparations and that it may not be more common with the estolate than with the others. Inman and Rawson (1983) reported three cases of similar jaundice associated with erythromycin stearate. The incidence of patients developing acute symptomatic liver disease resulting in hospitalization after treatment with a 10-day course of erythromycin was estimated at 2.3 per million patients (about 66 cases annually in the USA) (Carson *et al.*, 1993). None of these patients had taken erythromycin estolate, but this study demonstrated that jaundice occurred after erythromycin ethylsuccinate and erythromycin stearate. The risk of cholestatic jaundice was estimated at 0.4 per million patients by Derby *et al.* (1993), who studied a total of 366,064 patients who had received one or more prescriptions of erythromycin. They estimated that the risk of cholestatic jaundice associated with erythromycin was approximately 3.6 per 100,000 users. It did not appear that erythromycin estolate caused jaundice more frequently than other erythromycin preparations, although only 3036 patients received the estolate. Lehtonen *et al.* (1991) administered erythromycin ascitrate to 1549 patients. Only three patients (0.2%) developed hepatic damage attributable to the drug.

Thus, hepatotoxicity can occur with any erythromycin formulation (Diehl *et al.*, 1984; Ortuno *et al.*, 1984), although most of the initial reports implicated the estolate formulation (Eichenwald, 1986).

6c. Ototoxicity

The incidence of ototoxicity is uncertain, but it is probably underestimated. A prospective case–control study found evidence of ototoxicity in 21% of patients receiving 4 g/day erythromycin, when audiograms were performed and patients were closely monitored (Swanson *et al.*, 1992). Subjective symptoms begin within the first week of drug administration (Swanson *et al.*, 1992; Sacristan *et al.*, 1993), but are usually reversible within 1 to 30 days upon discontinuation of the drug (Brummett, 1993). However, irreversible unilateral tinnitus (Levin and Behrenth, 1986) and irreversible hearing loss (Agusti *et al.*, 1991) have been reported with intravenous administration of erythromycin lactobionate 4 and 2 g/day, respectively. The mechanism of erythromycin ototoxicity is not known, but it may occur by an effect on the central auditory pathway (Brummett, 1993) and it is probably dose dependent (Taylor *et al.*, 1981; Swanson *et al.*, 1992). Although auditory dysfunction is most common, vestibular dysfunction may also occur (Quinnan and McCabe, 1978). Erythromycin causes low local tinnitus, and hearing loss ranges from bilateral flat to high frequency sensorineural loss, which can be detected on audiograms at both conventional (0.25–8.0 kHz) and extended high frequencies (8–14 kHz). Ototoxicity can occur with all formulations, including lactobionate and stearate (Dylewski, 1988; Sacristan *et al.*, 1993). Pre-existing hepatic or renal abnormalities, advanced age, high dosages, and concurrent ototoxic medications are predisposing factors (Haydon *et al.*, 1984; Umstead and Neumann, 1986; Vasquez *et al.*, 1993). Ototoxicity has also been reported in patients without predisposing factors (Agusti *et al.*, 1991; Sacristan *et al.*, 1993).

6d. Skin rashes

Skin rashes may occur as a single manifestation, but are rare; as is eosinophilia and fever (Periti *et al.*, 1993). The risk of erythromycin

hypersensitivity appears to be higher in patients allergic to other antibiotics, such as the penicillins (Boguniewicz and Leung, 1995). Severe reactions such as Stevens–Johnson syndrome have been reported (Sullivan *et al.*, 1999). Erythromycin administered intramuscularly can cause pain at the injection side, and when administered intravenously causes thrombophlebitis (4%).

6e. Cardiac toxicity

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 (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. There is, however, no simple correlation between the prolongation of repolarization and the proarrhythmic potential (noted to be erythromycin > clarithromycin > azithromycin) in the rabbit experimental model; which suggests other interactions of the drugs with the myocardial cells (Milberg *et al.*, 2002). In humans, prolongation of QTc interval is most notable with erythromycin (Iannini, 2002) and reaches clinically significant values (>30 ms) (Oberg and Bauman, 1995). Torsades de pointes remains rare, however, except when combined with type Ia or III anti-arrhythmic agents, with other drugs that prolong the QTc interval such as cisapride (van Haarst *et al.*, 1998; Kyrmizakis *et al.*, 2002), terfenadine, or drugs that compete for the same metabolic routes as macrolides (Dresser *et al.*, 2000). A number of case reports have described episodes of cardiac toxicity in premature infants who have been treated with i.v. erythromycin, mainly for *U. urealyticum* infections (Farrar *et al.*, 1993; Waites *et al.*, 1993; Gouyon *et al.*, 1994; Sims *et al.*, 1994).

6f. Miscellaneous side-effects

Interstitial nephritis and acute renal failure has been reported after oral erythromycin (Rosenfeld *et al.*, 1983). An episode of erythromycin-induced hemolytic anemia has been described by Wong *et al.* (1981). Reversible selective factor X deficiency and acute liver failure have been reported in a patient with chest infection treated with erythromycin base (Hosker and Jewell, 1983).

6g. Risk in pregnancy

Erythromycin belongs to the B category. There is, however, no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed with erythromycin base before and during mating, during gestation, and through weaning of two successive litters.

7. CLINICAL USES OF THE DRUG

Owing to the availability of other macrolides with improved pharmacokinetic profile and lower rate of side-effects and drug interactions, erythromycin has only a few indications left as a first choice drug. If intravenous administration is necessary, it is an alternative for clarithromycin if intravenous clarithromycin is not available.

Macrolides were long considered as an alternative to beta-lactams for the treatment of respiratory tract infections. The increasing rate of erythromycin resistance among common pathogens has meant that macrolide usage for these indications should be limited to countries where resistance is still relatively low (Brunton and Iannini, 2005; Lode, 2007).

7a. Upper respiratory tract infections

Erythromycin is an effective alternative to penicillin G for the treatment of many infections caused by group A beta-hemolytic streptococci in penicillin-allergic patients (Feldman, 1993; Klein, 1994). Streptococcal tonsillitis, scarlet fever, and erysipelas can be successfully treated by erythromycin. Erythromycin base or estolate given twice daily is just as effective for streptococcal tonsillitis as when given 6- or 8-hourly, provided that the same total daily dose is used (Breese *et al.*, 1974; Ginsburg and Eichenwald, 1976; Hovi *et al.*, 1987). In one study, erythromycin estolate in a dose of 15 mg/kg 12-hourly proved to be superior to erythromycin ethylsuccinate, given in the same dosage (Ginsburg *et al.*, 1982). In another study erythromycin ethylsuccinate given at 50 mg/kg/day in two doses produced a high frequency of gastrointestinal symptoms and a greater bacteriologic failure rate in treating *S. pyogenes* pharyngitis than twice-daily estolate (30 mg/kg/day), each drug being given for 10 days (Ginsburg *et al.*, 1984). The increasing resistance of some of these organisms to erythromycin (and macrolides in general) all over the world is of concern (Bozdogan *et al.*, 2003; Ioannidou *et al.*, 2003; Yi *et al.*, 2006; Inoue *et al.*, 2008).

Erythromycin is one of the most effective antimicrobial agents for treatment of nonstreptococcal pharyngitis due to *Chlamydophila pneumoniae* and *M. pneumoniae* (McDonald *et al.*, 1985; Grayston, 1989). It is effective in pertussis infection when given early and is effective in decreasing transmission during pertussis outbreaks (Steketee *et al.*, 1988). For treatment of diphtheria and for the carrier state with *C. diphtheriae*, erythromycin remains the drug of choice (see below under 7j. Diphtheria).

Co-administration of erythromycin with a sulfonamide (most often sulfisoxazole, which has a half-life of about 5–6 hours) has previously been a popular treatment for otitis media, being more effective than erythromycin alone (Washington and Wilson, 1985; Bergeron *et al.*, 1987; Giebink and Canafax, 1991; Berman, 1995). Some failures of erythromycin therapy in otitis media may be due to erythromycin-resistant *S. pneumoniae* strains (Tarpay *et al.*, 1982). Amoxicillin is usually the preferred drug for otitis media (see Chapter 3, Ampicillin, Amoxicillin and Other Ampicillin-Like Penicillins). *S. pyogenes* and pneumococcal sinusitis also responds well to erythromycin, but that due to *H. influenzae* may not (Kalm *et al.*, 1975). Long-term erythromycin treatment (erythromycin base at 600 mg/day for more than four months) was effective for the treatment of sinobronchial syndrome-associated otitis media with effusion (Iino *et al.*, 1993).

7b. Community-acquired pneumonia and bronchitis

Pneumococci and *H. influenzae* are the common pathogens in bacterial bronchitis, and erythromycin is one of several effective drugs for the treatment of acute infections (Gordin *et al.*, 1988b; Söderström *et al.*, 1991). Erythromycin is an effective alternative to penicillin G for the treatment of pneumococcal pneumonia. It is also effective in severe related infections, such as pneumococcal meningitis, if it is used in large doses (4–6 g daily) i.v., but cefotaxime (see Chapter 26, Cefotaxime) or ceftriaxone (see Chapter 27, Ceftriaxone) (and in some developing countries, chloramphenicol), are preferable for this disease if penicillin G is contraindicated. Respiratory tract infections due to *M. catarrhalis* may respond well to erythromycin (Darelid *et al.*, 1993).

Erythromycin is also active against *M. pneumoniae* infections, when it appears to be as efficient as tetracycline in shortening the course of

the infection (Rasch and Mogabgab, 1965; Shames *et al.*, 1970; Wenzel *et al.*, 1976; Martin and Bates, 1991).

Although *Rhodococcus equi* can cause pneumonia in normal individuals, it more commonly causes a destructive cavitating pneumonia in patients with immune system dysfunction, especially in patients with AIDS. Several antibiotics are effective against this organism, such as erythromycin, rifampicin, ciprofloxacin, aminoglycosides, and vancomycin (Harvey and Sunstrum, 1991; Gillet-Juvin *et al.*, 1994; Verville *et al.*, 1994).

7c. Legionella infections

Erythromycin and other macrolides have been the drugs of choice for *L. pneumophila* pneumonia; however, some authors now consider fluoroquinolones to be better – although definitive studies regarding this are lacking (Pedro-Botet and Yu, 2006). Mild infections may be treated with oral erythromycin, but more severe cases should be treated intravenously with erythromycin 0.5–1.0 g 6-hourly. The higher intravenous dosage should always be given to immunosuppressed patients. A combination of i.v. erythromycin plus rifampicin (1200 mg daily) is recommended for very ill patients and for those not responding to erythromycin (Fraser *et al.*, 1978; Meyer, 1983; Muder *et al.*, 1989; Nguyen *et al.*, 1991; Edelstein, 1993; Roig *et al.*, 1993). Of importance, erythromycin and rifampicin have important opposite effects on hepatic metabolism, which may result in modification in the efficacy or toxicity of other co-administered drugs, such as ciclosporin, with an increased risk of ciclosporin toxicity (Ampel and Wing, 1990). Other combinations between newer macrolides and fluoroquinolones have been recommended by some authors (Klein and Cunha, 1998).

