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Review of Macrolides and Ketolides

Focus on Respiratory Tract Infections

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Abstract

The first macrolide, erythromycin A, demonstrated broad-spectrum antimicrobial activity and was used primarily for respiratory and skin and soft tissue infections. Newer 14-, 15- and 16-membered ring macrolides such as clarithromycin and the azalide, azithromycin, have been developed to address the limitations of erythromycin.

The main structural component of the macrolides is a large lactone ring that varies in size from 12 to 16 atoms. A new group of 14-membered macrolides known as the ketolides have recently been developed which have a 3-keto in place of the L-cladinose moiety. Macrolides reversibly bind to the 23S rRNA and thus, inhibit protein synthesis by blocking elongation. The ketolides have also been reported to bind to 23S rRNA and their mechanism of action is similar to that of macrolides. Macrolide resistance mechanisms include target site alteration, alteration in antibiotic transport and modification of the antibiotic.

The macrolides and ketolides exhibit good activity against Gram-positive aerobes and some Gram-negative aerobes. Ketolides have excellent activity versus macrolide-resistant *Streptococcus* spp. Including *mef*A and *erm*B producing *Streptococcus pneumoniae*. The newer macrolides, such as azithromycin and clarithromycin, and the ketolides exhibit greater activity against *Haemophilus influenzae* than erythromycin.

The bioavailability of macrolides ranges from 25 to 85%, with corresponding serum concentrations ranging from 0.4 to 12 mg/L and area under the concentration-time curves from 3 to 115 mg/L • h. Half-lives range from short for erythromycin to medium for clarithromycin, roxithromycin and ketolides, to very long for dirithromycin and azithromycin. All of these agents display large volumes of distribution with excellent uptake into respiratory tissues and fluids relative to serum. The majority of the agents are hepatically metabolised and excretion in the urine is limited, with the exception of clarithromycin.

Clinical trials involving the macrolides are available for various respiratory infections. In general, macrolides are the preferred treatment for community-acquired pneumonia and alternative treatment for other respiratory infections. These agents are frequently used in patients with penicillin allergies. The macrolides are well-tolerated agents. Macrolides are divided into 3 groups for likely occurrence of drug-drug interactions: group 1 (e.g. erythromycin) are frequently involved, group 2 (e.g. clarithromycin, roxithromycin) are less commonly involved, whereas drug interactions have not been described for group 3 (e.g. azithromycin, dirithromycin).

Few pharmacoeconomic studies involving macrolides are presently available. The ketolides are being developed in an attempt to address the increasingly prevalent problems of macrolide-resistant and multiresistant organisms.

The majority of macrolide antibiotics are metabolites of *Streptomyces* spp. The first macrolide used clinically, erythromycin A, consists of a 14-membered macrocyclic lactone ring with 2 appended sugar moieties. Erythromycin's spectrum of clinical activity includes Gram-positive cocci (e.g. *Streptococcus pneumoniae, Streptococcus pyogenes* and *Staphylococcus aureus*) as well as atypical pathogens (*Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae*).[1] Erythromycin has primarily been used in the treatment of respiratory and skin and soft tissue infections, especially in patients who are allergic to penicillin. Limitations to erythromycin include insufficient activity against *Haemophilus influenzae*, poor oral bioavailability, a short serum

half-life, high incidence of gastrointestinal (GI) adverse effects, phlebitis when administered parenterally, and a significant number of drug-drug interactions.[1-4]

Newer 14-, 15- and 16-membered ring macrolides such as clarithromycin and the azalide, azithromycin, have been developed and demonstrate improved pharmacokinetic properties, reduced gastric irritation and more potent activity against *H. influenzae*.[5] However, bacterial resistance to both erythromycin and the newer macrolides, particularly among isolates of *S. pneumoniae*, has emerged. The development of a new class of 14-membered ring macrolides known as the ketolides, which differ from other 14-membered ring macrolides by the replacement of the C-3 L-cladinose moiety with a keto group, may offer alternative therapy for Gram-positive infections attributable to resistant pathogens. Ketolides differ from macrolides in that they do not induce resistance to macrolides or MLS_B (macrolide-lincosamide-streptogramin B) in *S. pneumoniae*.[6]

In this review the macrolides and ketolides are compared with regard to their chemical structures, mechanisms of action and resistance, *in vitro* and *in vivo* activities, pharmacokinetics and pharmacodynamics, recent clinical data (post-1997), clinical applications, adverse effects, drug interactions and formulary/pharmacoeconomic considerations. Only the ketolides telithromycin (HMR-3647), HMR-3004 and ABT-773 are discussed in detail as significant published data are available.

1. Chemistry

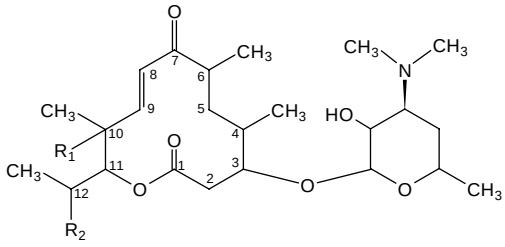
The main structural component of the macrolides is a large lactone ring that varies in size from 12 to 16 atoms (fig. 1). Glycosidic bonds attach one or more sugars to the ring, and the ring is substituted by hydroxyl or alkyl groups.[7] The natural macrolides (table I) are limited clinically with respect to their instability in gastric acid and their unfavourable pharmacokinetic properties. In order to overcome these challenges semisynthetic derivatives of natural macrolides have been developed through esterification, salt formation and/or structural modification.[15]

The macrolides can be subdivided into 4 classes based on the number of atoms in the lactone ring (fig. 1). The 12-membered ring macrolides (table I) have a ketone group at C-7.[7] Methymycin and neomethymycin are naturally occurring aglycone rings with desosamine moieties attached at the C-3 position via a glycosidic bond.[8] Attempts at creating semisynthetic 12-membered macrolides have been made but, to date, none have demonstrated significant clinical activity and they are not included in this review.

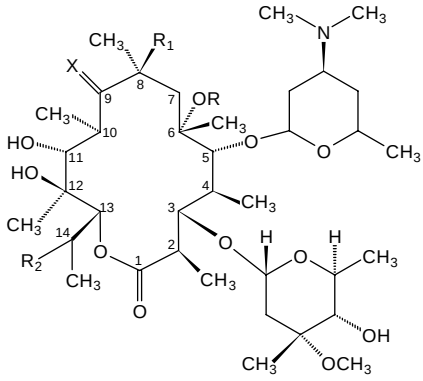
The prototype for 14-membered macrolides is erythromycin. Erythromycin has been demonstrated to decompose to inactive anhydroketal and spiroketal derivatives in gastric acid and is associated with a high incidence of GI adverse effects.[7] The creation of erythromycin salts/esters such as erythromycin stearate, erythromycin estolate and erythromycin ethylsuccinate has improved the acid stability of the drug, however, frequent dosing is still required.[16,17] Acid instability is minimised through structural modifications of the erythromycin ring at the sites prone to degradation, particularly the ketone at C-9, the hydrogen at C-8, the hydroxyl at C-6, and the diol at C-11 and C-12.[15-17]

Modification at the C-9 position of erythromycin yielded the first erythromycin derivative, roxithromycin, which substitutes an oxime group for the ketone (fig. 1). The C-9 position has also been modified in the prodrug dirithromycin. Dirithromycin is a 9-N-11-O-oxazine produced through the combination of the active drug, erythromycylamine, with an acetaldehyde in order to increase the tissue concentration of erythromycylamine.[7,17] The modifications made to the C-9 position increase acid stability but do not appear to affect the *in vitro* activities of either roxithromycin or dirithromycin.[16] The placement of a fluoride atom at the C-8 position yields the macrolide flurithromycin. The C-8 dehydration of erythromycin to an anhydrohemiketal is prevented through the addition of the fluoride atom.[7,17]

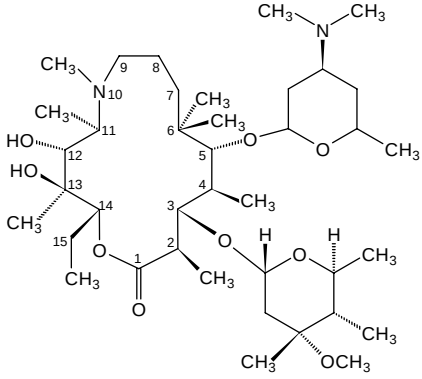
12-membered macrolides



14-membered macrolides



15-membered macrolides



16-membered macrolides

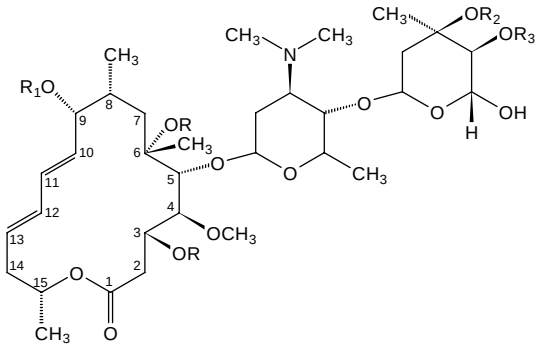


Fig. 1. Chemical structures of macrolides.
12-membered macrolides: Methymycin R_1 = OH, R_2 = H; Neomethymycin R_1 = H, R_2 = OH.
14-membered macrolides: Erythromycin X = O, R = H, R_1 = H, R_2 = H; Erythromycylamine X = NH_2, R = H, R_1 = H, R_2 = H; Clarithromycin X = O, R = CH_3, R_1 = O, R_2 = H; Flurithromycin X = O, R = H, R_1 = F, R_2 = H; Roxithromycin X = $NOCH_2O(CH_2)_2OCH_3$, R = H, R_1 = H, R_2 = H; Dirithromycin X = $NHCHCH_2O(CH_2)_2OCH_3$, R = H, R_1 = H, R_2 = H.
15-membered macrolides: Azithromycin.
16-membered macrolides: Spiramycin R = H, R_1 = forosamine, R_2 = H, R_3 = H; Kitasamycin (leucomycin) R = H, R_1 = H, R_2 = $COCH_2CH_3$, R_3 = H; Josamycin R = $COCH_3$, R_1 = H, R_2 = H, R_3 = $COCH_2CH(CH_3)_2$; Miokamycin (midecamycin acetate) R = $COCH_2CH_3$, R_1 = $COCH_3$, R_2 = $COCH_3$, R_3 = $COCH_2CH_3$; Midecamycin R = $COCH_2CH_3$, R_1 = H, R_2 = H, R_3 = $COCH_2CH_3$; Rokitamycin R = H, R_1 = H, R_2 = $COCH_2CH_3$, R_3 = $CO(CH_2)_2CH_3$.

Clarithromycin is produced through the alkylation of the C-6 hydroxyl group.[17] This modification prevents degradation to hemiketal and spiroketal metabolites through an increase in acid stability. This is an important modification as the hemiketal metabolite is thought to be responsible for causing GI adverse effects.[18,19] Clarithromycin demonstrates *in vitro* activity equal to, or greater than, that of erythromycin against common respiratory pathogens, and its increased antibacterial activity against *H. influenzae* is the result of the 14-hydroxyl metabolite which synergistically interacts with the parent compound.[16]

Azithromycin is a 15-membered erythromycin derivative formed by the addition of a methyl-substituted nitrogen at the C-9a position.[4,18] The addition of this second basic nitrogen atom to form an azalide structure appears to not only prevent

degradation of the drug, but also appears to increase antibacterial activity against *H. influenzae*, other Gram-negative bacteria and atypical pathogens.[7,15,16,18] This structural alternation also leads to better tissue penetration than with erythromycin and a significantly prolonged serum half-life.[18]

The naturally occurring 16-membered macrolides (table I) have been chemically altered in order to increase their activity against some resistant organisms and improve their pharmacokinetic profiles. The acylation of the 3′-hydroxyl group produces rokitamycin (a 3′-O-propionyl derivative) from leucomycin and miokamycin (midecamycin acetate; a 9,3′-di-O-acetyl derivative) from midecamycin.[17]

A new group of 14-membered macrolides, known as the ketolides, has recently been developed. The major structural difference of members of this group is the replacement of the L-cladinose moiety present in other 14-membered macrolides with a 3-ketone (fig. 2).[6,9,10,20] The removal of L-cladinose increases both acid stability and antibacterial potency against bacteria resistant to macrolides by an efflux mechanism (e.g. *S. pyogenes*,

Table I. Natural and semisynthetic macrolides and ketolides[6-14]

No. of atoms	Agent	N or SS	Producing strain (N) or chemical alteration (SS)
Macrolide			
12	Methymycin	N	*Streptomyces venezuelae*
	Neomethymycin	N	and *S. eurocidicus*
	Picromycin	N	*S. felleus*, *S. griseoflavus*, *S. albus* and *S. venezuelae*
14	Erythromycin	N	*S. erythreus*
	Oleandomycin	N	*S. antibioticus*
	Sporeamicin A	N	*S. venezuelae*
	Mycinamycin	N	*Micromonospora griscorubida*
	Roxithromycin	SS	C-9 oxime derivative of erythromycin
	Dirithromycin	SS	C-9, C-11 oxazine derivative of erythromycin
	Flurithromycin	SS	8-fluoro derivative of erythromycin
	Clarithromycin	SS	6-O-methyl derivative of erythromycin
15	Azithromycin (azalide)	SS	C-9a tertiary amino derivative of erythromycin
16	Josamycin	N	*S. narvonensis* var. *josamyceticus*
	Kitasamycin (Leucomycin)	N	*S. kitsocusis* and *S. hygroscopicus*
	Spiramycin (Rovamycin)	N	*S. ambofaciens*
	Midecamycin	N	*S. mycarofaciens*
	Rosaramycin (Rosamycin)	N	*Micromonospora rosaria*
	Tylosin	N	*S. fradiae*
	Rokitamycin	SS	3′-O-propionyl derivative of leucomycin A5
	Miokamycin (Midecamycin acetate; Miocamycin)	SS	9,3′-di-O-acetyl derivative of midecamycin
Ketolide			
14	HMR-3004	SS	Quinolone side chain linked to 11-12 position of the 3-keto-6-methoxy erythromycin via a cyclic hydrazano-carbamate
	Telithromycin (HMR-3647)	SS	3-keto-6-methoxy erythromycin with an 11-12 carbamate link via a C-4 alkyl chain to imidazolyl and pyridinyl rings
	ABT-773	SS	3-keto-6-quinolylallyl erythromycin with an 11,12 cyclic carbamate
	TE-802	SS	3-keto-6-methoxy erythromycin with an 11-12N-(9-iminoethyl)carbamate
	TE-810	SS	3-keto-6-methoxy erythromycin with an 11-12 carbamate
	2,3 anhydro-erythromycin A derivatives	SS	Descladinosyl erythromyin A aryl alkylhydrozo-carbamate derivatives with an unsaturated 2,3 double bond
	TEA-0769	SS	Descladinosyl erythromycin A derivative with a 3-O-(4-nitro-phenylacetate)

N = natural; **SS** = semisynthetic.