Some 20% of patients with *Legionella* pneumonia are septicemic and they may develop extrapulmonary lesions. Lesions such as *Legionella* peritonitis, bowel abscess, colitis, and cellulitis have been described. Bowel lesions may develop because of ingestion of the bacteria, rather than resulting from septicemia. The treatment of choice is, again, erythromycin or fluoroquinolones (Edelstein, 1993; Waldor *et al.*, 1993; Pedro-Botet and Yu, 2006).

Legionella micdadei also causes pneumonia, but this occurs mainly as a nosocomial infection in immunocompromised hosts, such as renal transplant and bone marrow transplant patients, patients receiving steroids, and those who are hospitalized for prolonged periods (Schwebke *et al.*, 1990). However, waterborne outbreaks have also occurred in the community (Goldberg *et al.*, 1989). For *L. micdadei* pneumonia, erythromycin is one of the drugs of choice (Wing *et al.*, 1981; Schwebke *et al.*, 1990). In cases of apparent failure of therapy with erythromycin, cotrimoxazole may be beneficial if fluoroquinolones cannot be used (Rudin *et al.*, 1984).

7d. Chemoprophylaxis

For endocarditis, chemoprophylaxis oral erythromycin stearate 1.0 g orally 2 hours before the dental procedure and 0.5 g 6 hours later is one option for standard-risk penicillin-allergic patients. This erythromycin regimen is also suitable for standard-risk patients who have been taking long-term penicillin prophylaxis for rheumatic fever. Erythromycin may cause some gastrointestinal side-effects in these patients (Sefton *et al.*, 1990).

Erythromycin has previously been considered a suitable alternative to penicillin for prophylaxis against rheumatic fever (Ginsburg and Eichenwald, 1976). Suitable dosage is a single daily dose of 200 mg for children and adults weighing more than 36 kg and 100 mg for those of lower weight. This chemoprophylaxis has been used continuously for over four years without side-effects or the development of resistant strains of *S. pyogenes*. Erythromycin-resistant strains of *S. viridans* often appear in the pharynx of patients receiving long-term erythromycin prophylaxis. In ten volunteers given three 1-g doses of erythromycin stearate, erythromycin-resistant strains of *S. viridans* persisted in eight of the ten subjects at 23 weeks and were still present in five of eight subjects examined at 43 weeks (Harrison *et al.*, 1985). In such patients with rheumatic heart disease receiving long-term erythromycin, who require temporary protection against endocarditis at the time of dental procedures etc., prophylaxis by an unrelated antibiotic, such as one of the cephalosporins, is indicated. Clindamycin is not suitable for this purpose, as erythromycin-resistant *S. viridans* strains are also often clindamycin resistant (Sprunt *et al.*, 1970).

7e. Sexually transmitted diseases

Erythromycin 500 mg four-times daily is recommended by the Centers for Disease Control and Prevention (CDC, 2002) for the treatment of lymphogranuloma venereum caused by *C. trachomatis* (21 days' treatment) and of recurrent urethritis (7 days' treatment, combination with a single dose of metronidazole 2 g). Erythromycin 500 mg four times daily for 7 days is also proposed as an alternative in nongonococcal urethritis or in granuloma inguinale (donovanosis). The main indication for macrolides is, without doubt, infection with *C. trachomatis* – erythromycin is used in a dose of 500 mg four times a day for 7 days for this indication. Azithromycin (see Chapter 62, Azithromycin) is now considered the drug of choice in many countries because it can be given in one high dose. Erythromycin was considered as a first choice in pregnant women, but more recent studies suggest that azithromycin is also safe and effective (Adair *et al.*, 1998; Miller and Martin, 2000). Chlamydia infection in children, including ophthalmia neonatorum, is treated with erythromycin 50 mg/kg/day for 14 days divided in four administrations (CDC, 2002). However, its use has been associated with signs of hypertrophic pyloric stenosis in children younger than 6 weeks, so that monitoring should be considered (Cooper *et al.*, 2002).

Mycoplasma hominis has been implicated in pelvic inflammatory disease, postabortal and postpartum fever. However, infections caused by this *Mycoplasma* spp. do not respond to erythromycin, but the tetracyclines are effective (see Chapter 66, Tetracycline, Chapter 67, Doxycycline) (Plummer *et al.*, 1987).

For nongonococcal urethritis due to *Ureaplasma urealyticum*, doxycycline is the drug of choice (see Chapter 67, Doxycycline), but erythromycin is also effective and is suitable for pregnant women (CDC, 1993). *Ureaplasma urealyticum* may also cause postpartum infections, which can be treated by doxycycline or erythromycin (Plummer *et al.*, 1987). This organism also causes neonatal bacteremia, pneumonia, and meningitis. Severe cases should be treated with i.v. erythromycin (Waites *et al.*, 1992; Waites *et al.*, 1993).

Erythromycin 500 mg orally four times daily for 7 days is one of several effective therapies for chancroid. However, ceftriaxone or azithromycin are most commonly recommended (Dangor *et al.*, 1990; Schmid, 1990; CDC, 1993). Chancroid is more difficult to cure in HIV-positive patients; the above dose of erythromycin is usually sufficient, but a lower dose such as 250 mg 8-hourly for 7 days may be inadequate (Behets *et al.*, 1995).

Erythromycin in a dosage of 2 g daily for 10–15 days has been used to treat primary or secondary syphilis in penicillin-allergic pregnant women. The disease in the mother is usually cured, but placental transfer of the drug is inconsistent and the fetus may remain infected (Rolfs, 1995). If possible, desensitization to penicillin G, is preferable (see Chapter 1, Benzylpenicillin (Penicillin G)).

7f. Gastrointestinal infections

In *Campylobacter* enteritis, if erythromycin is given early, there may be some lessening of pain and the postinfection carrier state is shortened. However, erythromycin therapy does not generally reduce the duration or severity of diarrhea and other symptoms. The disease is usually short-lived and self-limiting, and no chemotherapy is necessary, unless the eradication of organisms from stools is important. If erythromycin

is used, an oral dose of 0.5 g 6-hourly is sufficient (Pai *et al.*, 1983; Williams *et al.*, 1989). However, clarithromycin is now often used for this indication. For *C. jejuni* septicemia, gentamicin is also an excellent option (McNulty, 1987). In contrast, in immunosuppressed patients such as those with HIV infection, *C. jejuni* enteritis can be prolonged and severe, necessitating prolonged therapy. However, resistance may become problematic (Gibreel and Taylor, 2006).

In a series of patients with *C. fetus* bacteremia, relapse of one patient after therapy with erythromycin, and progress in vertebral osteomyelitis in another during treatment, suggested that erythromycin alone may not be suitable therapy (Francioli *et al.*, 1985).

7g. Staphylococcal infections

Severe *S. aureus* infections, such as septicaemia, may be successfully treated by large doses of i.v. erythromycin if the organism is susceptible (Shoemaker and Yow, 1954), but other drugs are preferred. Prolonged chemotherapy is often necessary for patients with severe disseminated staphylococcal infections, and oral erythromycin may be suitable for the extended treatment, although other alternatives are also now available. Oral erythromycin may be useful for the treatment of staphylococcal diseases such as boils, carbuncles, and wound infections when susceptible strains are involved. An oral dose of 1.0 g daily given for 7 days was effective in eradicating staphylococci from healthy nasal carriers in one study (Wilson *et al.*, 1977), but usually mupirocin (see Chapter 78, Mupirocin) or rifampicin [see Chapter 113, Rifampicin (Rifampin)] are preferred.

7h. *Bartonella* (formerly *Rochalimaea*) infections

Bacteria of this genus cause cat scratch disease, bacillary angiomatosis, bacillary peliosis, and trench fever. In bacillary angiomatosis, there are localized vascular proliferative lesions in skin and extracutaneous organs, and, in bacillary peliosis, there are changes in the hepatic or splenic parenchyma. In addition, bacteremia may occur in AIDS patients and lesions may develop in other parts of the body. There are numerous species in this genus, but three main species are *Bartonella quintana*, *B. henselae*, and *B. elizabethae*. In World War I, *B. quintana* caused trench fever, and this was probably louse-borne; *B. henselae* is carried by cats and it causes cat-scratch disease. All three species can cause the severe syndromes occurring in HIV-infected patients. Additionally, *B. quintana* bacteremia has been described in patients with chronic alcoholism (Spach *et al.*, 1995a), and endocarditis due to this organism has been reported in homeless men (Drancourt *et al.*, 1995; Spach *et al.*, 1995b). For mild disease, oral erythromycin may be used, but, for severe infections, the drug should be given i.v. or alternatives should be used including doxycycline. Therapy should usually be prolonged (Schwartzman, 1992; Koehler and Tappero, 1993; Koehler *et al.*, 1994; Tompkins, 1994; McGregor and Sorrell, 1995).

7i. Pertussis

Erythromycin may prevent whooping cough in exposed susceptible individuals, and may also attenuate the illness if given early in the course of the disease (Linnemann *et al.*, 1975; Altemeier and Ayoub, 1977; Bergquist *et al.*, 1987). Mothers with pertussis can safely nurse their infants if both receive erythromycin (Granström *et al.*, 1987). In one pertussis outbreak in a facility for the developmentally disabled, erythromycin prophylaxis was effective in exposed patients. Carbamazepine toxicity occurred in 7 (19%) of 37 residents when this drug was administered together with erythromycin (Steketee *et al.*, 1988).

Once the paroxysmal stage is reached, erythromycin, like other antibiotics, does not influence the natural course of the illness. It may be useful in preventing secondary bacterial infection and it also eliminates pertussis organisms from the nasopharynx, possibly rendering the patients noninfectious and reducing the number of secondary cases (Bass *et al.*, 1969; Nelson, 1969; Bergquist *et al.*, 1987). It appears worthwhile using erythromycin in pertussis in children younger than six months, diagnosed early, and for older children if they are seriously ill or diagnosed during the first week or so of their symptoms. Cases of erythromycin-resistant *B. pertussis* have been reported (Lewis *et al.*, 1995).