S. pneumoniae) or by an inducible MLS_B mechanism (e.g. staphylococci, enterococci, pneumococci).[21,22] HMR-3004 and telithromycin are ketolides possessing C11-C12 side chains which have increased potency relative to other 14-membered macrolides.[6,9,20] HMR-3004 has a quinolone side chain attached to the 11-12 carbamate via a propyl chain, whereas a similar propyl chain in telithromycin binds amidazolyl and pyridyl moieties to the 11-12 carbamate.[9,20] ABT-773, also a ketolide, has a distinct quinolylallyl moiety attached to the 6-0-position as well as a cyclic carbamate group at the 11,12 position.[10] Other ketolides such as TE-802, TE-810, TEA-0769, and a series of descladinosyl erythromycin A derivatives have been developed, however, few data are available (table I).[6]

2. Mechanisms of Action and Resistance

2.1 Mechanism of Action

Macrolides are bacteriostatic agents that reversibly bind to the 23S ribosomal RNA (rRNA) in the 50S-subunit of prokaryotic ribosomes, with 1 : 1 stoichiometry,[23] and block protein synthesis. The macrolides compete with each other for binding to the ribosomal 50S subunit, which suggests that they may bind to identical or overlapping sites on the ribosome.[7,18,23] The precise mechanism of action of the macrolides has not been elucidated, however many theories exist.

It has been proposed that the macrolides inhibit protein synthesis by blocking elongation. During elongation a new amino acid is added on to the growing peptide chain. This reaction, which occurs between the aminoacyl acceptor (A) site and the peptidyl (P) donor site, is catalysed by the enzyme peptidyl transferase. The growing peptide chain is then translocated from the A site to the P site.[23,24] It is believed that 16-membered macrolides inhibit the peptidyl transfer reactions and the peptidyl-transfer RNA (tRNA) translocation is blocked by 14-membered macrolides thus causing peptidyl-tRNA production to cease.[7,23,25]

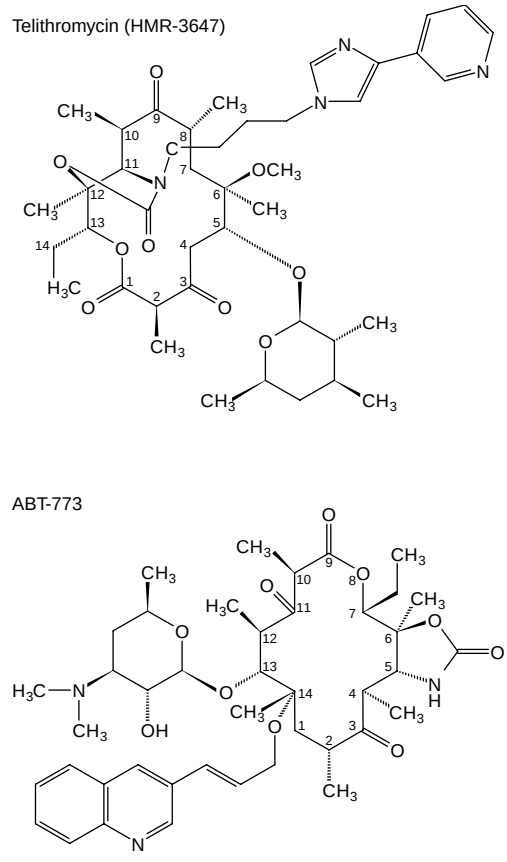


Fig. 2. Chemical structures of ketolides.

It has also been postulated that the macrolides inhibit protein synthesis by stimulating the dissociation of peptidyl-tRNA from ribosomes.[26] This effect, which occurs during translocation, is caused by the weakening of bonds between the ribosomes and the peptidyl-tRNA. Marked increases in peptidyl-tRNA concentrations (i.e. immature peptides) have been shown to occur in the presence of macrolides. The hypothesis is that more peptidyl-tRNA is produced as a result of repeated ribosome peptidyl-tRNA dissociation with the accumulation of dissociated peptidyl-tRNA leading to inhibition of protein synthesis.[7,23,26,27]

Champney and Burdine[28] have recently proposed that macrolides may secondarily inhibit 50S

ribosomal subunit assembly. Their experiments demonstrated that addition of macrolides to bacterial cells caused a decrease in the specific activity ratio of 50S to 30S subunits. This decrease in 50S subunit formation suggests the possibility of a second ribosomal target for the macrolides.[28]

The ketolides have also been reported to bind to 23S rRNA and their mechanism of action is similar to that of the macrolides. However, ketolides have been demonstrated to bind with 10- to 100-fold higher affinity to unmethylated ribosomes than erythromycin and, unlike erythromycin, also bind to methylated ribosomes, although less avidly than to unmethylated ribosomes.[29-31] The ketolides (because of the C11-12 carbamate) have been reported to interact with domain II of the 23s rRNA.[32]

2.2 Bacterial Resistance

Bacterial resistance to erythromycin was initially reported in staphylococci in 1956, only a few years after its introduction into clinical practice.[33,34] Since that time, resistance has been detected in a large number of bacteria including *Staphylococcus* spp., *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *Campylobacter* spp., *Corynebacterium diphtheriae*, *Propionibacterium* and members of the Enterobacteriaceae.[33] Three main mechanisms of microbial resistance to the macrolides have been identified in these bacteria: (i) target site alteration; (ii) alteration in antibiotic transport; and (iii) modification of the antibiotic.[33-36] As an example, the mechanisms of macrolide, as well as lincomycin and streptogramin B (i.e. MLS_B), resistance to streptococci are depicted in table II.

Alteration of the binding site on the ribosome appears to be the main mechanism of resistance to macrolides and may involve changes in either the ribosomal proteins or the rRNA.[36] Structural modifications in various ribosomal proteins of *Escherichia coli* have been detected with the most significant changes at proteins L4 and L22.[34] The mutation at L4 leads to a large reduction in the

Landscape table II to be placed here.

Table II. Mechanisms of resistance to macrolide (M), lincosamide (L) and streptogramin B (S_B) in streptococci

Mechanism	*Streptococcus* spp.	Genotype	Phenotype				Resistance phenotype		
				14-MM	15-MM	16-MM	clindamycin	streptogramin B	streptogramin A
Target modification	*S. pyogenes, S. pneumoniae, S. sanguis, S. agalactiae*	*ermAM*	MLS_B	R	R	R	R	R	S
	S. pyogenes	*ermTR*	MLS_B	R	R	S	S	R	S
Efflux	*S. pyogenes*	*mefA*	M	R	R	S	S	S	S
	S. pneumoniae	*mefE*	M	R	R	S	S	S	S
	S. agalactiae	*mreA*	M	R	R	R	S	S	S
Ribosomal mutation	*S. pneumoniae*	Domain V 23S rRNA, and ribosomal protein L4 mutations	M/MS_B	R	R	NA	S	S/R	NA

14-MM = 14-membered macrolide; **15-MM** = 15-membered macrolide; **16-MM** = 16-membered macrolide; **NA** = not available; **R** = resistant by NCCLS M100-S9 (1999) guidelines; **r-RNA** = ribosomal ribonucleic acid; **S** = susceptible by NCCLS M100-S9 (1999) guidelines.

binding affinity of the 50S ribosomal subunit for erythromycin. The L22 mutant, however, yields no change in binding constants and these amino acid alterations are therefore thought to have a secondary role in bacterial resistance.[34,37]

Similarity in mechanism of action and close proximity of binding within the 50S ribosomal subunit link resistance phenotypes of chemically distinct MLS_B agents.[33-36] A large number of clinical isolates resistant to the MLS_B antibiotics synthesise enzymes that perform post-transcriptional modification of the 23S rRNA through N^6dimethylation of a specific adenine residue (A2058, *E. coli* numbering system). *E. coli* residue number A2058 is used to keep the nomenclature uniform; however, the exact number of the residue in each species varies. The N-methyltransferases (methylases) are coded for by erythromycin ribosome methylation (*erm*) genes. Over 30 *erm* genes from a wide variety of sources have been characterised and the similarities in amino acid sequences may indicate that the *erm* genes are derived from a common ancestor.[33-35]

Resistance to MLS_B agents may be expressed either constitutively or inducibly based on the sequence of the regulatory region located upstream from the methylase coding sequence.[33] Constitutive resistance to the MLS_B group is expressed through the production of an active methylase messenger RNA (mRNA) resulting in high-level resistance.[19] Inducible resistance to the MLS_B group is expressed in bacteria producing inactive mRNA encoded for methylase production. Methylase production is activated through a translation attenuation mechanism which requires the presence of a strong enzyme inducer necessary to promote a conformational change in the mRNA. This induced rearrangement allows the ribosomes to translate the methylase coding sequence.[33] All of the 14- and 15-membered macrolides are strong inducers of methylase synthesis in *Staphylococci* spp., whereas the 16-membered macrolides cannot induce this synthesis on their own.[19] Induction of the mRNA is brought about by different antibiotics in each species, and once induced the organism becomes cross-resistant to all 14-, 15- and 16-membered macrolides.[19,24,33] Resistance to the MLS_B group may be plasmid mediated (*Staphylococci* spp., *Bacteroides* spp. and some *Clostridium* spp.) or chromosomally mediated (*S. pneumoniae* and some *Clostridium* spp.).[19,33]

Resistance through alteration of antibiotic uptake may be intrinsic or acquired. Gram-negative bacilli, particularly Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp., are intrinsically resistant to the MLS_B agents.[38] These hydrophobic agents are unable to pass through the outer membrane of the bacterial cell as the lipopolysaccharide bilayer limits movement. Passage of the MLS_B antibiotics is inhibited through the Gram-negative outer membrane porins as a consequence of the small size of these channels and the energetically favourable water barrier inside the channel.[38,39] Antibiotic accumulation alteration involves an active efflux mechanism. The efflux pump described in *Staphylococci* spp. actively removes 14- and 15-membered macrolides as well as streptogramin B antibiotics but is still susceptible to 16-membered macrolides and lincosamide drugs (an MS phenotype).[40] This efflux system requires multiple genes (*msrA*, *smp* and/or *stp*) in order to operate and is dependent on adenosine triphosphate.[38,40-44] Resistance to 14- and 15-membered macrolides (M phenotype) with susceptibility to the l6-membered macrolides, the lincosamides and the streptogramins has been described through an efflux mechanism in isolates of *S. pyogenes* and *S. pneumoniae*.[40] The M phenotype is characterised by low-level erythromycin resistance [minimum inhibitory concentration (MIC) range, 1-16 mg/L], cross-resistance to 14- and 15-member macrolides and susceptibility to clindamycin and streptogramin B.[40-42] The MLS_B (ribosomal methylation) phenotype differs from the M phenotype in that cross-resistance is present to all MLS_B agents and that erythromycin MICs are significantly higher (≥64 mg/L).[40-42] A proton-dependent, membrane-associated, macrolide efflux mechanism, controlled by a *mef*A, was identified as conferring the M phenotype in isolates of *S. pyogenes*.[40,42] *mef*A, and

the closely related *mef*E efflux system recently cloned from *S. pneumoniae*, are distinct from efflux systems previously identified in *Staphylococci* spp.[40] A novel efflux determinant, designated macrolide resistance efflux (*mreA*), which confers resistance to 14-, 15- and 16-membered macrolides, has also recently been cloned from a strain of *Streptococccus agalactiae*.[42]

Bacterial resistance through modification of the macrolide molecule by inactivating enzymes may be acquired and results in hydrolysis of the lactone ring, phosphorylation or glycosylation at the 2′ position.[35,38,43] Highly antibiotic resistant members of the family Enterobacteriaceae have been described which inactivate the lactone ring of 14-membered macrolides through the production of macrolide 2:-phosphotransferase or erythromycin esterases.[38] The esterases are encoded by erythromycin resistance esterase (*ere*) genes with the 2 genes, *ereA* and *ereB*, encoding for type I and II esterases, respectively.[38]

The ketolides lack the same ability of the MLS_B agents to induce resistance mechanisms observed with macrolides in some organisms (e.g. *S. pneumoniae*). This may be due to a lack of L-cladinose at the C-3 position which may be an essential component in induction of resistance, and/or may be related to affinity of the ketolides for methylated ribosomes.[11,45,46] The high therapeutic activity observed with ketolides irrespective of the phenotypes of the bacterial strains involved suggests that these new agents may be useful to treat infections of the respiratory tract no longer susceptible to commonly used macrolides.[47]

3. *In Vitro* Activity

The *in vitro* activities of the macrolides and ketolides against clinically important bacterial species are compared in tables III to V.[3,16,19,20,29,47-104,106-109] The tables present the minimum concentrations of antibacterial necessary to inhibit growth of 50% of isolates (MIC_{50}) and 90% of isolates (MIC_{90}). The MIC values represent the most commonly occurring values reported in the literature examined for each drug. Data obtained were not restricted as to growth conditions (including growth media) or the method used to carry out the study.

A bacteriostatic agent inhibits the growth or multiplication of bacteria whereas one that is bactericidal actually kills the bacteria.[106] The macrolides and ketolides are usually considered bacteriostatic, however, in some instances bactericidal activity may be achieved.[3,16] Factors such as the type of organism, drug concentration and inoculum size have a role in determining whether the drug displays bacteriostatic or bactericidal activity.[16] The pH at the site may also affect activity as macrolides and ketolides exhibit better cell membrane penetration in their unionised forms which occurs in an alkaline environment.[16] The list of organisms against which bactericidal activity is exerted varies for each drug, for example, erythromycin is bactericidal against *S.pneumoniae* and *S. pyogenes*, whereas clarithromycin and azithromycin are bactericidal against *S. pyogenes* and *H. influenzae*[3] and the ketolides are bactericidal against *S. pneumoniae* and *H. influenzae*.[47]

The macrolides and ketolides exhibit good activity against the Gram-positive aerobes (table III).[3,16,19,29,47-93,97,104] Penicillin susceptible *S. pneumoniae* (MIC ≤ 0.06 mg/L) is inhibited by the majority of macrolides at MIC_{90} levels of ≤0.12 mg/L, whereas the ketolides, telithromycin, HMR-3004 and ABT-773, display even greater inhibition with MIC_{90} values of 0.03, 0.06 and 0.06 mg/L, respectively (table II). Penicillin-intermediate (0.12-1 mg/L) and penicillin-resistant (≥2 mg/L) *S. pneumoniae* are frequently resistant to macrolides.[48,107] A recent Canadian study found that 14 to 18% of isolates intermediately resistant to penicillin and 21 to 38% of highly resistant strains were also resistant to macrolides, while a North American study reports macrolide resistance in 17 and 48% of penicillin-intermediate and penicillin-resistant strains, respectively.[38,107] Felmingham and Washington,[108] as part of the Alexander project, have reported the following rates of macrolide resistance: The Netherlands 1.5%, Belgium 22%, Switzerland 6.4%, Austria 4.6%, Poland 12.2%,

Table III. *In vitro* activity of macrolides and ketolides against Gram-positive and Gram-negative aerobic bacteria as minimum inhibitory concentrations (MIC) of 50% (50) and 90% (90) of isolates in mg/L (adapted from references: erythromycin,[3,16,19,29,47-66] clarithromycin,[3,16,19,48-57,59-73] roxithromycin,[16,29,48,50-56,59,62,64-66,74-76] dirithromycin,[16,50,53,55,64,67,70] erythromycylamine,[50] azithromycin,[3,16,29,47,48,50-55,59,62-66,69,70-91] spiramycin,[50,53] josamycin,[47,50,53,59,64,65] flurithromycin,[50] miokamycin,[50,68] rokitamycin,[50,66,71] HMR-3004,[29,47,48,56,65,70,71] telithromycin,[57,58,62,63,65,66,68,69,76,91] ABT-773[92,93])

Macrolides																						Ketolides					
ERY		CLA		ROX		DIR		EMC		AZI		SPI		JOS		FLU		MIO		ROK		HMR-3004		TEL		ABT-773	
50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90
Staphylococcus aureus (MS)																											
0.25	2	0.12	1	0.5	2	0.25	2	0.12	4	0.5	2	1	4	1	4	0.12	1	1	1	0.5	1	0.03	0.06	0.06	0.12	0.03	0.06
S. aureus (MR)																											
>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>128	>16	>16
Staphylcoccus epidermidis																											
8	>128	4	>128	32	>128	8	>128	16	>128	16	>128	1	>128	1	>128	11	16	>128	0.5	>128	0.25	>128	0.06	0.12	0.12	0.25	0.03	0.06
Streptococcus pyogenes																											
0.03	0.12	0.03	0.12	0.06	0.06	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.5	0.06	0.06	0.5	0.5	0.25	0.25	0.001	0.02	≤0.01	0.03	0.016	0.016
Streptococcus pneumoniae (PS)[a]																											
0.06	0.06	0.06	0.06	0.12	0.25	0.06	0.12	0.06	0.06	0.06	0.12	0.03	0.03	0.25	0.25	0.03	0.06	0.25	0.5	0.12	0.25	0.016	0.06	0.016	0.03	0.016	0.06
S. pneumoniae (PI)[a]																											
0.06	16	0.03	8	0.25	16	ND	0.3	ND	ND	0.12	8	ND	ND	0.5	0.5	ND	ND	ND	ND	0.12-0.25	0.5	0.016	0.06	0.016	0.12	0.016	0.03
S. pneumoniae (PR)[a]																											
1	>32	1	32	1	16	ND	32	ND	ND	1	32	ND	ND	ND	ND	ND	ND	2	>4	0.25	8	0.06	0.25	0.06	0.25	0.03	0.125
Enterococcus faecalis																											
4	>128	4	>128	8	>128	16	>64	ND	ND	4	>64	ND	ND	8	>64	ND	ND	ND	ND	ND	ND	0.06	4	0.12	2-4	0.03	8
Enterococcus faecium																											
32	>64	>128	>128	>128	>128	>64	>64	ND	ND	ND	>64	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	2	8	4	8	4	8
Listeria monocytogenes																											
0.5	0.5	0.25	0.25	0.5	1	2	2	1	1	1	2-4	4	4	2	2	0.5	0.5	2	2	1	1	0.03	0.06	0.06	0.06	0.06	0.06
Haemophilus influenzae[a]																											
4	8	2[b]	4[b]	4	8	8	16	8	8	1	2	8	16	8	16	8	8	>16	>16	8	16	1	2	2	4	2	4
H. influenzae (BLP)																											
4	8	2[b]	4[b]	4	8	8	16	ND	ND	1	2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1	2	2	4	2	4
Moraxella catarrhalis																											
0.12	0.25	0.12	0.25	0.5	1	0.1	0.2	ND	ND	0.06	0.12	ND	ND	0.5	1	ND	ND	ND	ND	ND	ND	0.08	0.08	0.06	0.125	0.125	0.2

a National Committee for Clinical Laboratory Standards Approved and Tentative Breakpoints:[94]

1. *S. pnuemoniae* – erythromycin and clarithromycin – 0.25 to 1.0 μg/ml is intermediate, ≤1.0 μg/ml is resisitant; azithromycin and dirithromycin – 0.5 to 2 μg/ml is intermediate, ≥2.0 μg/ml is resistant, others – no data.
2. *H. influenzae* – azithromycin ≤4 g/ml susceptible; clarithromycin ≤8 g/ml susceptible, 16 g/ml is intermediate, ≥32 is resistant (no breakpoints for other agents).

b Clarithromycin has increased activity against *H. influenzae* due to its active 14-OH metabolite. MIC values for the 14-OH derivative are: MIC_{50} = 2 and MIC_{90} = 4[19]

AZI = azithromycin; **BLP** = beta lactamase positive; **CLA** = clarithromycin; **DIR** = dirithromycin; **EMC** = erythromycylamine, the active metabolite of dirithromycin; **ERY** = erythromycin; **FLU** = flurithromycin; **JOS** = josamycin; **MIO** = miokamycin; **MS** = methicillin sensitive; **MR** = methicillin resistant; **ND** = no data available; **PI** = penicillin intermediate (penicillin MIC 0.12-1 g/ml); **PR** = penicillin resistant (penicillin MIC ≥ 2.0 μg/ml); **PS** = penicillin sensitive MIC ≤0.06 μg/ml); **ROK** = rokitamycin; **ROX** = roxithromycin; **SPI** = spiramycin; **TEL** = telithromycin.

UK 13.6%, France 40.6%, Spain 19.1%, Germany 2.7%, Italy 24.1%, Hungary 13.4%, Czech Republic 0%, Slovak Republic 17.9%, South Africa 6%, Saudi Arabia 3.7%, Mexico 31.4%, Brazil 3.2% and the Far East (China, Hong Kong) 68.2%. Although the clinical significance of macrolide-resistant *S.pneumoniae* is presently unclear, it appears that *mef*A producing *S.pneumoniae* with MICs of 1 to 8 mg/L can be eradicated in an *in vitro* pharmacodynamic model which simulates clinically achievable serum macrolide concentrations.[109] The ketolides exhibit good activity against penicillin-susceptible and -resistant, and erythromycin-susceptible and -resistant strains with each agent exhibiting an MIC_{90} of 0.12 to 0.25 mg/L (table III). Both telithromycin and ABT-773 are active against *mef*A (MIC_{90} 0.25 mg/L and 0.12 mg/L, respectively) and *erm*B (MIC_{90} 0.25 mg/L and 0.12 mg/L, respectively).[72,73] Although these MIC values are a few dilutions higher than with susceptible strains, they are still significantly lower than the MICs for the other macrolides.[65,66,71-73] Both the macrolides and ketolides will inhibit *S. pyogenes*.

Based on MIC_{90} values, the order of activity of the macrolides and ketolides against *S. aureus* (methicillin sensitive) is HMR-3004 = ABT-773 > telithromycin > clarithromycin = flurithromycin = miokamycin = rokitamycin > azithromycin = erythromycin = dirithromycin = roxithromycin > erythromycylamine = josamycin = spiramycin. None of these agents is active against methicillin-resistant *S. aureus* (MRSA) [table III].[16] The macrolides are only weakly active against *Enterococcus faecalis* and are inactive against *Enterococcus faecium* (table III).[64] The ketolides are active against *E. faecalis* but demonstrate poor activity against *E. faecium*. The macrolides inhibit the growth of *Listeria monocytogenes* with the majority of MIC_{90} values falling at or below 2 mg/L, whereas the ketolides exhibit even greater activity with each agent displaying MIC_{90} values of 0.06 mg/L (table III).

Gram-negative aerobes such as *E. coli* display intrinsic resistance to the macrolides and ketolides and, therefore, the majority remain outside of at-

Landscape table IV to be placed here.

Table IV. *In vitro* activity of macrolides and ketolides against anaerobic bacteria as minimum inhibitory concentrations of 50% (50) and 90% (90) of isolates in mg/L (adapted from references: erythromycin and clarithromycin,[16,19,50,53,54,64,95,96] roxithromycin,[16,50,53-55,64,95-97] dirithromycin,[16,50,53,55,64] erythromycylamine,[50] azithromycin,[16,50,54,55,64,74,75,95,96] spiramycin,[50,53] josamycin,[50,53,64] flurithromycin, miokamycin, rokitamycin,[50] HMR 3004,[95,96] telithromycin,[95] ABT-773[98])

Macrolides																				Ketolides					
ERY		CLA		ROX		DIR		EMC		AZI		SPI		JOS		FLU		MIO		ROK		HMR-3004		TEL		ABT-773	
50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90
Bacteroides fragilis																											
2	8	2	8	16	32	128	>128	32	32	2	8	8	16	2	8	4	8	2	8	0.25	4	4-8	8	16	16	8	8
Bacteroides spp.																											
0.25	4	0.25	4	0.5	16	8	64	1	16	0.5	4	0.5	8	0.25	1-2	2	8	0.12	8	0.03	0.5	4	64	8	>64	4	>32
Clostridium difficile																											
1	>64	0.5	>64	1	>64	2	8	ND	ND	2	16	ND	ND	0.25	16	ND	ND	ND	ND	ND	ND	0.12	>64	0.25	>64	0.125	>32
Clostridium perfringens																											
1	1	0.5	0.5	2	2	4	4	1	1	0.25	0.25	2	2	1	1	2	2	0.5	0.5	0.12	0.12	0.03	0.06	0.12	0.12	≤0.06	≤0.06
Clostridium spp.																											
0.25	2	0.125	1	1	2	ND	ND	ND	ND	0.5	1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.016	0.03	0.03	0.06	1	>32
Fusobacterium spp.																											
≥64	>64	32	>64	≥64	>64	ND	ND	ND	ND	16	≥64	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	32	>64	16	>64	2	8

AZI = azithromycin; **CLA** = clarithromycin; **DIR** = dirithromycin; **EMC** = erythromycylamine, the active metabolite of dirithromycin; **ERY** = erythromycin; **FLU** = flurithromycin; **JOS** = josamycin; **MIO** = miokamycin; **ND** = no data available; **ROK** = rokitamycin; **ROX** = roxithromycin; **SPI** = spiramycin; **TEL** = telithromycin.