7j. Diphtheria

Erythromycin is active against *C. diphtheriae*, but the administration of specific diphtheria antitoxin is essential for treatment of the disease itself; a course of erythromycin (or penicillin G or V) for 7–14 days should also be given so that the organism will be eradicated, toxin production terminated, and the likelihood of transmission decreased (Farízo *et al.*, 1993; Wilson, 1995). Erythromycin is effective in eliminating *C. diphtheriae* from carriers (Ginsburg and Eichenwald, 1976). Miller *et al.* (1974), however, found a 21% relapse rate 2 weeks after a 6-day course of erythromycin, but this may have been a result of reinfection. Erythromycin for 7 days or i.m. benzathine penicillin are options for unimmunized household contacts of diphtheria (CDC, 1985).

7k. Mycobacterial infections

The newer macrolides, such as clarithromycin and azithromycin, are now preferred for the treatment of nontuberculous mycobacterial infections (see Chapter 61, Clarithromycin). Nevertheless, *M. chelonae* chest infection was successfully treated with 2.0 g oral erythromycin daily in one patient (Irwin *et al.*, 1982). Erythromycin has also been combined with various other drugs, such as cefoxitin and amikacin, for the treatment of *M. chelonae* and *M. fortuitum* infections.

Erythromycin demonstrated no advantage over isoniazid in a controlled trial of treatment of adverse reactions to bacille Calmette–Guérin (BCG) vaccination (Hanley *et al.*, 1985). Caglayan *et al.* (1987) could not demonstrate any superiority of erythromycin over placebo for the treatment of regional lymphadenitis and abscesses which followed BCG vaccinations. However, Murphy *et al.* (1989) reported two patients in whom post-BCG vaccination abscesses appeared to heal with erythromycin therapy.

7l. Q fever

A number of authors have reported treatment success with erythromycin for Q fever, although tetracyclines, especially doxycycline, remain the drug of choice. Five patients with Q fever pneumonia all showed reduction or resolution of fever within 48 hours of commencing treatment with i.v. erythromycin in a dosage of 500 mg 6-hourly (D'Angelo and Hetherington, 1979). Pérez-del-Molino *et al.* (1991) had a similar experience with both i.v. and oral erythromycin.

7m. Inflammatory diseases of the respiratory tract

Erythromycin or other macrolides are used as adjuvant therapy for a series of chronic respiratory tract conditions, such as diffuse panbronchiolitis (a pathology which is frequent in Japan), chronic sinusitis, asthma, bronchiectasis, and pulmonary infections in cystic fibrosis patients, even if the causative organisms are not susceptible to the activity of erythromycin (Hoyt and Robbins, 2001; Garey *et al.*, 2003). Improvement in patients has been attributed to the anti-inflammatory effect of the macrolide rather to any antibiotic activity.

7n. Other infections

Large doses of i.v. erythromycin were used in the past for viridans streptococcal endocarditis in penicillin-allergic patients, but now cephalothin (see Chapter 18, Cephalothin and Cefazolin) or ceftriaxone (see Chapter 27, Ceftriaxone) are preferred. It also has been used under the same circumstances for *E. faecalis* endocarditis, but the role of erythromycin in this diseases has been questioned and, in any case, vancomycin plus gentamicin is now preferred.

Erythromycin in large doses i.v. is an effective alternative to penicillin G for the treatment of gas gangrene in penicillin-allergic patients. Occasionally strains of C. *perfringens* may be resistant to erythromycin. In such cases, clindamycin, chloramphenicol, or metronidazole can be used.

Erythromycin or one of the tetracyclines are alternatives to penicillin G for the treatment of actinomycosis in penicillin-allergic patients (Holmberg *et al.*, 1977).

Flavobacterium meningosepticum meningitis usually occurs in children. In addition to i.v. erythromycin, intraventricular and intrathecal drug has been used in 1.0- or 10-mg doses without evidence of toxicity (Maderazo *et al.*, 1974). Treatment failure has been reported in some adults owing to the development of resistance to erythromycin during therapy. Rifampicin may be a suitable alternative (Rios *et al.*, 1978).

A single oral dose of 0.5 g erythromycin (or tetracycline) may be suitable therapy for louse-borne relapsing fever due to *Borrelia recurrentis*. Erythromycin rather than tetracycline should be used in pregnant patients and children. Both drug regimens may produce the Jarisch–Herxheimer reaction.

Erythromycin has been used to treat acne, on the same basis as the tetracyclines (see Chapter 66, Tetracycline, Chapter 67, Doxycycline) and roxithromycin (see Chapter 60, Roxithromycin) (Ginsburg and Eichenwald, 1976). The drug in various suitable vehicles has also been used topically (Stoughton, 1979; Eady *et al.*, 1982).

References

Abbott Laboratories (1966). *Erythromycin A Review of Its Properties and Clinical Status*. North Chicago, Illinois: Abbott Laboratories, Scientific Division.

Adair CD, Gunter M, Stovall TG *et al.* (1998). Chlamydia in pregnancy: a randomized trial of azithromycin and erythromycin. *Obstet Gynecol* 91: 165–8.

Agusti C, Ferran F, Gea J, Picado C (1991). Ototoxic reaction to erythromycin. *Arch Intern Med* 151: 380.

Altemeier WAIII, Ayoub EM (1977). Erythromycin prophylaxis for pertussis. *Pediatrics* 59: 623.

Ampel NM, Wing EJ (1990). *Legionella* infection in transplant patients. *Semin Resp Infect* 5: 30.

Anderson R (1989). Erythromycin and roxithromycin potentiate human neutrophil locomotion *in vitro* by inhibition of leukoattractant-activitated superoxide generation and autooxidation. *J Infect Dis* 159: 966.

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.

Arthur M, Courvalin P (1986). Contribution of two different mechanisms to erythromycin resistance in *Escherichia coli*. *Antimicrob Agents Chemother* 30: 694.

Arthur M, Brisson-Nšel A, Courvalin P (1987). Origin and evolution of genes specifying resistance to macrolide, lincosamide and streptogramin antibiotics: data and hypotheses. *J Antimicrob Chemother* 20: 783.

Bach MC, Sabath LD, Finland M (1973). Susceptibility of *Nocardia asteroides* to 45 antimicrobial agents *in vitro*. *Antimicrob Agents Chemother* 3: 1.

Bannatyne RM, Cheung R (1982). Antimicrobial susceptibility of *Bordetella pertussis* strains isolated from 1960 to 1981. *Antimicrob Agents Chemother* 21: 666.

Bass JW, Klenk EL, Kotheimer JB *et al.* (1969). Antimicrobial treatment of pertussis. *J Pediatr* 75: 768.

Bass JW, Steele RW, Wiebe RA, Dierdorff EP (1971). Erythromycin concentrations in middle ear exudates. *Pediatrics* 48: 417.

Behets FM-T, Liomba G, Lule G *et al.* (1995). Sexually transmitted diseases and human immunodeficiency virus control in Malawi: a field study of genital ulcer disease. *J Infect Dis* 171: 451.

Ben-Ari J, Eisenstein B, Davidovits M *et al.* (1988). Effect of erythromycin on blood ciclosporin concentrations in kidney transplant patients. *J Pediatrics* 112: 992.

Bergan T, Engeset A, Olszewski W *et al.* (1982). Penetration of erythromycin into human peripheral lymph. *J Antimicrob Chemother* 10: 319.

Bergeron MG, Ahronheim G, Richard JE *et al.* (1987). Comparative efficacies of erythromycin-sulfisoxazole and cefaclor in acute otitis media: a double blind randomized trial. *Pediatr Infect Dis J* 6: 654.

Bergquist S-O, Bernander S, Dahnsjö H, Sundelfö B (1987). Erythromycin in the treatment of pertussis: a study of bacteriologic and clinical effects. *Pediatr Infect Dis J* 6: 458.

Berman S (1995). Otitis media in children. *New Engl J Med* 332: 1560.

Berryman DI, Rood JI (1989). Cloning and hybridization analysis of ermP, a macrolide-lincosamide-streptogramin B resistance determinant from *Clostridium perfringens*. *Antimicrob Agents Chemother* 33: 1346.

Berryman DI, Lyristis M, Rood JI (1994). Cloning and sequence analysis of erm Q, the predominant macrolide-lincosamide-streptogramin B resistance gene in *Clostridium perfringens*. *Antimicrob Agents Chemother* 38: 1041.

Bérubé D, Kirouac D, Croteau D *et al.* (1988). Plasma bactericidal activity after administration of erythromycin estolate and erythromycin ethylsuccinate to healthy volunteers. *Antimicrob Agents Chemother* 32: 1227.

Bilgeri YR, Ballard RC, Duncan MO *et al.* (1982). Antimicrobial susceptibility of 103 strains of *Haemophilus ducreyi* isolated in Johannesburg. *Antimicrob Agents Chemother* 22: 686.

Boguniewicz M, Leung DYM (1995). Hypersensitivity reactions to antibiotics commonly used in children. *Pediatr Infect Dis J* 14: 221.

Bonnefoy A, Girard AM, Agouridas C, Chantot JF (1997). Ketolides lack inducibility properties of MLS(B) resistance phenotype. *J Antimicrob Chemother* 40: 85–90.

Bozdogan B, Appelbaum PC, Kelly LM *et al.* (2003). Activity of telithromycin compared with seven other agents against 1039 *Streptococcus pyogenes* pediatric isolates from ten centers in central and eastern Europe. *Clin Microbiol Infect* 9: 741–5.

Brause BD, Borges JS, Roberts RB (1976). Relative efficacy of clindamycin, erythromycin and penicillin in treatment of *Treponema pallidum* in skin syphilomas of rabbits. *J Infect Dis* 134: 93.

Brazier JS, Levett PN, Stannard AJ *et al.* (1985). Antibiotic susceptibility of clinical isolates of *Clostridia*. *J Antimicrob Chemother* 15: 181.

Breese BB, Disney FA, Talpey W *et al.* (1974). Streptococcal infections in children Comparison of the therapeutic effectiveness of erythromycin administered twice daily with erythromycin, penicillin phenoxymethyl, and clindamycin administered three times daily. *Am J Dis Child* 128: 457.

Brogden RN, Peters DH (1994). Dirithromycin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 48: 599–616.

Brorson J-E, Martinell J, Wilske H (1981). *Branhamella catarrhalis*: antibiotic susceptibility and beta-lactamase production. *J Antimicrob Chemother* 7: 208.

Brown AR (1963). Two cases of untoward reaction after 'Ilosone'. *BMJ* 2: 913.

Brummett RE (1993). Ototoxic liability of erythromycin and analogues. *Otolaryngol Clin North Am* 26: 811–9.

Brunton S, Iannini P (2005). Macrolide-resistant *Streptococcus pneumoniae*: clinical implications for the empiric treatment of community-acquired respiratory tract infections. *MedGenMed* 7: 63.

Burns L, Hodgman J (1963). Studies of prematures, given erythromycin estolate. *Am J Dis Child* 106: 280.