Landscape table V to be placed here.

tainable serum and tissue concentrations.[50] For clinically important organisms the MIC values are found in table III.[3,16,19,29,47-93,97,104] The development of new agents has been prompted because of the frequency of *H. influenzae* as a cause of respiratory tract infections and the inadequate activity of erythromycin against *H. influenzae*. Ranking the drugs by MIC_{90} values, the order of activity against *H. influenzae* (β lactamase negative) is azithromycin > HMR-3004 > telithromycin = ABT-773 = clarithromycin (with its 14-OH metabolite) > clarithromycin (without its metabolite) > erythromycin = roxithromycin > flurithromycin > dirithromycin = spiramycin = josamycin = rokitamycin > miokamycin. Activity against β lactamase positive *H. influenzae* is similar (table III). The majority of the agents exhibit MIC_{90} values of < 2 mg/L against *Moraxella catarrhalis*, *Neisseria gonorrhoeae* and *Neisseria meningitidis* (table III).

The activities of the macrolides and ketolides against anaerobic bacteria are presented in table IV.[16,19,50,53-55,64,76-91,100,101] The macrolides have poor activity against *Bacteroides fragilis*, however, they do possess weak activity against non-fragilis *Bacteroides* spp.[54] The ketolides exhibit poor activity against all *Bacteroides* spp. Activity of the macrolides and ketolides is poor against *Clostridium difficile*, while MIC_{90} values for other *Clostridium* species are generally below 2 mg/L (table IV). The macrolides and ketolides exhibit poor activity against *Fusobacterium* spp. and *Peptostreptococcus* spp. are variably inhibited by the macrolides but are consistently inhibited by the ketolides (table IV).

Intracellular bacteria such as *C. pneumoniae*, *L. pneumophila*, *M. pneumoniae* and *Ureaplasma urealyticum* are important respiratory pathogens and the macrolides and ketolides exhibit excellent activity against these organisms (table V).[3,16,19,20,50-53,59,76-91,94,97,102,104] In general, the ketolides are more active than the macrolides against these intracellular pathogens. The macrolides and ketolides all have MIC_{90} values ≤2 mg/L against *C. pneumoniae* and 0.1 mg/L against *M. pneumoniae*. With the exceptions of dirithromycin, erythro-

Table V. *In vitro* activity of macrolides and ketolides against clinically important intracellular bacteria as minimum inhibitory concentrations of 50 % (50) and 90% (90) of isolates in mg/L (adapted from references: erythromycin,[3,16,19,20,50-53,55,59,99,100] clarithromycin,[3,16,19,20,50-53,55,59,67,99,100] roxithromycin,[16,50-53,55,59,97,99-101] dirithromycin,[16,50,53,55,67] erythromycylamine,[50] azithromycin,[3,16,50-53,55,59,74,75,99,100] spiramycin,[50,53] josamycin,[50,53,59,100] flurithromycin, miokamycin, rokitamycin,[50] HMR 3004,[20,102] telithromycin,[20,99-101,103] ABT-773,[104,105])

Macrolides																					Ketolides					
ERY		CLA		ROX		DIR		EMC		AZI		SPI		JOS		FLU		MIO		ROK		HMR-3004		TEL		ABT-773	
50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90	50	90
Chlamydia pneumoniae																											
0.12	0.12	ND	0.03	0.25	0.5	ND	2	ND	ND	0.03	0.25	ND	ND	ND	0.25	ND	ND	ND	ND	ND	ND	ND	ND	0.06	0.25	0.015	0.015
Legionella pneumophila																											
1	2	0.12	0.25	0.25	0.5	4	16	4	8	0.5	2	16	64	0.5	1	1	2	0.12	0.12	0.25	0.25	0.008	0.03	0.015	0.06	0.015	0.06
Mycoplasma pneumoniae																											
ND	≤0.01	0.004	0.012	0.03	0.03	ND	0.1	ND	ND	ND	≤0.01	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	≤0.01	≤0.015	0.06	ND	ND
Ureaplasma urealyticum																											
1	4	0.5	1	1	4	ND	ND	ND	ND	1	2	ND	ND	32	>128	ND	ND	ND	ND	ND	ND	ND	0.02	0.25	2	ND	ND

AZI = azithromycin; **CLA** = clarithromycin; **DIR** = dirithromycin; **EMC** = erythromycylamine, the active metabolite of dirithromycin; **ERY** = erythromycin; **FLU** = flurithromycin; **JOS** = josamycin; **MIO** = miokamycin; **ND** = no data available; **ROK** = rokitamycin; **ROX** = roxithromycin; **SPI** = spiramycin; **TEL** = telithromycin.

mycylamine and spiramycin the MIC_{90} values against *L. pnuemophila* are less than or equal to 2 mg/L.

4. Pharmacokinetics

The pharmacokinetic attributes of a drug (e.g. absorption, distribution, metabolism and excretion) play a key role in determining its activity *in vivo*. The pharmacokinetic parameters of the macrolides and ketolides after a single oral dose are presented in table VI.[1,3,12-14,16,19,24,51-55,61,67,110-127]

4.1 Absorption

The macrolides are generally characterised by low to moderate (30 to 55%) oral bioavailability with the exception of roxithromycin (table VI) with enhanced bioavailability (72 to 80%). The erythromycin salts/esters have variable bioavailabilities depending on their formulation (45 to 80%). The effect of food on macrolide absorption varies by formulation, in that, the capsule and powdered suspension forms of azithromycin must be taken 1 hour before or 2 hours after meals to prevent a decrease in both the rate and extent of absorption, whereas the tablets may be taken without regard to meals.[13,116] Food may also hinder the absorption of erythromycin base and erythromycin stearate because of increased gastric acid concentrations which lead to increased drug degradation, whereas erythromycin ethylsuccinate is best taken just after a meal as food increases its absorption.[110]

The rate of macrolide absorption (t_{max}) is variable (table VI). Erythromycin ethylsuccinate, clarithromycin, roxithromycin, azithromycin, josamycin and flurithromycin reach peak serum concentrations (C_{max}) in 2 hours or less, while the remainder of the drugs take up to 4 hours to reach C_{max} (table VI). The C_{max} attained by macrolides are also variable ranging from as low as 0.3 mg/L for erythromycin base, dirithromycin and erythromycylamine to as high as 11 or 12 mg/L for higher doses of roxithromycin. These C_{max} values differ with changes in dose (table VI). The effect on absorption of replacing the L-cladinose sugar with a 3-keto group has not been studied in humans.

4.2 Distribution

The macrolides are lipophilic in nature and have a low degree of ionisation.[54] This allows extensive penetration into tissues and fluids and results in a large volume of distribution.[16,112,116,128] Concentrations of macrolides and ketolides in respiratory tract tissues and fluids are, in most cases, higher than concurrent serum concentrations as shown in table VII.[51,52,54,61,112,124,128-164] This extensive distribution into respiratory tissues and fluids makes predictions of pharmacodynamic activity difficult as serum concentrations frequently used as predictors do not necessarily provide a good indication of macrolide activity.[12] Telithromycin appears to have a pharmacokinetic profile similar to that of the dibasic macrolides (e.g. azithromycin, dirithromycin and erythromycylamine), while HMR-3004 is more like monobasic macrolides (e.g. erythromycin, clarithromycin).[134,139,155,158] The volume of distribution for ABT-773 is 1.5 to 9.2 L/kg (depending on the animal species) and lung concentrations exceed plasma concentration by >25-fold.[159]

Unlike β-lactams and aminoglycosides, macrolides and ketolides enter host defence cells, particularly macrophages and polymorphonuclear leucocytes (PMNs) [table VII].[160] The exact mechanism of entry of macrolides and ketolides into phagocytes has not been elucidated, however, it has been proposed that either liposolubility or a carrier-mediated transport mechanism may be involved.[157,161] The presence of calcium is necessary for proper functioning of both the uptake of macrolides and the Na^+/Ca^{2+} exchanger, making carrier-mediated transport the more likely mechanism.[155,157] Intracellular concentrations achieved vary among the macrolides with the dibasic macrolides (azithromycin, dirithromycin and erythromycylamine) exhibiting the highest intracellular concentrations.[161,162] Greater ionisation of these agents may lead to trapping of the protonated drugs within the neutrophil granules.[162] This accumula-

Table VI. Pharmacokinetic parameters of macrolides and ketolides (adapted from references: erythromycin,[1,3,12,13,16,24,53,54,110-114] clarithromycin/14-OH clarithromycin,[3,12-14,16,19,52-54,60,67,110,111,115,116] roxithromycin,[12,14,16,110,112-114,117,118] dirithromycin,[12,14,53,67,112,113] erythromycylamine,[67,113] azithromycin,[3,12-14,16,51,53-55,110,111,115,116,119-123] spiramycin,[12,53,110,124,125] josamycin,[53,110,112,124,126] flurithromycin and rokitamycin,[14] telithromycin[127])

Agent	Dosage (mg)	% F	C_{max} (mg/L)	t_{max} (h)	AUC (mg/L • h)	$t_{1/2}$ (h)	Vd/F (L/kg)	Protein binding (%)	Urinary excretion (%)	Dose adjustment		Effects of food on absorption
										renal	hepatic	
Erythromycin base	500	25	0.3-0.9	3-4	8	2-3	0.6	74-90	2.5	No	No	↓
Erythromycin ethylsuccinate	500	50-60	1.5	2	12-18	2-3	0.6	74-90	2.5	No	No	↑
Erythromycin estolate	500	70-80	4.2	2-4	22-30	2-3	0.6	74-90	2.5	No	No	↔
Erythromycin stearate	500	45-60	0.4-1.8	3	12-18	2-3	0.6	74-90	2.5	No	No	↓
Azithromycin	500	37	0.4	2	3.4	40-68	31	7-50	6	No	No	↔/↓
Clarithromycin[a]	250	55	0.6-1.0	2	4-6	3-5	3-5	65-75	20-40	Yes	No[b]	↔
	500	55	2.1-2.4	2	19	3-5	3-5	65-75	20-40	Yes	No[b]	↔
	1200	55	4.7	2	54	3-5	3-5	65-75	20-40	Yes	No[b]	↔
14-OH Clarithromycin	250	NA	0.4	2-3	3	4-7	ND	ND	ND	Yes	No	NA
	500	NA	0.6	2-3	5.7	4-7	ND	ND	ND	Yes	No	NA
	1200	NA	1.4	2-3	25	4-7	ND	ND	ND	Yes	No	N/A
Dirithromycin	500	10	0.3	4	3.5	20-50	11-100	15-30[c]	ND	No	No	↑
Erythromycylamine	NA	NA	0.3	2.8	2.4	20-40	ND	15-30	ND	No	No	NA
Flurithromycin	500	ND	1.2-2.0	1-2	16	8	ND	ND	ND	ND	ND	ND
Josamycin	1000	ND	3.8	0.7	7.9	1.2	ND	15	<20	ND	ND	↔
Rokitamycin	300	ND	0.5	ND	0.9	ND	ND	ND	ND	ND	ND	ND
Roxithromycin	150	72-85	5-7	1.5	70	11[d]	ND	73-96[c]	7-10	No	Yes	↔
	300	72-85	9-11	1.5	115	11[d]	ND	73-96[c]	7-10	No	Yes	↔
	450	72-85	11-12	1.5	150	11[d]	ND	73-96[c]	7-10	No	Yes	↔
Spiramycin	1000	30-40	1	3	ND	6	ND	ND	5-15	ND	ND	↔
	2000	30-40	3	3	8.5	6	ND	ND	5-15	ND	ND	↔
Telithromycin	800	ND	2.0	1.0	7.9	13	ND	ND	12	ND	ND	↔

a Approximately 25% of an absorbed dose of clarithromycin is metabolised by cytochrome P450 to the active 14-OH clarithromycin.[80]

b Metabolism of clarithromycin to its 14-OH metabolite may be decreased in liver dysfunction which may lead to a decrease in coverage of *H. influenzae*.[80]

c Protein binding decreases with an increase in dose suggesting that binding may be saturable.[71] 60 to 90% of the absorbed dose of dirithromycin is converted to erythromycylamine within 35 minutes.[80]

d Half-life may increase with an increase in dose.[16]

AUC = area under the plasma/serum concentration time curve; **C_{max}** = maximum plasma/serum concentration; **F** = bioavailability; **NA** = not applicable; **ND** = no data available; **t_{max}** = time to C_{max}; **$t_{1/2}$** = half-life; **Vd** = volume of distribution; ↔ indicates food has no effect on absorption; ↓ indicates decreased absorption with food; ↑ indicates increased absorption with food.

tion also leads to a slowed efflux of these agents from drug-loaded neutrophils.[9] Telithromycin exhibits rapid penetration and intracellular concentrations higher than those observed with the macrolides (table VIII). These concentrations are reported to be well sustained.[134]

Intracellular concentrations are important in the defence against respiratory pathogens including *L. pneumophila*, *C. pneumoniae*, *M. pneumoniae* and *U. urealyticum*.[157,160] However, the role of high macrolide/ketolide intracellular concentrations is unclear in the treatment of extracellular respiratory pathogens (e.g. *S. pneumoniae*). Table VII displays the intracellular to extracellular concentrations of the macrolides.[9,24,51,113,123,125,128,129,153,155,156,160,163,164] However, penetration and high intracellular concentrations alone may not guarantee antimicrobial action. Many factors play a role in determining the efficacy of an agent including the mechanism of action of the drug, the effects of the subcellular environment on the drug, the effects of the drug on phagocytic functioning, and drug penetration in the pathogen.[160] The location of the drug in relation to the location of the pathogen in the subcellular environment is also an important factor.[157,160] The majority of the macrolides concentrate in the lysosomes (table VII). This is thought to occur as a result of trapping caused by the lower pH (4 to 5) found in the lysosomes compared with the cytoplasm (pH 7).[160,161] The dibasic macrolides display the highest concentrations in the lysosomes as the presence of two basic amine groups leads to greater ionisation and a subsequent increased ion trapping.[129] These agents also display a much slower efflux from phagocytes.[164]

Many pathogens concentrate inside phagosomes (including *Chlamydia* spp., *Legionella* spp., and *Enterococcus* spp.), whereas others exist in the cytoplasm (including *Listeria* spp. and *Rikettsia* spp.). *Mycoplasma* spp. are located both in the phagosomes and the cytoplasm.[161] The macrolides are able to exert their effects as lysosome fusion with the phagosomes is an essential event in the phagocytic killing process and thus, high concen-

Landscape table VII to be placed here.

Table VII. Penetration of macrolides and ketolides into selected fluids and tissues of the respiratory tract. No data were available for various macrolides and the ketolides. PMN levels (intracellular:extracellular) of 13-20, 13, 25-31, and 200-461 were reported for josamycin, spiramycin, rokitamycin, and HMR-3004, respectively.[9,125,128,129] Macrophage levels (intracellular:extracellular) for josamycin, spiramycin, and rokitamycin are 20, 21-24, and 120, respectively.[125,128,129] HMR-3004 is primarily located in the granules intracellularly.[9]

Site	Tissue/serum or fluid/serum ratio					
	eythromycin (sampling time unknown)[a]	azithromycin (sampling time = 12 to 96 hours post dose)	clarithromycin/14-OH clarithromycin (sampling time = 6 to 24 hours post dose)	dirithromycin (sampling time = 1 to 24 hours post dose)	roxithromycin (sampling time = 4 to 24 hours post dose)	telithromycin (sampling time = 24 hours)
Bronchial mucosa	1.7[130,131]b	29[131]	27.5/16[52,132]b	13[131]	0.5[133]b	48[134]
Bronchial secretions	0.5[112,135]b	ND	3.1/2.5[133,132]b	1.8[112,136]	1.0[137,138]b	ND
Epithelial lining fluid	ND	60[139,140]b	39.6/0[52,141]	ND	0.2[142]b	14.3[134]
Lung tissue	5.5[112,143]b	10-20[131,144]	8.8/9.0[131,133]b	40[112,131]b	0.5[133]b	ND
Sputum	ND	67[54,139,144]b	1.1/1.1[52,145]	ND	1.6[137]b	ND
Middle ear fluid	0.5[146]b	355[147]	8.8/3.8[52,148]b	ND	ND	ND
Tonsils	2.5[149]b	≥150[51]	33.1/10.6[132]	12[112]	1.4[150]b	ND
Sinus fluid	ND	ND	1.5/ND[151]	ND	ND	ND
Alveolar macrophages	29[51]	170[51,54]	471/75[141]	ND	ND	535[134]
PMNs	7-13[51,136,152-154]	79[51,54,153]	16.4[154]	ND	23.7[152,154]	31-348[155,156]
Intracellular location of the drug	Cytoplasm and lysosomes	Lysosomes	Lysosomes	Granules and cytosol[c]	Granules and cytosol	Granules

a Erythromycin sampling time unknown as all samples were taken after multiple doses while telithromycin sampling times are not relevant to the data presented.
b Multiple doses of the macrolide were administered to patients before sample was taken. All other data were collected after a single administration of the study drug.
c Erythromycylamine, the active metabolite of dirithromycin, accumulates in the granules less than dirithromycin.[157]
ND = no data available; **PMN** = polymorphonuclear leukocyte.

Table VIII. Results of clinical trials involving erythromycin (E)

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Community-acquired pneumonia (CAP)							
Bohte et al.[165]	Prospective, randomised, nonblind, comparative	Adults ≥18 to 75 years of age with CAP were divided into 2 groups: a) pneumococcal pneumonia; or b) non-pneumococcal pneumonia	108 (104)	a) A 500mg bid then 500mg od	Day 1 days 2-5	29/35 (83%)	ND
				BPen 1x10^{6}IU qid IV until afebrile for 5 days	Variable	19/29 (66%)	ND
				b) A 500mg bid then 500mg od	Day 1 days 2-5	15/19 (79%)	ND
				E 500mg qid	10 days	15/21 (71%)	ND
Lode et al.[166]	Prospective, randomised, double-blind, double-dummy, parallel-group, multicentre	CAP in adults aged ≥18 years	808 (644)	E 1000mg bid	7-14 days	135/158 (85%)	SP 38/45 (84%) HI 13/14 (93%)
				Spar 400mg loading dose then 200mg od	7-14 days	269/310 (87%)	SP 61/72 (85%) HI 26/27 (96%)
				A/C 500/125mg tid	7-14 days	121/152 (80%)	SP 20/25 (80%) HI 19/21 (90%)
Liippo et al.[167]	Prospective, randomised, double-blind, multicentre	Bacterial CAP in adults aged 16-75 years	591 (241)	E 250mg qid	10-14 days	92%	90%
				D 500mg od	10-14 days	95%	93%
Hernández et al.[168]	A retrospective review of 2 prospective, randomised, double-masked, multicentre trials	CAP and bacteraemic pneumonia in adults aged 16-69 years	CAP: 1108 (1108) BP: 24 (22)	E 250mg qid	10-14 days	CAP 487/553 (88%) BP 8/9 (89%)	152/171 (89%)
				D 500mg od	10-14 days	CAP 482/555 (87%) BP 12/13 (92%)	161/185 (87%)
Jang et al.[169]	Prospective, randomised	CAP in adults aged 16-81 years	40 (40)	E 500mg qid	14 days	18/20 (90%)	ND
				C 250mg bid	14 days	19/20 (95%)	ND
Block et al.[170]	Prospective, randomised, single-(investigator) blind, multicentre	CAP in children aged 3-12 years	260 (234)	E 40 mg/kg/day (max 1600mg) divided bid-tid	10 days	105/110 (95%)	16/18 (89%)
				C 15 mg/kg/day (max 1000mg) divided bid	10 days	121/124 (98%)	24/27 (89%)
Acute exacerbations of chronic bronchitis (AECB)							
Wasilewski et al.[171]	2 identically designed, prospective, well-controlled, randomised, double-blind trials	AECB in adults aged ≥12 years weighing ≥37kg	1057 (690)	E 250mg qid	7 days	270/336 (80%)	178/228 (78%)
				D 500mg od	5 days	298/354 (84%)	170/216 (79%)

Table VIII. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Kawahara et al.[172]	Prospective, randomised, multicentre, crossover	Acute exacerbations of chronic respiratory tract infections in adults aged 44-91 years	77 (64)	Group I: 300mg Oflox tid then 600mg E tid Group II: 600mg E tid then 300mg Oflox tid	24 weeks (12 per drug) 24 weeks (12 per drug)	50/64 (78%) experienced no acute exacerbations with oflox while the same was true for 44/64 (69%) of E recipients	ND ND
Otitis media							
Scholtz et al.[122]	Prospective, randomised, double-blind, multicentre	AOM in children aged 6 months to 11 years	302 (280)	E 40 mg/kg/day divided bid Amox 50 mg/kg/day divided bid	10 days 10 days	132/141 (94%) 133/139 (96%)	ND ND
Streptococcal pharyngitis							
Peterson et al.[173]	Prospective, randomised, double-blind, placebo-controlled	Streptococcal pharyngitis not caused by GABHS in adults aged 18-50 years	215 (186)	E 333mg tid Placebo 333mg tid	10 days 10 days	75 % at day 6 65% at day 6	ND ND
McCarty[174]	Prospective, randomised, nonblind, comparative, multicentre	Mild to moderate GABHS tonsillitis and pharyngitis in patients aged ≥2 years	256 (203)	E 30 mg/kg/day (max 1600mg) divided qid Cefpro 20 mg/kg/day (max 500mg) od	10 days 10 days	91% 95%	84-91% 84-91%
Adam et al.[175]	Prospective, randomised, multicentre	GABHS tonsillopharyngitis in children aged 3 to 17 years	227 (201)	E 40 mg/kg/day divided bid Pen V 30 mg/kg/day divided tid	5 days 10 days	100/102 (98%) 97/99 (98%)	85/102 (83%) 87/99 (88%)
Esposito et al.[176]	Prospective, randomised	GABHS pharyngitis in children aged 2-12 years	245 (217)	E 15 mg/kg tid Cef 25 mg/kg bid A/C 15 mg/kg tid	10 days 10 days 10 days	53/69 (77%) 68/74 (92%) 67/74 (91%)	49/53 (92%) 63/68 (93%) 64/67 (96%)
Lower respiratory tract infections (LRTIs)							
Roord et al.[177]	Prospective, randomised, nonblind, multicentre	Community-acquired LRTIs (pneumonia or bronchitis) in children aged 2-16 years	89 (85)	E 40 mg/kg/day divided tid A 10 mg/kg/day od	10 days 3 days	36/40 (90%) 42/45 (93%)	ND ND

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

A = azithromycin; **AB** = acute bronchitis; **A/C** = amoxcillin/clavulanic acid; **AMOX** = amoxicillin; **AOM** = acute otitis media; **AS** = acute sinusitis; **bid** = twice a day; **BPen** = benzyl penicillin; **C** = clarithromycin; **Cef** = cefaclor; **Cefpro** = cefprozil; **D** = dirithromycin; **GABHS** = group A β-haemolytic streptococcus; **HI** = *Haemophilus influenzae*; **IV** = intravenous; **ND** = no data available; **od** = once daily; **oflox** = ofloxacin; **Pen** = penicillin; **qid** = 4 times daily; **R** = roxithromycin; **SP** = *Streptococcus pneumoniae*; **Spar** = sparfloxacin; **tid** = 3 times a day.

trations of the agents are deposited in the compartment where the pathogens reside.[160,161]

Telithromycin exhibited high intracellular concentrations, with intracellular to extracellular ratios (I : E) as high as 348 : 1 in PMNs, 535 : 1 in alveolar macrophages, and 6 : 1 in fibroblasts (table VII).[134,155,156] The accumulation within the PMNs is gradual and without saturation, whereas accumulation within alveolar macrophages is rapid and sustained.[134,155,178] HMR-3004 exhibits rapid, saturable accumulation with I : Es of up to 461 : 1 in PMNs.[9,155] Accumulation of both agents appears to be caused by a transport system similar to that of the macrolides, and both agents accumulate in the granules.[155,178]

The PMNs are believed to act as carriers in the transport of azithromycin to the site of infection through chemotaxis.[4,129,153] The release of this agent from the PMNs is enhanced by exposure to pathogens. For example, azithromycin release from loaded phagocytes under normal (pathogen free) conditions is approximately 23% within 1.5 hours, whereas 82% of the drug is released in this same time period in the presence of *S. aureus*.[153] Fibroblasts also uptake azithromycin but are thought to be drug reservoirs for the PMNs as they do not exhibit 'dumping' in the presence of pathogens but rather slowly release drug to the PMNs for activity against intracellular organisms and transport to infected areas.[129,153]

The slow efflux of telithromycin from PMNs and relatively high concentrations in fibroblasts suggest that this agent may also be transported to the site of infection by phagocytes.[156] Gia et al.[179] obtained telithromycin concentrations 44 times higher in white blood cells than in plasma 1 hour after administration, with concentrations still quantifiable after 48 hours. This also suggests a transport system for the drug to the site of infection.[179] HMR-3004 exhibits moderate efflux similar to that of the monobasic macrolides making this mechanism less likely.[155]

4.3 Metabolism and Excretion

With the exception of the dibasic macrolides (dirithromycin and erythromycylamine), the 14C member macrolides display an affinity for cytochrome P450 (CYP).[67,110] These agents are associated with potential drug interactions as their interactions with CYP interfere with the metabolism of a number of drugs. The 15 member macrolide azithromycin and the 16 member macrolides spiramycin and josamycin do not share this affinity for CYP.[110]

The newer macrolides, with the exception of josamycin, exhibit increased half-lives when compared with erythromycin (table VI). This allows less frequent administration of these agents.[2] The half-lives of clarithromycin and roxithromycin may vary with changes in dose (table VI). Telithromycin exhibits a biphasic half-life (table VI).[127] The half-lives of HMR-3004 and ABT-773 in humans are presently unknown.