Caglayan S, Yegin O, Kayran K *et al.* (1987). Is medical therapy effective for regional lymphadenitis following BCC vaccination. *Am J Dis Child* 141: 1213.

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.

Canu A, Leclercq R (2002). Les macrolides: une diversité de mécanismes de résistance. *Méd Mal Infect* 32: 32–44.

Canu A, Malbruny B, Coquemont M *et al.* (2002). Diversity of ribosomal mutations conferring resistance to macrolides, clindamycin, streptogramin, and telithromycin in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 46: 125–31.

Carlier MB, Zenebergh A, Tulkens PM (1987). Cellular uptake and subcellular distribution of roxithromycin and erythromycin in phagocytic cells. *J Antimicrob Chemother* 20 (Suppl B): 47–56.

Carson JL, Strom BL, Duff A *et al.* (1993). Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. *Ann Intern Med* 119: 576–83.

CDC (Center for Disease Control) (1977a). Follow-up on Legionnaires' disease. *MMWR* 26: 111.

CDC (Center for Disease Control) (1977b). Follow-up on Legionnaires' disease – Pennsylvania. *MMWR* 26: 152.

CDC (Center for Disease Control) (1978). Penicillinase- (beta-lactamase-) producing *Neisseria gonorrhoeae worldwide*. *MMWR* 27: 10.

CDC (Centers for Disease Control) (1985). ACIP, diphtheria, tetanus and pertussis guidelines for vaccine prophylaxis and other preventive measures. *MMWR* 34: 405.

CDC (Centers for Disease Control) (1993). Sexually transmitted diseases treatment guidelines. *MMWR* 42 (No RR-14): 20–47.

CDC (Center for Disease Control) (2002). Sexually transmitted diseases treatment guidelines 2002. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 51: 1–78.

Chalker DK, Shalita A, Smith Jr JG, Swann RW (1983). A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. *J Am Acad Dermatol* 9: 933.

Chambers HF (2006). Protein synthesis inhibitors and miscellaneous antibacterial agents. In *The Pharmacological Basis of Therapeutics* (Brunton LL, Lazo JS, Parker KL, eds), pp. 1173–202. New-York, NY: McGraw-Hill.

Chirgwin K, Roblin PM, Hammerschlag MR (1989). *In vitro* susceptibilities of *Chlamydia pneumoniae* (*Chlamydia* sp. strain TWAR). *Antimicrob Agents Chemother* 33: 1634.

Clancy J, Petitpas J, Dib-Hajj F *et al.* (1996). Molecular cloning and functional analysis of a novel macrolide- resistance determinant, mefA, from *Streptococcus pyogenes*. *Mol Microbiol* 22: 867–79.

Clarke CW, May CS, Robinson W, Hampshire P (1980). A new formulation of erythromycin stearate: blood and sputum levels in patients with chronic lower respiratory tract infection. *J Antimicrob Chemother* 6: 389.

Cooper WO, Griffin MR, Arbogast P *et al.* (2002). Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. *Arch Pediatr Adolesc Med* 156: 647–50.

Croteau D, Bergeron MG, Le Bel M (1988). Pharmacokinetic advantages of erythromycin estolate over ethylsuccinate as determined by high-pressure liquid chromatography. *Antimicrob Agents Chemother* 32: 561.

Csonka GW, Spitzer RJ (1969). Lincomycin, non-gonococcal urethritis, and mycoplasmata. *Br J Vener Dis* 45: 52.

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.

D'Angelo LJ, Hetherington R (1979). Q fever treated with erythromycin. *BMJ* 2: 305.

Dangor Y, Ballard RC, Miller SD, Koornhof HJ (1990). Treatment of chancroid. *Antimicrob Agents Chemother* 34: 1308.

Darelid J, Lšfgren S, Malmvall B-E (1993). Erythromycin treatment is beneficial for longstanding *Moraxella catarrhalis* associated cough in children. *Scand J Infect Dis* 25: 323.

de Duve C, de Barsy T, Poole B *et al.* (1974). Commentary. Lysosomotropic agents. *Biochem Pharmacol* 23: 2495–531.

Decre D, Bure A, Pangon B, Phillippon A, Bergogne-Berezin E (1991). *In-vitro* susceptibility of *Rhodococcus equi* to 27 antibiotics. *J Antimicrob Chemother* 28: 311–13.

Delmée M, Avesani V (1988). Correlation between serogroup and susceptibility to chloramphenicol, clindamycin, erythromycin, rifampicin and tetracycline among 308 isolates of *Clostridium difficile*. *J Antimicrob Chemother* 22: 325.

Derby LE, Jick H, Henry DA, Dean AD (1993). Erythromycin-associated cholestatic hepatitis. *Med J Aust* 158: 600–02.

Descotes J, Andre P, Evreux JC (1985). Pharmacokinetic drug interactions with macrolide antibiotics. *J Antimicrob Chemother* 15: 659.

Diehl AM, Latham P, Boitnott JK *et al.* (1984). Cholestatic hepatitis from erythromycin ethylsuccinate Report of two cases. *Am J Med* 76: 931–4.

Disanto AR, Chodos DJ (1981). Influence of study design in assessing food effects on absorption of erythromycin base and erythromycin stearate. *Antimicrob Agents Chemother* 20: 190.

Doern GV, Brown SD (2004). Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000–01. *J Infect* 48: 56–65.

Dowling JN, Weyant RS, Pasculle AW (1982). Bactericidal activity of antibiotics against *Legionella micdadei* (Pittsburg pneumonia agent). *Antimicrob Agents Chemother* 22: 272.

Drancourt M, Mainardi JL, Brouqui P *et al.* (1995). *Bartonella (Rochalimae) quintana* endocarditis in three homeless men. *New Engl J Med* 332: 419.

Dresser GK, Spence JD, Bailey DG (2000). Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 38: 41–57.

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.

Dylewski J (1988). Irreversible sensorineural hearing loss due to erythromycin. *CMAJ* 139: 230–1.

Eady EA, Holland KT, Cunliffe WJ *et al.* (1982). The use of antibiotics in acne therapy: oral or topical administration. *J Antimicrob Chemother* 10: 89.

Edelstein PH (1993). Legionnaires disease. *Clin Infect Dis* 16: 741.

Edelstein PH, Meyer RD (1980). Susceptibility of *Legionella pneumophila* to twenty antimicrobial agents. *Antimicrob Agents Chemother* 18: 403.

Eichenwald HF (1986). Adverse reactions to erythromycin. *Pediatr Infect Dis* 5: 147–50.

Ellsworth AJ, Christensen DB, Volpone-McMahon MT (1990). Prospective comparison of patient tolerance to enteric-coated vs nonenteric-coated erythromycin. *J Fam Pract* 31: 265–70.

Eriksson M, Bolme P, Blennow M (1981). Absorption of erythromycin from pediatric suspension in infants and children. *Scand J Infect Dis* 13: 211.

Fallon RJ, Stack BHR (1990). Legionaires' disease due to *Legionella anisa*. *J Infect* 20: 227.

Farízo KM, Strebel PM, Chen RT *et al.* (1993). Fatal respiratory disease due to *Corynebacterium diphtheriae*: case report and review of guidelines for management, investigation, and control. *Clin Infect Dis* 16: 59.

Farrar HC, Walsh-Sukys MC, Kyllonen K, Blumer JL (1993). Cardiac toxicity associated with intravenous erythromycin lactobionate: Two case reports and a review of the literature. *Pediatr Infect Dis J* 12: 688–91.

Farrell DJ, Douthwaite S, Morrissey I *et al.* (2003). Macrolide resistance by ribosomal mutation in clinical isolates of *Streptococcus pneumoniae* from the PROTEKT 1999–2000 Study. *Antimicrob Agents Chemother* 47: 1777–83.

Feldman WE (1993). Pharyngitis in children. *Postgrad Med* 93: 141–5.

Fenelon LE, Mumtaz G, Ridgway GL (1990). The *in vitro* antibiotic susceptibility of *Chlamydia pneumoniae*. *J Antimicrob Chemother* 26: 763.

Ford DK, Smith JR (1974). Non-specific urethritis associated with a tetracycline-resistant T-mycoplasma. *Br J Vener Dis* 50: 373.

Francioli P, Herzstein J, Grob JP *et al.* (1985). *Campylobacter fetus* subspecies *fetus* bacteremia. *Arch Intern Med* 145: 289.

Fraser DW, Wachsmuth IK, Bopp C *et al.* (1978). Antibiotic treatment of guinea-pigs infected with agent of Legionnaires' disease. *Lancet* i: 175.

Garey KW, Alwani A, Danziger LH, Rubinstein I (2003). Tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary diseases. *Chest* 123: 261–5.

Gephart JF, Washington JAII (1982). Antimicrobial susceptibilities of nutritionally variant streptococci. *J Infect Dis* 146: 536.

Gibreel A, Taylor DE (2006). Macrolide resistance in *Campylobacter jejuni* and *Campylobacter coli*. *J Antimicrob Chemother* 58: 243–55.

Giebink GS, Canafax DM (1991). Antimicrobial treatment of otitis media. *Semin Respir Infect* 6: 85–93.

Gilbert FI (1962). Cholestatic hepatitis caused by esters of erythromycin and oleandomycin. *JAMA* 182: 1048.

Gillet-Juvin K, Stern M, Israël-Biet D *et al.* (1994). A highly unusual combination of pulmonary pathogens in an HIV infected patient. *Scand J Infect Dis* 26: 215.

Ginsburg CH, Eichenwald HF (1976). Erythromycin: a review of its uses in pediatric practice. *J Pediatr* 89: 872.

Ginsburg CH, McCracken Jr GH, Culbertson Jr MC (1976). Concentrations of erythromycin in serum and tonsil: comparison of the estolate and ethyl succinate suspensions. *J Pediatr* 89: 1011.

Ginsburg CH, McCracken Jr GH, Crow SD *et al.* (1984). Erythromycin therapy for Group A streptococcal pharyngitis. *Am J Dis Child* 138: 536.

Ginsburg CM, McCracken Jr GH, Steinberg JB *et al.* (1982). Management of Group A streptococcal pharyngitis: a randomized controlled study of twice-daily erythromycin ethylsuccinate versus erythromycin estolate. *Pediatr Infect Dis* 1: 384.

Goldberg DJ, Wrench JG, Collier PW *et al.* (1989). Lochgoilheed fever: outbreak of non-pneumonic legionellosis due to *Legionella micdadei*. *Lancet* i: 316.

Goldman RC, Capobianco JO (1990). Role of an energy-dependent efflux pump in plasmid pNE24-mediated resistance to 14- and 15-membered macrolides in *Staphylococcus epidermidis*. *Antimicrob Agents Chemother* 34: 1973–80.

Goldman RC, Fesik SW, Doran CC (1990). Role of protonated and neutral forms of macrolides in binding to ribosomes from Gram-positive and Gram-negative bacteria. *Antimicrob Agents Chemother* 34: 426.

Goldstein EJC, Citron DM, Richwald GA (1988). Lack of *in vitro* efficacy of oral forms of certain cephalosporins, erythromycin and oxacillin against *Pasteurella multocida*. *Antimicrob Agents Chemother* 32: 213.

Gorbach SL, Bartlett JG (1974). Anaerobic infections (third of three parts). *New Engl J Med* 290: 1289.

Gordin A, Männistö PT, Antikainen R *et al.* (1988a). Concentrations of erythromycin, 2^1 – acetyl erythromycin, and their anhydro forms in plasma and tonsillar tissue after repeated dosage of erythromycin stearate and erythromycin acistrate. *Antimicrob Agents Chemother* 32: 1019.

Gordin A, Kalima S, Hulmi S *et al.* (1988b). Comparison of erythromycin ascitrate and enterocoated erythromycin base in acute respiratory infections. *J Antimicrob Chemother* 21 (Suppl D): 85.

Gouyon JB, Benoit A, Bétremieux P *et al.* (1994). Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 13: 840.

Granström G, Sterner G, Nord CE, Granström M (1987). Use of erythromycin to prevent pertussis in newborns of mothers with pertussis. *J Infect Dis* 155: 1210.

Grayston JT (1989). Chlamydia pneumoniae, strain TWAR. *Chest* 95: 664–9.

Griffith RS, Black HR (1962). A comparison of blood levels after oral administration of erythromycin and erythromycin estolate. *Antibiot Chemother* 12: 398.

Griffith RS, Black HR (1964). Comparison of the blood levels obtained after single and multiple doses of erythromycin estolate and erythromycin stearate. *Am J Med Sci* 247: 69.

Griffith RS, Black HR (1970). Erythromycin. *Med Clin N Am* 54: 1199.

Gryczan T, Israeli-Reches M, Del Bue M, Dubnau D (1984). DNA sequence and regulation of ermD, a macrolide-lincosamide-streptogramin B resistance element from *Bacillus licheniformis*. *Mol Gen Genet* 194: 349–56.

Hächler H, Berger-Bächi B, Kayser FH (1987). Genetic characterization of a *Clostridium difficile* erythromycin-clindamycin resistance determinant that is transferable to *Staphylococcus aureus*. *Antimicrob Agents Chemother* 31: 1039.

Haight TH, Finland M (1952a). Antibacterial action of erythromycin. *Proc Soc Exp Biol Med* 81: 175–83.

Haight TH, Finland M (1952b). Mode of action of erythromycin. *Proc Soc Exp Biol Med* 81: 188–93.

Hammerschlag MR (1994). Antimicrobial susceptibility and therapy of infections caused by *Chlamydia pneumoniae*. *Antimicrob Agents Chemother* 38: 1873.

Hand WL, Boozer RM, King-Thompson NL (1985). Antibiotic uptake by alveolar macrophages of smokers. *Antimicrob Agents Chemother* 27: 42.

Hanley SP, Guml J, Macforlave JT (1985). Comparison of erythromycin and isoniazid in treatment of adverse reactions to BCG vaccinations. *BMJ* 290: 970.

Harrison GAJ, Stross WP, Rubin MP *et al.* (1985). Resistance in oral streptococci after repeated three-dose erythromycin prophylaxis. *J Antimicrob Chemother* 15: 471.

Harvey KJ, Miles H, Hurse A, Carson M (1981). *In-vitro* activity of erythromycin against anaerobic microorganisms. *Med J Aust* 1: 474.

Harvey RL, Sunstrum JC (1991). *Rhodococcus equi* infection in patients with and without human immunodeficiency virus infection. *Rev Infect Dis* 13: 139.

Haydon RC, Thelin JW, Davis WE (1984). Erythromycin ototoxicity: analysis and conclusions based on 22 case reports. *Otolaryngol Head Neck Surg* 92: 678–84.

Holmberg K, Nord C-E, Dornbusch K (1977). Antimicrobial *in vitro* susceptibility of *Actinomyces israelii* and *Arachnia propionica*. *Scand J Infect Dis* 9: 40.

Hosker JP, Jewell DP (1983). Transient, selective Factor X deficiency and acute liver failure following a chest infection treated with erythromycin BP. *Postgrad Med J* 59: 514.

Hovi T, Svahn T, Valtonen V (1987). Twice-a-day regimen of erythromycin base is effective in the treatment of acute streptococcal tonsillitis. *Scand J Infect Dis* 19: 661.

Hoyt JC, Robbins RA (2001). Macrolide antibiotics and pulmonary inflammation. *FEMS Microbiol Lett* 205: 1–7.

Iannini PB (2002). Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. *Expert Opin Drug Saf* 1: 121–8.

Iino Y, Sugita K, Toriyama M, Kudo K (1993). Erythromycin therapy for otitis media with effusion in sinobronchial syndrome. *Arch Otolaryngol Head Neck Surg* 119: 648–51.

Inman WHW, Rawson NSB (1983). Erythromycin estolate and jaundice. *BMJ* 286: 1954.

Inoue M, Farrell DJ, Kaneko K *et al.* (2008). Antimicrobial susceptibility of respiratory tract pathogens in Japan during PROTEKT years 1–5 (1999–2004). *Microb Drug Resist* 14: 109–17.

Ioannidou S, Tassios PT, Zachariadou L *et al.* (2003). *In vitro* activity of telithromycin (HMR 3647) against Greek *Streptococcus pyogenes* and *Streptococcus pneumoniae* clinical isolates with different macrolide susceptibilities. *Clin Microbiol Infect* 9: 704–07.

Irwin RS, Pratter MR, Corwin RW *et al.* (1982). Pulmonary infection with *Mycobacterium chelonei*: successful treatment with one drug based on disk diffusion susceptibility data. *J Infect Dis* 145: 772.

Ishiguro M, Koga H, Kohno S *et al.* (1989). Penetration of macrolides into human polymorphonuclear leucocytes. *J Antimicrob Chemother* 24: 719.

Itoh Z, Nakaya M, Suzuki T *et al.* (1984). Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. *Am J Physiol* 247: G688–94.

Itoh Z, Suzuki T, Nakaya M *et al.* (1985). Structure-activity relation among macrolide antibiotics in initiation of interdigestive migrating contractions in the canine gastrointestinal tract. *Am J Physiol* 248: G320–5.

Jao RL, Finland M (1967). Susceptibility of *Mycoplasma pneumoniae* to 21 antibiotics *in vitro*. *Am J Med Sci* 253: 639.

Johnson RC, Kodner C, Russell M (1987). *In vitro* and *in vivo* susceptibility of the Lyme disease spirochete *Borrelia burgdorferi* to four antimicrobial agents. *Antimicrob Agents Chemother* 31: 164.

Jones RN, Sader HS, Fritsche TR, Pottumarthy S (2007). Comparisons of parenteral broad-spectrum cephalosporins tested against bacterial isolates

from pediatric patients: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). *Diagn Microbiol Infect Dis* 57: 109–16.

Kalm O, Kamme C, Bergström B *et al.* (1975). Erythromycin stearate in acute maxillary sinusitis. *Scand J Infect Dis* 7: 209.

Karmali MA, DeGrandis S, Fleming PC (1981). Antimicrobial susceptibility of *Campylobacter jejuni* with special reference patterns of Canadian isolates. *Antimicrob Agents Chemother* 19: 593.

Kearney BP, Aweeka FT (1999). The penetration of anti-infectives into the central nervous system. *Neurol Clin* 17: 883–900.

Kirst HA, Sides GD (1989). New directions for macrolide antibiotics: pharmacokinetics and clinical efficacy. *Antimicrob Agents Chemother* 33: 1419–22.

Klaassen CH, Mouton JW (2005). Molecular detection of the macrolide efflux gene: to discriminate or not to discriminate between *mef*(A) and *mef*(E). *Antimicrob Agents Chemother* 49: 1271–8.

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.

Klein NC, Cunha BA (1998). Treatment of legionnaires' disease. *Semin Respir Infect* 13: 140–6.

Koehler JE, Tappero JW (1993). Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 17: 612.

Koehler JE, Glaser CA, Tappero JW (1994). *Rochalimaea henselae* infection A new zoonosis with the domestic cat as reservoir. *JAMA* 271: 531.

Kroboth PD, Brown A, Lyon JA *et al.* (1982). Pharmacokinetics of single-dose erythromycin in normal and alcoholic liver disease subjects. *Antimicrob Agents Chemother* 21: 135.

Kunin CM (1967). A guide to use of antibiotics in patients with renal disease. A table of recommended doses and factors governing serum levels. *Ann Intern Med* 67: 151–8.

Kuo C-C, Wang S-P, Grayston JT (1977). Antimicrobial activity of several antibiotics and a sulfonamide against *Chlamydia trachomatis* organisms in cell culture. *Antimicrob Agents Chemother* 12: 80.

Kyrmizakis DE, Chimona TS, Kanoupakis EM *et al.* (2002). QT prolongation and torsades de pointes associated with concurrent use of cisapride and erythromycin. *Am J Otolaryngol* 23: 303–07.

Lai CJ, Weisblum B (1971). Altered methylation of ribosomal RNA in an erythromycin-resistant strain of *Staphylococcus aureus*. *Proc Natl Acad Sci U S A* 68: 856–60.

Lake B, Bell SM (1969). Variations in absorption of erythromycin. *Med J Aust* 1: 449.

Leclercq R (2001). Overcoming antimicrobial resistance: profile of a new ketolide antibacterial, telithromycin. *J Antimicrob Chemother* 48 (Suppl T1): 9–23.

Leclercq R (2002). Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. *Clin Infect Dis* 34: 482–92.

Leclercq R, Courvalin P (1991). Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. *Antimicrob Agents Chemother* 35: 1267–72.

Lee CK, Bowie WR, Alexander ER (1978). *In vitro* assays of the efficacy of antimicrobial agents in controlling *Chlamydia trachomatis* propogation. *Antimicrob Agents Chemother* 13: 441.

Lee EL, Robinson MJ, Thong ML *et al.* (1977). Intraventricular chemotherapy in neonatal meningitis. *J Pediatr* 91: 991.

Lehtonen L, Lankinen KS, Wikberg R *et al.* (1991). Hepatic safety of erythromycin ascitrate in 1549 patients with respiratory tract and skin infections. *J Antimicrob Chemother* 27: 233.

Lesher Jr JL, Chalker DK, Smith Jr JG *et al.* (1985). An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. *J Am Acad Dermatol* 12: 526.