Macrolide excretion is primarily accomplished through the bile.[53] Renal excretion of macrolides is relatively limited with clarithromycin being the only macrolide to exhibit any significant urinary concentrations (table VI).[67,110,116] Dosage adjustments are required in patients with hepatic dysfunction with roxithromycin, whereas clarithromycin requires a decreased dose in patients with renal impairment (table VI).[52,67,118] The remainder of the macrolides do not require dosage adjustments in patients with hepatic or renal dysfunction, however, care should be used in their administration especially in severe hepatic or renal dysfunction. Only small amounts of telithromycin are excreted in the urine (table VI).[127] Excretion data for HMR-3004 and ABT-773 in humans are not available.

5. Pharmacodynamics

Antibacterial activity requires that the antibacterial agent bind to or interact with a specific target(s) in the pathogen which, in the case of the macrolides, are located on the ribosomes.[116] The bound drug must also occupy a critical number of

binding sites and, in most cases, the antibacterial activity associated with this binding can be estimated by measuring the serum concentrations of the agent.[116] Finally, the agent must remain at the binding site(s) for long enough to exert its effect.[116] The relationship between drug concentration and antibacterial effect describes the pharmacodynamic characteristics of a drug, therefore parameters such as C_{max} and the area under the serum concentration-time curve (AUC) relative to the MIC (AUC/MIC) or time above the MIC (T/MIC) may serve as ways to predict antibacterial activity.[116,180]

Antibacterial activity may be either concentration-dependent or concentration-independent (time-dependent).[116,180] Bacterial killing by concentration-dependent drugs (e.g. aminoglycosides, fluoroquinolones) is exerted by high concentrations of a drug at the site of infection. A good predictor of bacterial eradication is the ratio of C_{max} to the MIC (C_{max} : MIC). Under conditions in which a C_{max} : MIC ratio of at least 10 : 1 is achieved, concentration-dependent agents achieve excellent levels of bacterial death, clinical cure and prevent the development of bacterial resistance.[181-186] Bacterial death, clinical cure and prevention of resistance development for concentration-dependent agents are also highly correlated with AUC : MIC.[185,186] Antibacterial agents whose activity is concentration-independent require drug concentrations above the MIC for extended periods of time (T/MIC) in order to exert their effects.[116] These agents reach their peak bacteriocidal rates at relatively low serum concentrations and, therefore, length of exposure rather than C_{max} becomes important.[16,180] These agents exhibit maximum efficacy when serum concentrations are kept above the MIC for at least 40 to 50% of the administration interval.[116,180] The penicillins and cephalosporins are examples of concentration-independent agents.[180]

The classification of macrolides as concentration-dependent or concentration-independent is difficult. The majority of data regarding macrolides suggests that they exhibit concentration-independent characteristics.[12,116,180] For example, maintenance of azithromycin and clarithromycin concentrations above the MIC for *S. pneumoniae* inhibited growth of the pathogen.[116] However, a time-dependent model does not appear to describe the effects of these agents against *H. influenzae*.[116] Azithromycin and clarithromycin serum concentrations do not reach the MIC for this pathogen, however, they effectively inhibit its growth.[116] This may be because of the high concentrations of these agents which are achieved in tissues and fluids which exceed the MIC.[117] This example reinforces the fact that because of their unique pharmacokinetics, serum concentrations are not a good predictor of macrolide activity.[116]

The macrolides exhibit antibacterial activity which persists after exposure.[180] The post-antibiotic effect (PAE) of an agent is used to describe this type of persistent antibacterial activity and becomes important when the concentration of drug declines below the MIC.[54,180] Varying PAEs are exhibited by the macrolides depending on the pathogen, drug concentration, duration of exposure, pH, etc.[187] PAEs tend to be longer against Gram-positive cocci compared with Gram-negatives, and streptococci compared with staphylococci.[12] Theoretically, agents with prolonged PAEs could be administered intermittently, whereas agents with shorter PAE would benefit from a more frequent or continuous administration regimen.[12]

Other factors such as subinhibitory drug concentrations (sub-MICs), post-antibiotic sub-MIC effects (PA SMEs) as well as host defences, are important in the success of an administration schedule.[188] PA SMEs show that the effects of giving subinhibitory drug concentrations following suprainhibitory macrolide concentrations provide long (6.4 to 19.6 hours) and varied coverage.[188] This bacterial growth suppression between doses allows long administration intervals for the macrolides.[188]

Ketolides are slowly bactericidal (over 24 hours) against *S. pneumoniae, H. influenzae* and *M. catarrhalis*.[189-192] In addition, these agents demonstrate prolonged PAE (>4h) and PA SME (>6h) against respiratory pathogens.[190,191]

6. Clinical Trials

Clinical trials involving macrolides in the treatment of respiratory infections are summarised in tables VIII to XIII.[164-176,192-250] This review includes clinical trials focussing on community-acquired pneumonia (CAP), otitis media, acute exacerbations of chronic bronchitis (AECB), sinusitis and streptococcal pharyngitis. All available studies in this review were obtained by searching MEDLINE for English language trials published between the years 1994 and the first quarter of 1999. Abstracts were not included and restrictions were not placed on the design, sample size, etc., of the studies used. Clinical trials could not be identified for josamycin, spiramycin, miokamycin, rokitamycin or the ketolides. Variables that must be considered when choosing an antibacterial agent for the treatment of respiratory tract infections include the severity of the illness, the presence or absence of comorbid illnesses, the age of the patient and the setting in which treatment is to be administered (e.g., hospital, community, nursing home).[246]

6.1 Community-Acquired Pneumonia (CAP)

6.1.1 Erythromycin

Several studies have been conducted using erythromycin in the treatment of adults with CAP (table VIII).[165-169,177] Bohte et al.[165] showed that erythromycin and azithromycin were equally effective in the treatment of patients with non-pneumococcal pneumonia. Clinical and radiological success rates were 71 and 76% for erythromycin and azithromycin achieved 79% success in both categories.[165] A similar trial in patients with community-acquired lower respiratory tract infections yielded much higher results with clinical response in 90 and 93% of erythromycin and azithromycin recipients, respectively.[177] Although significant differences in efficacy were not reported between the 2 agents in either study (p-values not reported), azithromycin has the advantage of increased compliance because it requires less frequent administration and a shorter duration of therapy.[165,177]

Erythromycin was compared with sparfloxacin and amoxicillin/clavulanic acid in a double-blind study conducted by Lode et al.[166] In this study, erythromycin was given as 1g twice a day for 1 to 2 weeks, with a success rate of 85%. Sparfloxacin and amoxicillin/clavulanic acid had overall success rates of 87 and 80%, respectively, where success was defined as cure or improvement on chest radiography and clinical end-points. *S. pneumoniae*, *H. influenzae* and *M. pneumoniae* were the most commonly isolated organisms, with 4% of *S. pneumoniae* showing resistance to erythromycin. Bacterial eradication rates were statistically similar with all 3 agents.[166]

Liippo et al.[167] conducted a double-blind study comparing erythromycin with dirithromycin in the treatment of bacterial pneumonia. Similar clinical and bacteriological response rates were seen with values of 92 and 90% in the erythromycin group, and 95 and 93% in the dirithromycin group, respectively. Similarly, Hernández et al.[168] reported clinical response rates of 88 and 87% post-therapy and 96 and 97% late post-therapy (1 to 2 weeks after completion of therapy) with erythromycin and dirithromycin, respectively. Dirithromycin was considered the preferred treatment in both of these studies because its less frequent administration is likely to improve compliance.[167,168] A similar result was found in a study conducted by Jang et al.[169] comparing erythromycin with clarithromycin. The authors suggest that although the two agents show similar rates of clinical response (90 and 95%, respectively), clarithromycin is preferred because of less frequent administration and improved tolerance.[169]

Block et al.[170] compared erythromycin with clarithromycin for the treatment of CAP in children. Clinical success was defined as resolution or improvement of signs and symptoms and was seen in 95 and 98% of patients receiving erythromycin and clarithromycin, respectively (table VIII). Focus was placed on infections caused by *C. pneumoniae* (found in 28% of patients) and *M. pneumoniae* (27%). Erythromycin eradicated *C. pneumoniae* in 86% of patients compared with 79% by clarithromycin, whereas both agents eradicated 100% of infections caused by *M. pneumoniae*. Although

the study was conducted on children aged 3 through 12 years, the study concludes that macrolides may be the antibacterial agent of choice in children aged 3 through 8 years with uncomplicated pneumonia as these agents are effective in eradicating the atypical infections which cause nearly half of all treated cases.[170]

6.1.2 Azithromycin

Azithromycin was evaluated as a treatment option for adults with CAP in several studies (table IX).[165,177,193-195,198,199,220,221] A study conducted by Schönwald et al.[193] compared the efficacy of azithromycin with that of roxithromycin in the treatment of atypical pneumonia. Clinical cure was defined as the disappearance of signs and symptoms of the disease with regression of infiltrate on chest radiograph.[193] Azithromycin and roxithromycin had clinical cure rates of 99 and 94%, respectively. Bohte et al.[165] conducted a 2-part study comparing the effectiveness of azithromycin and benzylpenicillin in pneumococcal pneumonia, and azithromycin and erythromycin in non-pneumococcal pneumonia. In the pneumococcal group the reported clinical and radiological success rates were 83% for azithromycin and 66% for benzylpenicillin (p-values not reported). Comparisons between azithromycin and erythromycin in treating non-pneumococcal pneumonia were previously discussed in the erythromycin section (6.1.1). Both parts of the trial conclude that azithromycin may be used as first-line therapy in CAP.[165] Azithromycin was also deemed to be of equal efficacy to erythromycin in a study by Roord et al.[177] which is summarised in section 6.1.1. Rizzato et al.[194] reported favourable response rates when comparing azithromycin with clarithromycin in a study described in section 6.1.3.

Three studies have been conducted in order to determine the efficacy of azithromycin in the treatment of lower respiratory tract infections (LRTIs).[220-222] The study by Laurent[220] comparing azithromycin with roxithromycin found clinical response rates of 90 and 78% in the treatment of CAP, respectively (see table XIII). Trials by Zachariah and Gris[221,222] both report 100% effectiveness for azithromycin and amoxicillin/clavulanic acid. However, the sample size was very small.

Three studies involving azithromycin[195-197] focus on CAP in children. Roblin et al.[195] conducted a 2-part study of CAP caused by *C. pneumoniae*. The first part of the study is a non-comparative description of azithromycin bacterial eradication rates. Eradication was achieved in 70% of patients. The second part of the study compared 5 days of azithromycin therapy with a 10 day treatment of amoxicillin/clavulanic acid in children under 5 years, and erythromycin in those over 5 years of age. *C. pneumoniae* was eradicated in 83% of azithromycin treated patients, while the other 2 treatment groups each reported 100% success rates, however group sizes (4 of 4, 7 of 7) were too small to draw definite conclusions.[195] Similar studies were performed by Harris et al.[196] and Wubbel et al.[197] in order to determine the efficacy of azithromycin compared with amoxicillin/clavulanic acid (in children ≤5 years of age) and erythromycin (in children >5 years of age).[196,197] Favourable clinical response rates of 95, 94 and 99% were noted with azithromycin, amoxicillin/clavulanic acid, and erythromycin, respectively, by Harris et al.,[196] while Wubbel et al.[197] reported values of 99, 96 and 97%, respectively. The study by Harris et al.[196] describes microbiological eradication of *C. pneumoniae* in 81% of azithromycin-treated patients compared with 100% for the comparator group (amoxicillin/clavulanic acid and erythromycin), while *M. pneumoniae* eradication was 100% with azithromycin and 57% with the comparative agents. The study by Wubbel et al.[197] suggests that the choice of antibacterial be based on clinical judgement, whereas Harris et al.[196] conclude that azithromycin is advantageous in treatment of paediatric pneumonia because it can be administered once daily as a short course of therapy and has coverage of atypical pathogens which cause a large percentage of CAP.[196,197]

Treatment of CAP caused by *L. pneumophila* is the focus of a non-comparative, retrospective study conducted by Kuzman et al.[198] All patients were successfully cured (resolution of fever and

Table IX. Results of clinical trials involving azithromycin (A)

Study	Design	Indication and study population	n[a]	Regimen	Duration	Clinical response (cured and improved)	Bacterial eradication
Community-acquired pneumonia (CAP)							
Schönwald et al.[193]	Prospective, randomised, nonblind, multicentre	Atypical pneumonia (*Mycoplasma pneumoniae*, *Chlamydia* spp., and *Coxiella burnetti*) in adults aged 14 to 69 years	150 (142)	A 500 mg od R 150 mg bid	3 days 10 days	88/89 (99%) 50/53 (94%)	ND ND
Bohte et al.[165]	Prospective, randomised, nonblind, comparative	Adults aged ≥18 to 75 years with CAP were divided into 2 groups: a) pneumococcal pneumonia; or b) non-pneumococcal pneumonia	108 (104)	a) A 500mg bid then 500mg od BPen 1×10^6 IU qid IV until afebrile for 5 days b) A 500mg bid then 500mg od E 500mg qid	Day 1 days 2-5 Variable Day 1 days 2-5 10 days	29/35 (83%) 19/29 (66%) 15/19 (79%) 15/21 (71%)	ND ND ND ND
Rizzato et al.[194]	Prospective, randomised, nonblind, comparative	Low to moderate CAP in patients aged >75 years	40 (39)	A 500mg C 250mg bid	3 days 10 ± 2 days	20/20 (100%) 17/19 (89%)	ND
Roblin & Hammerschlag[195]	Nonblind, non-comparative, multicentre	CAP caused by *Chlamydia pneumoniae* in patients aged ≥12 years	48 (10) 456 (34)	A 1.5g divided over 5 days A 10 mg/kg od then 5 mg/kg od	5 days Day 1 days 2-5	ND ND	7/10 (70%) 19/23 (83%)
	Randomised, comparative, multicentre	CAP caused by *C. pneumoniae* in children aged 6 months to 16 years		A/C (if <5y) 40 mg/kg/day divided tid E (if >5y) 40 mg/kg/day divided tid	10 days 10 days	ND ND	4/4 (100%) 7/7 (100%)
Harris et al.[196]	Prospective, randomised, double-blind, double-dummy, parallel group, multicentre	CAP in children aged 6 months to 16 years	456 (420)	A 10 mg/kg od then 5 mg/kg od A/C (if ≤5 years) 40 mg/kg/day divided tid E (if > 5 years) 40 mg/kg/day divided tid	Day 1 days 2-5 10 days 10 days	262/277 (95%) 59/63 (94%) 66/67 (99%)	CP 17/21 (81%) MP 14/14 (100%) SP 2/3 (67%) CP 10/10 (100%) MP 4/7 (57%) SP 1/1 (100%) ND
Wubbel et al.[197]	Prospective, randomised, unblinded	CAP in children aged 6 months to 16 years	174 (168)	A 10 mg/kg od then 5 mg/kg od A/C (if <5 years) 40 mg/kg/day divided tid E (if ≥5 years) 40 mg/kg/day divided tid	Day 1 days 2-5 10 days 10 days	68/69 (99%) 47/49 (96%) 28/29 (97%)	ND ND ND

Table IX. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration	Clinical response (cured and improved)	Bacterial eradication
Kuzman et al.[198]	Retrospective, non-comparative	CAP caused by *Legionella pneumophila*	16 (16)	1500mg divided: a) 500mg od × 3 days or b) 500mg od then 250mg od × 4 days	3 days Day 1 days 2-5	16 (16)	ND
Socan[199]	Retrospective	Atypical pneumonia in adults aged >15 years	81	A 500mg od then 250mg od A 500mg od	Day 1 days 2-5 3 days	32/40 (80%) 36/41 (88%)	ND
Acute exacerbations of chronic bronchitis (AECB)							
Biebuyck et al.[200]	Prospective, randomised, nonblind, multicentre	Acute tracheobronchitis and infectious AECB in adults aged 18 to 75 years	759 (728)	A 500mg od A/C 625mg tid	3 days 5 to 10 days	446/497 (90%) 206/257 (80%)	ND ND
Beghi et al.[201]	Prospective, randomised, nonblind	Purulent AECB in patients aged ≥18 years	142 (142)	A 500mg od A/C 875/125mg bid	3 days 5-11 days	46/69 (68%) 71/73 (97%)	45/67 (67%) 70/71 (99%)
Otitis media							
Khurana[202]	Randomised, nonblind, multicentre	AOM in children aged 6 months to 12 years weighing at least 10 lbs and attending daycare or school	526 (444)	A 10 mg/kg od then 5 mg/kg od A/C 40 mg/kg/day divided tid	Day 1 days 2-5 10 days	215/233 (92%) 207/230 (90%)	ND ND
Aronovitz[203]	Prospective, randomised, nonblind, multicentre	AOM in children aged 2 to 15 years and weighing >10kg	169 (92)	A 10 mg/kg od then 5 mg/kg od A/C ≈40 mg/kg/day divided tid	Day 1 days 2-5 10 days	43/49 (88%) 43/43 (100%)	43/49 (88%) 43/43 (100%)
McCarty[204]	Nonblind, non-comparative, multicentre	AOM in children aged 2-15 years and weighing at least 10kg	201 (131)	A 10 mg/kg od then 5 mg/kg od	Day 1 days 2-5	84%	SP 86% HI 79% MP 82%
McLinn[205]	Prospective, randomised, double-blind, double-dummy, multicentre	AOM in children aged 1 to 15 years	677 (553)	A 10 mg/kg od then 5 mg/kg od A/C 40 mg/kg/day divided tid	Day 1 days 2-5 10 days	245/280 (88%) 240/273 (88%)	ND ND
Principi[206]	Prospective, nonblind, comparative, multicentre	Otitis media in children aged 6 months to 12 years	483 (413)	A 10 mg/kg od A/C 40 mg/kg/day divided tid	3 days 10 days	199/215 (93%) 186/198 (94%)	29/31 (94%) 25/26 (96%)
Rodriguez[207]	Randomised, nonblind, multicentre	AOM in children aged 5 months to 13 years	259 (234)	A 10 mg/kg od Cef 40 mg/kg/day dosed Q8h	3 days 10 days	112/114 (98%) 116/120 (97%)	ND ND

Table IX. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration	Clinical response (cured and improved)	Bacterial eradication
Marchisio et al.[208]	Prospective, randomised, single-blind, comparative	Recurrent AOM in children aged 9 months to 5 years at least 3 episodes of AOM in the past 6 months	159 (148)	A 5 or 10 mg/kg once a week	6mo	5 mg/kg group-discontinued due to high failure rate 10 mg/kg group-63/74 (85%)	73/74 (99%)
				Amox 20 mg/kg od	6mo	51/74 (69%)	68/73 (93%)
Arguedas et al.[209]	Prospective, randomised, nonblind	AOM with effusion in children aged 6 months to 12 years	100 (97)	A 10 mg/kg od C 15 mg/kg/day divided bid	3 days 10 days	50/50 (100%) 45/47 (96%)	ND ND
Streptococcal pharyngitis							
Schaad et al.[210]	Prospective, nonblind, comparative, multicentre	Acute streptococcal pharyngitis in children aged 6 months to 14 years	343 (320)	A 10 mg/kg od Pen V 100 000 IU/kg divided tid	3 days 10 days	149/160 (93%) 143/160 (89%)	51/93 (55%) 96/120 (80%)
O'Doherty et al.[211]	Prospective, randomised, double-blind, double-dummy	Acute streptococcal pharyngitis and tonsillitis in children aged 2-13 years	489 (358)	A 10 mg/kg od A 20 mg/kg od Pen V 125-250mg QID	10 days 10 days 10 days	122/123 (99%) 103/103 (100%) 128/132 (97%)	98% 98% 92%
Pacifico et al.[212]	Prospective, randomised, comparative	GABHS pharyngitis in children aged 3-12 years	183 (154)	A 10 mg/kg od Pen V 50 000 IU/kg/day divided bid	3 days 10 days	57/76 (75%) 71/78 (91%)	41/76 (54%) 67/78 (86%)
Cremer et al.[213]	Prospective, nonblind, comparative	Acute GABHS tonsillopharyngitis in children aged 1-12 years	122 (98)	A 10 mg/kg od Cef 30 mg/kg divided tid	3 days 10 days	44/51 (86%) 44/51 (86%)	19/52 (37%) 34/46 (74%)
Venuta et al.[214]	Prospective, randomised, observer-blind, comparative	Streptococcal pharyngitis in children aged 4-13 years	174 (137)	A 10 mg/kg od (max 500mg) C 7.5 mg/kg bid (max 500 mg/day)	3 days 10 days	71/74 (96%) 61/63 (97%)	70/74 (95%) 60/63 (95%)
Sinusitis							
Haye et al.[215]	Prospective, randomised, double-blind, parallel group, multicentre	Acute maxillary sinusitis in adults aged 18 to 70 years	438 (434)	A 500mg od PMP 1.3g tid	3 days 10 days	97% 95%	ND ND
Clement & De Gandt[216]	Prospective, randomised, nonblind	Non-severe acute maxillary/ethmoidal sinusitis in adults	254 (240)	A 500mg od A/C 500mg tid	3 days 10 days	119/136 (88%) 62/74 (84%)	47/52 (90%) 26/31 (84%)
Amin & Breadon[217]	Prospective, non-comparative, nonblind	Acute sinusitis in patients aged ≥16 years	163 (102)	A 500mg od then 250mg od	Day 1 days 2-5	96/102 (94%)	ND

Table IX. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration	Clinical response (cured and improved)	Bacterial eradication
Upper respiratory tract infections (URTIs)							
Müller[218]	Prospective, randomised, nonblind, multicentre	Acute URTIs (AOM, acute sinusitis, acute GABHS P/T in adults aged >12 years	440 (431)	A 500mg od	3 days	AOM 51/52 (98%) AS 64/68 (94%) P/T 91/91 (100%)	18/21 (86%)
				R 150mg bid	10 days	AOM 54/55 (98%) AS 69/73 (94%) P/T 91/92 (99%)	11/12 (92%)
O'Doherty[219]	Prospective, randomised, nonblind, multicentre	URTIs (AOM, streptococcal P/T, maxillary sinusitis) in patients aged ≥12 years	530 (486)	A 500mg od	3 days	AOM 47/52 (90%) P/T 143/152 (94%) MS 38/41 (93%)	116/117 (99%) 115/119 (97%)
				Cef 250mg tid	10 days	AOM 46/48 (96%) P/T 152/156 (97%) MS 35/37 (95%)	
Lower respiratory tract infections (LRTIs)							
Roord et al.[177]	Prospective, randomised, nonblind, multicentre	Community-acquired LRTIs (pneumonia or bronchitis) in children aged 2-16 years	89 (85)	E 40 mg/kg/day divided tid A 10 mg/kg/day od	10 days 3 days	36/40 (90%) 42/45 (93%)	ND ND
Laurent[220]	Prospective, randomised, nonblind, multicentre	LRTIs (AB, AECB, CAP) in adults aged ≥18 years	204 (193)	A 500mg od	3 days	AB 22/23 (96%) AECB 52/57 (91%) CAP 17/19 (90%)	46/50 (92%)
				R 150mg bid	10 days	AB 23/25 (92%) AECB 41/46 (90%) CAP 18/23 (78%)	30/37 (81%)
Zachariah[221]	Prospective, randomised, double-blind, multicentre	Acute LRTIs (AB, AECB, CAP) in adults aged ≥18 years	369 (346)	A 500mg od	3 days	AB 109/113 (96%) AECB 55/59 (94%) CAP 1/1 (100%)	82/82 (100%)
				A/C 375mg tid	10 days	AB 112/115 (97%) AECB 53/57 (93%) CAP 1/1 (100%)	73/74 (99%)
Gris[222]	Prospective, randomised, double-blind, multicentre	LRTIs (AB, AECB, CAP) in adults aged ≥18 years	78 (67)	A 500mg od	3 days	AB 2/4 (50%) AECB 24/28 (86%) CAP 2/2 (100%)	9/10 (90%)
				A/C 625mg tid	10 days	AB 3/3 (100%) AECB 24/26 (92%) CAP 4/4 (100%)	10/10 (100%)

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

AB = acute bronchitis; **A/C** = amoxicillin/clavulanic acid; **AMOX** = amoxicillin; **AOM** = acute otitis media; **AS** = acute sinusitis; **bid** = twice a day; **BPen** = benzyl penicillin; **C** = clarithromycin; **Cef** = cefixime; **CP** = *Chlamydia pneumoniae*; **E** = erythromycin; **GABHS** = group A β-haemolytic streptococcus; **HI** = Haemophilus influenzae; **IV** = intravenous; **MP** = *Mycoplasma pneumoniae*; **MS** = maxillary sinusitis; **ND** = no data available; **od** = once daily; **Pen V** = penicillin or phenoxymethyl penicillin; **PMP** = phenoxymethyl penicillin; **P/T** = pharyngitis/tonsillitis; **PO** = oral; **qid** = 4 times daily; **R** = roxithromycin; **SP** = *Streptococcus pneumoniae*; **Spar** = sparfloxacin; **tid** = 3 times a day.

improvement of other signs and symptoms), which suggests that azithromycin is useful in the treatment of Legionnaires' disease.[198]

Socan[199] performed a retrospective study to determine whether a 3- or a 5-day course of azithromycin was more effective in the treatment of atypical pneumonia. The therapies were equally effective against atypical pneumonia, therefore, the study recommends use of a 3-day treatment as it is likely to increase compliance.[199]

6.1.3 Clarithromycin

Several studies have evaluated the use of clarithromycin in the treatment of patients with CAP (table X).[170,194,223,233] Genné et al.[223] conducted a nonblind, randomised study in adults comparing the effectiveness of intravenously administered clarithromycin and oral amoxicillin/clavulanic acid. Clinical cure or improvement was seen in 86% of clarithromycin-treated patients and 84% of patients receiving amoxicillin/clavulanic acid. Pathogens were isolated from 54% of patients, with *S. pneumoniae* and *H. influenzae* isolated in 44 and 18% of these patients, respectively. Diagnosis was based on sputum cultures (48%), serological testing (30%) and blood cultures (22%).[223] Atypical pneumonia was identified in 22% of patients. Total bacteriological eradication rates in clarithromycin and amoxicillin/clavulanic acid groups were 89 and 86%, respectively.[223] Rizzato et al.[194] compared clarithromycin to azithromycin in a randomised, nonblind trial. Both agents showed favourable responses with cure rates of 89% in clarithromycin recipients and 100% in azithromycin recipients; however, study numbers (n = 39) were too small to draw firm conclusions from these results. Both agents were considered to be effective in patients with mild to moderately severe CAP.[194] A study of various types of LRTIs was conducted by Tatsis et al.[233] in which clarithromycin and roxithromycin were compared. Both treatments were considered effective (80% in clarithromycin and 88% in roxithromycin), however, the success rate was not reported by type of infection.