Lesmana M, Lebron CI, Taslim D *et al.* (2001). *In vitro* antibiotic susceptibility of *Neisseria gonorrhoeae* in Jakarta, Indonesia. *Antimicrob Agents Chemother* 45: 359–62.

Levin G, Behrenth E (1986). Irreversible ototoxic effect of erythromycin. *Scand Audiol* 15: 41–2.

Lewis K, Saubolle MA, Tenover FC *et al.* (1995). Pertussis caused by an erythromycin-resistant strain of *Bordetella pertussis*. *Pediatr Infect Dis J* 14: 388.

Lewis VJ, Thacker WL, Shepard CC, McDade JE (1978). *In vivo* susceptibility of the Legionnaires' disease bacterium to ten anti-microbial agents. *Antimicrob Agents Chemother* 13: 419.

Lina G, Quaglia A, Reverdy ME *et al.* (1999). Distribution of genes encoding resistance to macrolides, lincosamides, and streptogramins among staphylococci. *Antimicrob Agents Chemother* 43: 1062–6.

Linnemann Jr CC, Ramundo N, Perlstein PH *et al.* (1975). Use of pertussis vaccine in an epidemic involving hospital staff. *Lancet* 2: 540.

Lode HM (2007). Managing community-acquired pneumonia: a European perspective. *Respir Med* 101: 1864–73.

Ludden TM (1985). Pharmacokinetic interactions of the macrolide antibiotics. *Clin Pharmacokinet* 10: 63.

McCarthy LR, Mickelson PA, Smith EG (1979). Antibiotic susceptibility of *Haemophilus vaginalis* (*Corynebacterium vaginale*) to 21 antibiotics. *Antimicrob Agents Chemother* 16: 186.

McCormack WM, George H, Donner A *et al.* (1977). Hepatotoxicity of erythromycin estolate during pregnancy. *Antimicrob Agents Chemother* 12: 630.

McDonald CJ, Tierney WM, Hui SL *et al.* (1985). A controlled trial of erythromycin in adults with nonstreptococcal pharyngitis. *J Infect Dis* 152: 1093–4.

McGregor AR, Sorrell TC (1995). Infectious diseases. *Med J Aust* 162: 104.

McGuire JM, Bunch RL, Anderson RC *et al.* (1952). Ilotycin, a new antibiotic. *Antibiot Chemother* 2: 281–3.

McNulty CA (1987). The treatment of campylobacter infections in man. *J Antimicrob Chemother* 19: 281–4.

McNulty CAM, Dent J, Wise R (1985). Susceptibility of clinical isolates of *Campylobacter pyloridis* to 11 antimicrobial agents. *Antimicrob Agents Chemother* 28: 837.

McNulty CAM, Dent JC, Ford GA, Wilkinson SP (1988). Inhibitory antimicrobial concentrations against *Campylobacter pylori* in gastroc mucosa. *J Antimicrob Chemother* 22: 729.

Maderazo EG, Bassaris HP, Quintiliani R (1974). *Flavobacterium meningosepticum* meningitis in a newborn infant. Treatment with intraventricular erythromycin. *J Pediatr* 85: 675.

Männistö PT, Taskinen J, Ottoila P *et al.* (1988). Fate of single oral doses of erythromycin ascitrate, erythromycin stearate, and pelleted erythromycin base analysed by mass-spectrometry in plasma of healthy human volunteers. *J Antimicrob Chemother* 21 (Suppl D): 33.

Maple PAC, Efstratiou A, Tseneva G *et al.* (1994). The *in vitro* susceptibilities of toxigenic strains of *Corynebacterium diphtheriae* isolated in northwestern Russia and surrounding areas to ten antibiotics. *J Antimicrob Chemother* 34: 1037.

Marchandin H, Jean-Pierre H, Jumas-Bilak E *et al.* (2001). Distribution of macrolide resistance genes erm (B) and mef (A) among 160 penicillin-intermediate clinical isolates of *Streptococcus pneumoniae* isolated in southern France. *Pathol Biol (Paris)* 49: 522–7.

Marlin GE, Thompson PJ, Jenkins CR *et al.* (1983). Study of serum levels, venous irritation and gastrointestinal side-effects with intravenous erythromycin lactobionate in patients with bronchopulmonary infection. *Hum Toxicol* 2: 593–605.

Martell R, Heinrichs D, Stiller CR *et al.* (1986). The effects of erythromycin in patients treated with ciclosporin. *Ann Intern Med* 104: 660.

Martin JR, Johnson P, Miller MF (1985). Uptake, accumulation, and egress of erythromycin by tissue culture cells of human origin. *Antimicrob Agents Chemother* 27: 314–19.

Martin RE, Bates JH (1991). Atypical pneumonia. *Inf Dis Clin N Am* 5: 585.

Masel MA (1962). Erythromycin hepato-sensitivity: a preliminary report of two cases. *Med J Aust* 1: 560.

Matsuoka M, Endou K, Kobayashi H *et al.* (1998). A plasmid that encodes three genes for resistance to macrolide antibiotics in *Staphylococcus aureus*. *FEMS Microbiol Lett* 167: 221–7.

Maurin M, Raoult D (1993). Antimicrobial susceptibility of *Rochalimaea quintana*, *Rochalimaea vinsonii*, and the newly recognized *Rochalimaea henselae*. *J Antimicrob Chemother* 32: 587.

Metzger WI, Jenkins Jr CJ, Harris CJ *et al.* (1959). Laboratory and clinical studies of intramuscular erythromycin. *Antibiot Annual 1958–1959*: 383.

Meyer RD (1983). *Legionella* infections: a review of five years of research. *Rev Infect Dis* 5: 258.

Milberg P, Eckardt L, Bruns HJ *et al.* (2002). Divergent proarrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. *J Pharmacol Exp Ther* 303: 218–25.

Miller JM, Martin DH (2000). Treatment of *Chlamydia trachomatis* infections in pregnant women. *Drugs* 60: 597–605.

Miller LW, Bickham S, Jones WL *et al.* (1974). Diphtheria carriers and the effect of erythromycin therapy. *Antimicrob Agents Chemother* 6: 166.

Moffie BG, Mouton RP (1988). Sensitivity and resistance of *Legionella pneumophila* to some antibiotics and combination of antibiotics. *J Antimicrob Chemother* 22: 457.

Molavi A, Weinstein L (1971). *In vitro* activity of erythromycin against atypical mycobacteria. *J Infect Dis* 123: 216.

Monod M, Mohan S, Dubnau D (1987). Cloning and analysis of ermG, a new macrolide-lincosamide-streptogramin B resistance element from *Bacillus sphaericus*. *J Bacteriol* 169: 340–50.

Morrissey I, Robbins M, Viljoen L, Brown DF (2005). Antimicrobial susceptibility of community-acquired respiratory tract pathogens in the UK during 2002/3 determined locally and centrally by BSAC methods. *J Antimicrob Chemother* 55: 200–08.

Mourad A, Sweet RL, Sugg N, Schachter J (1980). Relative resistance to erythromycin in *Chlamydia trachomatis*. *Antimicrob Agents Chemother* 18: 696.

Mouton JW, Theuretzbacher U, Craig WA *et al.*(2008). Tissue concentrations: do we ever learn? *J Antimicrob Chemother* 61: 235–7.

Muder RR, Yu VL, Fang G-D (1989). Community-acquired Legionnaires' disease. *Semin Resp Infect* 4: 32.

Mulazimoglu L, Tulkens PM, Van Bambeke F (2005). Macrolides. In *Antimicrobial Therapy and Vaccines. Volume II: Antimicrobial Agents* (Yu VL, Edwards G, McKinnon PS *et al.*, eds), 243–79. Pittsburgh, PA: ESun Technologies, LLC.

Murphy PM, Mayers DL, Brock NF, Wagner KF (1989). Cure of Bacille Calmette–Guérin vaccination abscesses with erythromycin. *Rev Infect Dis* 11: 335.

Naess A, Solberg CO (1988). Effects of two macrolide antibiotics on human leukocyte membrane receptors and functions. *APMIS* 96: 503.

Nakajima Y (1999). Mechanisms of bacterial resistance to macrolide antibiotics. *J Infect Chemother* 5: 61–74.

Neaverson MA (1976). Intravenous administration of erythromycin; serum, sputum and urine levels. *Curr Med Res Opin* 4: 359.

Neeleman C, De Valk JA, Klaassen CH *et al.* (2005). *In-vitro* susceptibility and molecular characterisation of macrolide resistance mechanisms among *Streptococcus pneumoniae* isolates in The Netherlands: the DUEL 2 study. *Clin Microbiol Infect* 11: 312–8.

Nelson JD (1969). Antibiotic treatment of pertussis. *Pediatrics* 44: 474.

Ng WS, Chau PY, Ling J *et al.* (1983). Penicillinase-producing *Neisseria gonorrhoeae* isolates from different localities in South East Asia. Susceptibility to 15 antibiotics. *Br J Vener Dis* 59: 232.

Nguyen MH, Stout JE, Yu VL (1991). Legionellosis. *Inf Dis Clin N Am* 5: 561.

Niitu Y, Hasegawa S, Suetake T *et al.* (1970). Resistance of *Mycoplasma pneumoniae* to erythromycin and other antibiotics. *J Pediatr* 76: 438.

Niitu Y, Hasegawa S, Kibota H (1974). *In vitro* development of resistance to erythromycin, other macrolide antibiotics, and lincomycin in *Mycoplasma pneumoniae*. *Antimicrob Agents Chemother* 5: 513.

Nimmo GR, Bull JZ (1995). Comparative susceptibility of *Legionella pneumophila* and *Legionella longbeachae* to 12 antimicrobial agents. *J Antimicrob Chemother* 36: 219.

Norris SJ, Edmondson DG (1988). *In vitro* culture system to determine MICs and MBCs of antimicrobial agents against *Treponema pallidum* subsp *pallidum* (Nichols strain). *Antimicrob Agents Chemother* 32: 68.

Novelli A, Fallani S, Cassetta MI *et al.* (2002). *In vivo* pharmacodynamic evaluation of clarithromycin in comparison to erythromycin. *J Chemother* 14: 584–90.

Oberg KC, Bauman JL (1995). QT interval prolongation and torsades de pointes due to erythromycin lactobionate. *Pharmacotherapy* 15: 687–92.

Oliver LE, Iser JH, Stening GF, Smallwood RA (1973). 'Biliary colic' and ilosone. *Med J Aust* 1: 1148.

Ortuno JA, Olaso V, Berenguer J (1984). [Cholestasis hepatitis caused by erythromycin propionate]. *Med Clin (Barc)* 82: 912.

Osono T, Umezawa H (1985). Pharmacokinetics of macrolides, licosamides and streptogramins. *J Antimicrob Chemother* 16 (Suppl A): 151.

Pai CH, Gillis F, Tuomanen E, Marks MI (1983). Erythromycin in treatment of *Campylobacter enteritis* in children. *Am J Dis Child* 137: 286–8.

Papavasileiou E, Voyatzi A, Papavasileiou K *et al.* (2007). Antimicrobial susceptibilities of *Campylobacter jejuni* isolates from hospitalized children in Athens, Greece, collected during 2004–2005. *Eur J Epidemiol* 22: 77–8.

Pasculle AW, Dowling JN, Frola FN *et al.* (1981). Susceptibility of Pittsburg pneumonia agent (*Legionella micdadei*) and other newly recognized members of the genus *Legionella* to nineteen antimicrobial agents. *Antimicrob Agents Chemother* 20: 793.

Patamasucon P, Kaojarer S, Kusmiez H, Nelson JD (1981). Pharmacokinetics of erythromycin ethylsuccinate and estolate in infants under 4 months of age. *Antimicrob Agents Chemother* 19: 736.

Patole S, Rao S, Doherty D (2005). Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 90: F301–06.

Pedro-Botet L, Yu VL (2006). Legionella: macrolides or quinolones? *Clin Microbiol Infect* 12 (Suppl 3): 25–30.

Peeters T, Matthijs G, Depoortere I *et al.* (1989). Erythromycin is a motilin receptor agonist. *Am J Physiol* 257: G470–4.

Peeters TL (2001). GM-611 (Chugai Pharmaceutical). *Curr Opin Investig Drugs* 2: 555–7.

Pérez-del-Molino A, Aguado JM, Riancho JA *et al.* (1991). Erythromycin and the treatment of *Coxiella burnetii* pneumonia. *J Antimicrob Chemother* 28: 455.

Periti P, Mazzei T, Mini E, Novelli A (1989). Clinical pharmacokinetic properties of the macrolide antibiotics. Effects of age and various pathophysiological states (Part II). *Clin Pharmacokinet* 16: 261–82.

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.

Pessayre D, Larrey D, Funck-Brentano C, Benhamou JP (1985). Drug interactions and hepatitis produced by some macrolide antibiotics. *J Antimicrob Chemother* 16 (Suppl A): 181–94.

Philipson A, Sabath LD, Charles D (1973). Transplacental passage of erythromycin and clindamycin. *New Engl J Med* 288: 1219.

Plummer DC, Garland SM, Gilbert GL (1987). Bacteraemia and pelvic infection in women due to *Ureaplasma urealyticum* and *Mycoplasma hominis*. *Med J Aust* 146: 135.

Poehlsgaard J, Douthwaite S (2003). Macrolide antibiotic interaction and resistance on the bacterial ribosome. *Curr Opin Investig Drugs* 4: 140–8.

Prokesch RC, Hand WL (1982). Antibiotic entry into human polymorphonuclear leukocytes. *Antimicrob Agents Chemother* 21: 373.

Putzi R, Blaser J, Luthy R *et al.* (1983). Side-effects due to the intravenous infusion of erythromycin lactobionate. *Infection* 11: 161–3.

Quinnan GV, McCabe WR (1978). Ototoxicity of erythromycin. *Lancet* 1: 1160–1.

Raoult D, Roussellier P, Tamalet J (1988). *In vitro* evaluation of josamycin, spiramycin, and erythromycin against *Rickettsia rickettsii* and *R. conorii*. *Antimicrob Agents Chemother* 32: 255.

Rasch JR, Mogabgab WJ (1965). Therapeutic effect of erythromycin on *Mycoplasma pneumoniae* pneumonia. *Antimicrob Agents Chemother (Bethesda)* 5: 693–9.

Rasmussen JL, Odelson DA, Macrina FL (1986). Complete nucleotide sequence and transcription of ermF, a macrolide-lincosamide-streptogramin B resistance determinant from *Bacteroides fragilis*. *J Bacteriol* 168: 523–33.

Regnery R, Tappero J (1995). Unraveling mysteries associated with cat-scratch disease, bacillary angiomatosis, and related syndromes. *Emerging Infect Dis* 1: 16.

Reinert RR, Wild A, Appelbaum P *et al.* (2003). Ribosomal mutations conferring resistance to macrolides in *Streptococcus pneumoniae* clinical strains isolated in Germany. *Antimicrob Agents Chemother* 47: 2319–22.

Reinert RR, Lutticken R, Reinert S *et al.* (2004). Antimicrobial resistance of *Streptococcus pneumoniae* isolates of outpatients in Germany, 1999–2000. *Chemotherapy* 50: 184–9.

Renaudin H, Tully JG, Bebear C (1992). *In vitro* susceptibilities of *Mycoplasma genitalium* to antibiotics. *Antimicrob Agents Chemother* 36: 870.

Report of a WHO Scientific Group (1978). *Neisseria gonorrhoeae* and gonococcal infections. *Wld Hlth Org Rep Ser*, 616, p. 99.

Righter J, Luchsinger I (1988). *Haemophilus influenzae* from four laboratories in one Canadian city. *J Antimicrob Chemother* 22: 333–9.

Ringertz S, Rockhill RC, Ringertz O, Sutomo A (1981). Susceptibility of *Campylobacter fetus* subsp. *jejuni*, isolated from patients in Jakarta, Indonesia, to ten antimicrobial agents. *J Antimicrob Chemother* 8: 333.

Rios I, Klimek JJ, Maderazzo E, Quintiliani R (1978). *Flavobacterium meningosepticum* meningitis: report of selected aspects. *Antimicrob Agents Chemother* 14: 444.

Robinson MM (1961). Antibiotics increase incidence of hepatitis. *JAMA* 178: 89.

Roblin PM, Montalban G, Hammerschlag MR (1994). Susceptibilities to clarithromycin and erythromycin of isolates of *Chlamydia pneumoniae* from children with pneumonia. *Antimicrob Agents Chemother* 38: 1588.

Roden DM (2008). Cellular basis of drug-induced torsades de pointes. *Br J Pharmacol* 154: 1502.

Roig J, Carreres A, Domingo C (1993). Treatment of Legionnaires' disease. Current recommendations. *Drugs* 46: 63–79.

Rolfs RT (1995). Treatment of syphilis. *Clin Infect Dis* 20 (Suppl 1): 23.

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.

Rosdahl VT, Sørensen TS, Colding H (1979). Determination of antibiotic concentrations in bone. *J Antimicrob Chemother* 5: 275.

Rosenfeld J, Gura J, Boner G *et al.* (1983). Interstitial nephritis with acute renal failure after erythromycin. *BMJ* 286: 938.

Ross JI, Eady EA, Cove JH *et al.* (1990). Inducible erythromycin resistance in staphylococci is encoded by a member of the ATP-binding transport super-gene family. *Mol Microbiol* 4: 1207–14.

Rudin JE, Evans TL, Wing EJ (1984). Failure of erythromycin in treatment of *Legionella micdadei* pneumonia. *Am J Med* 76: 318.

Sabath LD, Gerstein DA, Loder PB, Finland M (1968). Excretion of erythromycin and its enhanced activity in urine against Gram-negative bacilli with alkalinization. *J Lab Clin Med* 72: 916.

Sacristan JA, Soto JA, de Cos MA (1993). Erythromycin-induced hypoacusis: 11 new cases and literature review. *Ann Pharmacother* 27: 950–5.

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.

Sandström I, Ringertz O (1988). Levels of erythromycin in tear fluid and serum in infants with conjunctivitis. *Scand J Infect Dis* 20: 429.

Santagati M, Iannelli F, Cascone C *et al.* (2003). The novel conjugative transposon tn1207.3 carries the macrolide efflux gene mef(A) in *Streptococcus pyogenes*. *Microb Drug Resist* 9: 243–7.

Schachter J, Sweet RL, Grossman M *et al.* (1986). Experience with the routine use of erythromycin for chlamydial infections in pregnancy. *New Engl J Med* 314: 276.

Schito AM, Schito GC, Debbia E *et al.* (2003). Antibacterial resistance in *Streptococcus pneumoniae* and *Haemophilus influenzae* from Italy and Spain: data from the PROTEKT surveillance study, 1999–2000. *J Chemother* 15: 226–34.

Schlunzen F, Zarivach R, Harms J *et al.* (2001). Structural basis for the interaction of antibiotics with the peptidyl transferase centre in eubacteria. *Nature* 413: 814–21.

Schmid GP (1990). Treatment of chancroid. *Rev Infect Dis* 12 (Suppl 6): 580.

Schmitz FJ, Sadurski R, Kray A *et al.* (2000). Prevalence of macrolide-resistance genes in *Staphylococcus aureus* and *Enterococcus faecium* isolates from 24 European university hospitals. *J Antimicrob Chemother* 45: 891–4.

Schoenenberger RA, Haefeli WE, Weiss P, Ritz RF (1990). Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 300: 1375–6.

Schwartzman WA (1992). Infections due to *Rochalimaea*: the expanding clinical spectrum. *Clin Infect Dis* 15: 893.

Schwebke JR, Hackman R, Bowden R (1990). Pneumonia due to *Legionella micdadei* in bone marrow transplant recipients. *Rev Infect Dis* 12: 824.

Sefton AM, Maskell JP, Kerawalla C *et al.* (1990). Comparative efficacy and tolerance of erythromycin and josamycin in the prevention of bacteraemia following dental extraction. *J Antimicrob Chemother* 25: 975.

Shames JM, George RB, Holliday WB *et al.* (1970). Comparison of antibiotics in the treatment of mycoplasmal pneumonia. *Arch Intern Med* 125: 680–4.

Sherlock S (1968). Drugs and the liver. *BMJ* 1: 227.

Shivakumar AG, Dubnau D (1981). Characterization of a plasmid-specified ribosome methylase associated with macrolide resistance. *Nucleic Acids Res* 9: 2549–62.

Shoemaker EH, Yow EM (1954). Clinical evaluation of erythromycin. *Arch Intern Med* 93: 397.

Sims PJ, Waites KB, Crouse DT (1994). Erythromycin lactobionate toxicity in preterm neonates. *Pediatr Infect Dis J* 13: 164.

Sivapalasingam S, Steigbigel NH (2005). Macrolides, clindamycin, and ketolides. In *Principles and Practice of Infectious Diseases* (Mandell GL, Bennet JE, Dolin R, eds), Philadelphia, PA: Elsevier/Churchill Livingstone.

Söderström M, Blomberg J, Christensen P, Hovelius B (1991). Erythromycin and phenoxymethylpenicillin (penicillin V) in the treatment of respiratory tract infections as related to microbiological findings and serum C-reactive protein. *Scand J Infect Dis* 23: 347.

South MA, Short DH, Knox JM (1964). Failure of erythromycin estolate therapy in *in utero* syphilis. *JAMA* 190: 70.

Spach DH, Kanter AS, Dougherty MJ *et al.* (1995a). *Bartonella (Rochalimaea) quintana* bacteremia in inner city patients with chronic alcoholism. *New Engl J Med* 332: 424.

Spach DH, Kanter AS, Daniels NA *et al.* (1995b). *Bartonella (Rochalimaea)* species as a cause of apparent culture negative endocarditis. *Clin Infect Dis* 20: 1044.

Spaepen MS, Kundsin RB, Horne HW (1976). Tetracycline-resistant T-mycoplasmas (*Ureaplasma urealyticum*) from patients with a history of reproductive failure. *Antimicrob Agents Chemother* 9: 1012.

Sprunt K, Leidy G, Redman W (1970). Cross-resistance between lincomycin and erythromycin in viridans streptococci. *Pediatrics* 46: 84.

Stamm LV, Stapleton JT, Bassford Jr PJ (1988). *In vitro* assay to demonstrate high-level erythromycin resistance of a clinical isolate of *Trepanema pallidum*. *Antimicrob Agents Chemother* 32: 164.

Steketee RW, Wassilak SG, Adkins Jr WN *et al.* (1988). Evidence for a high attack rate and efficacy of erythromycin prophylaxis in a pertussis outbreak in a facility for the developmentally disabled. *J Infect Dis* 157: 434–40.

Stoughton RB (1979). Topical antibiotics for acne vulgaris. Current usage. *Arch Dermatol* 115: 486.

Sullivan S, Harger B, Cleary JD (1999). Stevens–Johnson syndrome secondary to erythromycin. *Ann Pharmacother* 33: 1369.

Sutcliffe J, Tait-Kamradt, Wondrack L (1996). *Streptococcus pneumoniae* and *Streptococcus pyogenes* resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. *Antimicrob Agents Chemother* 40: 1817.

Sutter VL, Finegold SM (1976). Susceptibility of anaerobic bacteria to 23 antimicrobial agents. *Antimicrob Agents Chemother* 10: 736–52.

Swanson DJ, Sung RJ, Fine MJ *et al.* (1992). Erythromycin ototoxicity: prospective assessment with serum concentrations and audiograms in a study of patients with pneumonia. *Am J Med* 92: 61–8.

Swenson JM, Thornsberry C, Silcox VA (1982). Rapidly growing mycobacteria: testing of susceptibility to 34 antimicrobial agents by broth microdilution. *Antimicrob Agents Chemother* 22: 186.

Tait-Kamradt A, Clancy J, Cronan M *et al.* (1997). mefE is necessary for the erythromycin-resistant M phenotype in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 41: 2251–5.

Tait-Kamradt A, Davies T, Appelbaum PC *et al.* (2000). Two new mechanisms of macrolide resistance in clinical strains of *Streptococcus pneumoniae* from Eastern Europe and North America. *Antimicrob Agents Chemother* 44: 3395–401.

Tarpay MM, Welch DF, Salari H, Marks MI (1982). *In vitro* activity of antibiotics commonly used in the treatment of otitis media against *Streptococcus pneumoniae* isolates with different susceptibilities to penicillin. *Antimicrob Agents Chemother* 22: 145.

Taylor R, Schofield IS, Ramos JM *et al.* (1981). Ototoxicity of erythromycin in peritoneal dialysis patients. *Lancet* 2: 935–6.

Thompson PJ, Burgess KR, Marlin GE (1980). Influence of food absorption of erythromycin ethyl succinate. *Antimicrob Agents Chemother* 18: 829.

Thornsberry C, Baker CN, Kirven LA (1978). *In vitro* activity of antimicrobial agents on Legionnaires' disease bacterium. *Antimicrob Agents Chemother* 13: 78.

Tolman KG, Sannella JJ, Freston JW (1974). Chemical structure of erythromycin and hepatotoxicity. *Ann Intern Med* 81: 58.

Tompkins LS (1994). *Rochalimaea* infections Are they zoonoses? *JAMA* 271: 553.

Triggs EJ, Ashley JJ (1978). Oral administration of erythromycin stearate: effect of dosage form of plasma levels. *Med J Aust* 2: 121.

Tuominen RK, Mönnistö PT, Pohto P *et al.* (1988). Absorption of erythromycin acistrate and erythromycin base in the fasting and non-fasting state. *J Antimicrob Chemother* 21 (Suppl D): 45.

Umstead GS, Neumann KH (1986). Erythromycin ototoxicity and acute psychotic reaction in cancer patients with hepatic dysfunction. *Arch Intern Med* 146: 897–9.

Van Bambeke F, Tulkens PM (2002). Médicaments anti-infectieux dans les pathologies infectieuses du SNC. In *Neuro-Infectiologie* (Sindic C, ed.), pp. 355–88. France: Doin éditions.

van Haarst AD, 't Klooster GA, van Gerven JM *et al.* (1998). The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. *Clin Pharmacol Ther* 64: 542–6.

Vanhoof R, Gordts B, Dierickx R *et al.* (1980). Susceptibility of *Campylobacter fetus* subsp. *jejuni* to 25 antimicrobial agents. *Antimicrob Agents Chemother* 14: 533.

Vasquez EM, Maddux MS, Sanchez J, Pollak R (1993). Clinically significant hearing loss in renal allograft recipients treated with intravenous erythromycin. *Arch Intern Med* 153: 879–82.

Verville TD, Huycke MM, Greenfield RA *et al.* (1994). *Rhodococcus equi* infections of humans. *Medicine* 73: 119.

Vester B, Douthwaite S (2001). Macrolide resistance conferred by base substitutions in 23S rRNA. *Antimicrob Agents Chemother* 45: 1–12.

Vildé JL, Dournon E, Rajagopalan P (1986). Inhibition of *Legionella pneumophila* multiplication within human macrophages by antimicrobial agents. *Antimicrob Agents Chemother* 30: 743.

von Rosensteil NA, Adam D (1995). Macrolide antibacterials. Drug interactions of clinical significance. *Drug Saf* 13: 105–22.

Waites KB, Crouse DT, Cassell GH (1992). Antibiotic susceptibilities and therapeutic options for *Ureaplasma urealyticum* infections in neonates. *Pediatr Infect Dis J* 11: 23.

Waites KB, Crouse DT, Cassell GH (1993). Therapeutic concentrations for *Ureaplasma urealyticum* infections in neonates. *Clin Infect Dis* 17 (Suppl 1): 208.

Waites KB, Sims PJ, Crouse DT *et al.* (1994). Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for *Ureaplasma urealyticum* infection. *Pediatr Infect Dis J* 13: 287.

Waldor MK, Wilson B, Swartz M (1993). Cellulitis caused by *Legionella pneumophila*. *Clin Infect Dis* 16: 51.

Wang H, Liu Y, Sun H *et al.* (2008). *In vitro* activity of ceftobiprole, linezolid, tigecycline, and 23 other antimicrobial agents against *Staphylococcus aureus* isolates in China. *Diagn Microbiol Infect Dis*

Washington JA, Wilson WR (1985). Erythromycin: a microbial and clinical perspective after 30 years of clinical use (2). *Mayo Clin Proc* 60: 271–8.

Weisblum B (1995). Erythromycin resistance by ribosome modification. *Antimicrob Agents Chemother* 39: 577–85.

Wenzel RP, Hendley JO, Dodd WK, Gwaltney Jr JM (1976). Comparison of josamycin and erythromycin in the therapy of *Mycoplasma pneumoniae* pneumonia.. *Antimicrob Agents Chemother* 10: 899.

Wiggins GL, Albritton WL, Feeley JC (1978). Antibiotic susceptibility of clinical isolates of *Listeria* monocytogenes. *Antimicrob Agents Chemother* 13: 854–60.

Williams MD, Schorling JB, Barrett LJ *et al.* (1989). Early treatment of *Campylobacter jejuni* enteritis. *Antimicrob Agents Chemother* 33: 248–50.

Wilson APR (1995). Treatment of infection caused by toxigenic and non-toxigenic strains of *Corynebacterium diphtheriae*. *J Antimicrob Chemother* 35: 717.

Wilson SZ, Martin RR, Putman M (1977). *In vitro* effects of josamycin, erythromycin, and placebo therapy on nasal carriage of *Staphylococcus aureus*. *Antimicrob Agents Chemother* 11: 407.

Wing EJ, Schafer FJ, Pasculle AW (1981). Successful treatment of *Legionella micdadei* (Pittsburgh pneumonia agent) pneumonia with erythromycin. *Am J Med* 71: 386.

Winslow DL, Damme J, Dieckman E (1983). Delayed bactericidal activity of beta-lactam antibiotics against *Listeria monocytogenes*: antagonism of chloramphenicol and rifampin. *Antimicrob Agents Chemother* 23: 555.

Wisseman Jr CL, Waddell AD, Walsh WT (1974). *In vitro* studies of the action of antibiotics on *Rickettsia prowazeki* by two methods of cell culture. *J Infect Dis* 130: 564.

Wollmer P, Pride NB, Rhodes CG *et al.* (1982). Measurement of pulmonary erythromycin concentration in patients with lobar pneumonia by means of positron tomography. *Lancet* ii: 1361.

Wondrack L, Massa M, Yang BV, Sutcliffe J (1996). Clinical strain of *Staphylococcus aureus* inactivates and causes efflux of macrolides. *Antimicrob Agents Chemother* 40: 992–8.

Wong KY, Boose GM, Issitt CH *et al.* (1981). Erythromycin-induced hemolytic anaemia. *J Pediatr* 98: 647.

Wroblewski BA, Singer WD, Whyte J (1986). Carbamazepine-erythromycin interaction. Case studies and clinical significance. *JAMA* 255: 1165.

Yazawa K, Mikami Y, Sakamoto T *et al.* (1994). Inactivation of the macrolide antibiotics erythromycin, midecamycin, and rokitamycin by pathogenic *Nocardia* species. *Antimicrob Agents Chemother* 38: 2197.

Yi YH, Choi JH, Lee HK *et al.* (2006). Characterization of erythromycin resistance of *Streptococcus pyogenes* isolated from pharyngitis patients in Korea. *Jpn J Infect Dis* 59: 192–4.

Zabransky RJ, Johnston JA, Hauser KJ (1973). Bacteriostatic and bactericidal activities of various antibiotics against *Bacteroides fragilis*. *Antimicrob Agents Chemother* 3: 152.

Zamiri I, McEntegart MG (1972). The sensitivity of diphtheria bacilli to eight antibiotics. *J Clin Pathol* 25: 716–7.