6.1.4 Dirithromycin

Dirithromycin was compared with erythromycin for the treatment of CAP in 2 studies (table XI).[167,168] Clinical efficacy of dirithromycin was found to be comparable with that of erythromycin in a double-blind study conducted by Liippo et al.,[167] and in a retrospective study by Hernández et al.[168] These studies are summarised in section 6.1.1.

6.1.5 Flurithromycin

The effectiveness of flurithromycin in the treatment of CAP was examined in two studies of LRTIs (table XII).[234,239] Bariffi et al.[239] conducted a non-comparative study that reported success rates of 79% for flurithromycin in the treatment of adults with CAP. The study concludes that flurithromycin is an effective way to treat LRTIs. The same conclusion is drawn in a study conducted by Vagliasindi,[234] although success of treatment was not reported by type of infection.

6.1.6 Roxithromycin

The ability of roxithromycin to treat CAP in adults was evaluated in 7 clinical trials (table XIII).[193,220,233,240-242,245] A nonblind study by Salvarezza et al.[240] reports clinical cure rates (defined as complete resolution of signs and symptoms as well as improvement of radiological findings) of 100 and 94% when comparing roxithromycin with cefixime. *S. pneumoniae* was found in 43% of sputum cultures obtained, while *S. aureus*, *H. influenzae*, *M. catarrhalis* and atypical pathogens were also detected. Roxithromycin was reported to provide effective treatment of mild to moderate CAP.[240] High clinical cure rates were found with roxithromycin in the treatment of atypical pneumonia, however, in comparison with azithromycin, the study by Schönwald et al.,[193] concludes that roxithromycin is less convenient in terms of length of treatment required (summarised in section 6.1.2). Roxithromycin was also reported to be less effective than azithromycin in the treatment of patients with CAP in a trial by Laurent.[220] This study suggests that the advantage of azithromycin is due to its increased convenience and the possibility of early discharge of patients from hospital (table IX).[220]

Table X. Results of clinical trials involving clarithromycin (C)

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Community-acquired pneumonia (CAP)							
Genné et al.[223]	Prospective, randomised, nonblind	CAP in adults ≥18 years of age	127 (112)	C 500mg IV bid (3-5 days) then 500mg PO bid	At least 10 days	48/56 (86%)	31/35 (89%)
				A/C 1.2g IV qid (3-5 days) then 625mg PO tid	At least 10 days	47/56 (84%)	24/28 (86%)
Rizzato et al.[194]	Prospective, randomised, nonblind, comparative	Low to moderate CAP in patients >75 years of age	40 (39)	A 500mg od	3 days	20/20 (100%)	ND
				C 250mg bid	10 ± 2 days	17/19 (89%)	ND
Jang et al.[169]	Prospective, randomised	CAP in adults 16 to 81 years of age	40 (40)	C 250mg bid	14 days	19/20 (95%)	ND
				E 500mg qid	14 days	18/20 (90%)	ND
Block et al.[170]	Prospective, randomised, investigator-blind, multicentre	CAP in children aged 3-12 years	260 (234)	C 15 mg/kg/day (max 1000mg) divided bid	10 days	121/124 (98%)	24/27 (89%)
				E 40 mg/kg/day (max 1600mg) divided bid-tid	10 days	105/110 (95%)	16/18 (89%)
Acute exacerbations of chronic bronchitis (AECB)							
Chodosh et al.[224]	Prospective, randomised, double-blind multicentre	Mild to moderate AECB in adults aged ≥18 years	234 (190)	C 500mg bid	14 days	75/91 (82%)	67/87 (77%)
				Cipro 500mg bid	14 days	89/99 (90%)	86/95 (91%)
Ziering & McElvaine[225]	Prospective, evaluator-blind, parallel, multicentre	AECB in adults aged >18 years	309 (262)	C 500mg bid	7-14 days	119/128 (93%)	34/38 (89%)
				Cef 400mg od	7-14 days	122/134 (91%)	28/33 (85%)
Hosie et al.[226]	Prospective, randomised, single-blind, parallel, multicentre	AECB in adults aged ≥18 years	212 (191)	C 250mg bid	7 days	91/96 (95%)	23/32 (72%)
				D 500mg od	5 days	85/95 (90%)	22/32 (69%)
Otitis media							
Arguedas et al.[209]	Prospective, randomised, nonblind	AOM with effusion in children aged 6 months to 12 years	100 (97)	C 15 mg/kg/day divided bid	10 days	45/47 (96%)	ND
				A 10 mg/kg od	3 days	50/50 (100%)	ND
Pavlopoulou et al.[227]	Prospective, randomised	AOM in children aged 5 months to 12 years	55 (47)	C 7.5 mg/kg bid	10 days	24/27 (89%)	ND
				Cef 13 mg/kg tid	10 days	20/23 (87%)	ND
Aspin et al.[228]	Prospective, randomised, investigator-blind, multicentre	AOM in children aged 6 months to 12 years	180 (172)	C 15 mg/kg/day divided bid	10 days	80/86 (93%)	ND
				A/C 40 mg/kg/day divided tid	10 days	82/86 (95%)	ND

Table X. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Streptococcal pharyngitis							
Kearsley et al.[229]	Prospective, randomised, physician-blind, multicentre	Streptococcal pharyngitis and tonsillitis in children aged 1-12 years	229 (189)	C 7.5 mg/kg bid Amox 125mg tid (<25kg) or 250mg tid (>25kg)	7 days 7 days	96/98 (98%) 88/91 (97%)	42/48 (88%) 36/42 (86%)
Venuta et al.[214]	Prospective, randomised, observer-blind, comparative	Streptococcal pharyngitis in children aged 4-13 years	174 (137)	C 7.5 mg/kg bid A 10 mg/kg od	10 days 3 days	61/63 (97%) 71/74 (96%)	60/63 (95%) 70/74 (95%)
Sinusitis							
Adelglass et al.[230]	Prospective, randomised, investigator-blind, parallel, multicentre	Acute bacterial sinusitis in adults aged ≥18 years	216 (190)	C 500mg bid Levo 500mg od	14 days 14 days	83/89 (93%) 97/101 (96%)	ND ND
Hashiba & Baba[231]	Prospective	Intractable chronic sinusitis in adults aged 18-78 years	45	C 200mg bid	8-12 weeks	71%	ND
Lower respiratory tract infections (LRTIs)							
Fong et al.[232]	Prospective, randomised, multicentre	LRTIs (acute purulent bronchitis, acute exacerbations of COPD, CAP) in adults aged >18 years	212 (197)	C 250 or 500mg bid Cef 250 or 500mg tid	7-14 days 7-14 days	90/95 (95%) 92/102 (90%)	26/36 (72%) 28/40 (70%)
Tatsis et al.[233]	Prospective, randomised, nonblind, parallel, multicentre	AECB and CAP in adults aged 18-83 years	60 (50)	C 500mg bid R 300mg od	4-17 days 4-17 days	20/25 (80%) 22/25 (88%)	50% 60%
Vagliasindi et al.[234]	Prospective, randomised, double-blind, double-dummy, parallel	Acute LRTIs (bronchitis, bronchopneumonia, etc.) in patients aged 18-84 years	152 (149)	C 250mg bid F 375mg bid	4-14 days 4-14 days	74/76 (97%) 69/73 (95%)	62/76 (82%) 60/72 (83%)

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

A = azithromycin; **A/C** = amoxicillin/clavulanic acid; **AOM** = otitis media; **bid** = twice a day; **Cef** = cefixime; **COPD** = chronic obstructive pulmonary disease; **Cipro** = ciprofloxacin; **E** = erythromycin; **F** = flurithromycin; **IV** = intravenous; **Levo** = levofloxacin; **ND** = no data available; **od** = once daily; **PO** = oral; **qid** = 4 times daily; **R** = roxithromycin; **tid** = 3 times a day.

Table XI. Results of clinical trials involving dirithromycin (D)

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Community-acquired pneumonia (CAP)							
Liippo et al.[167]	Prospective, randomised, double-blind, multicentre	Bacterial CAP in adults aged 16-75 years	591 (241)	D 500mg od E 250mg qid	10-14 days 10-14 days	95% 92%	93% 90%
Hernández et al.[168]	A retrospective review of 2 prospective, randomised, double-masked, multicentre trials	CAP and BP in adults aged 16-69 years	CAP: 1108 (1108) BP: 24 (22)	D 500mg od E 250mg qid	10-14 days 10-14 days	CAP 482/555 (87%) BP 12/13 (92%) CAP 487/553 (88%) BP 8/9 (89%)	161/185 (87%) 152/171 (89%)
Acute exacerbations of chronic bronchitis (AECB)							
Wasilewski et al.[171]	Two identically designed, prospective, well-controlled, randomised, double-blind trials	AECB in adults aged ≥12 years weighing ≥37kg	1057 (690)	D 500mg od E 250mg qid	5 days 7 days	298/354 (84%) 270/336 (80%)	178/228 (78%) 170/216 (79%)
Hosie et al.[226]	Prospective, randomised, single-blind, parallel, multicentre	Bacterial AECB in adults aged ≥18 years	212 (191)	D 500mg od C 250mg bid	5 days 7 days	85/95 (90%) 91/96 (95%)	22/32 (69%) 23/32 (72%)
Van Royen et al.[235]	Prospective, randomised, nonblind, multicentre	AECB in adults	334 (321)	D 500mg od A/C 500mg tid	5 days 7-10 days	153/162 (95%) 148/159 (93%)	ND ND
Cazzola et al.[236]	Prospective, nonblind, non-comparative	Acute exacerbations of COPD in patients aged 40-75 years	20 (20)	D 500mg od	5 days	18/20 (90%)	18/20 (90%)
Streptococcal pharyngitis							
Watkins et al.[237]	Prospective, randomised, double-blind, double-dummy, parallel, multicentre	GABHS pharyngitis in patients aged ≥12 years	345 (257)	D 500mg od Pen VK 250mg qid	10 days 10 days	117/121(97%) 128/136 (94%)	109/121 (85%) 123/136 (83%)

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

A/C = amoxcillin/clavulanic acid; **AS** = acute sinusitis; **bid** = twice a day; **BP** = bacteraemic pneumonia; **C** = clarithromycin; **COPD** = chronic obstructive pulmonary disease; **E** = erythromycin; **GABHS** = group A β-haemolytic streptococcus; **ND** = no data available; **od** = once daily; **Pen VK** = penicillin VK or phenoxymethylpenicillin K; **qid** = 4 times daily; **tid** = 3 times a day.

Landscape table XII to be placed here.

Kaku et al.[241] observed that roxithromycin was effective in 92% (12 of 13) of patients infected with *M. pneumoniae*, but was only able to eradicate 67% (4 of 6) of the pathogens, while the other 33% (2 of 6) results were unchanged. Örtqvist et al.[242] found roxithromycin (80%) to be less effective than sparfloxacin (95%) in producing a positive clinical response.

Karalus et al.[245] found a response rate of 98% for roxithromycin and 95% for amoxicillin/clavulanic acid in a study of LRTIs in adults. The study concludes that roxithromycin is a more appropriate choice for treatment of LRTIs than is amoxicillin/clavulanic acid, as roxithromycin is more convenient and offers greater tolerability.[245] A study comparing roxithromycin with clarithromycin in the treatment of LRTIs is outlined in section 6.1.3.[233]

6.2. Acute Exacerbations of Chronic Bronchitis (AECB)

6.2.1 Erythromycin

A meta-analysis of 2 identically designed, double-blind trials was conducted by Wasilewski et al. (table VIII).[171] This meta-analysis compared the clinical efficacy of a 7-day course of erythromycin to that of 5 days of dirithromycin. Favourable responses (cure or improvement) were obtained in 80% of erythromycin and 84% of dirithromycin recipients. The most commonly occurring pathogens in the sputum were *S. pneumoniae*, *H. influenzae*, *S. aureus* and *M. catarrhalis*. Eradication rates observed were 78% in the erythromycin-treated group compared to 79% in dirithromycin group. Erythromycin and dirithromycin are considered clinically and microbiologically equivalent in the treatment of acute exacerbations of chronic bronchitis (AECB).[171] Kawahara et al.[172] conducted a randomised, crossover study comparing erythromycin treatment with that of ofloxacin in the prevention of AECB. Group I received ofloxacin 300mg 3 times a day for 12 weeks, then erythromycin 600mg 3 times daily for 12 weeks, while group II received the same treatments in reverse order. AECB were experienced by 31% (20 of 64)

Table XII. Results of clinical trials involving flurithromycin (F)

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Upper respiratory tract infections (URTIs)							
Galioto et al.[238]	Prospective, nonblind, multicentre	URTIs (P/T, RS, OM, sial) in patients aged 18-75 years	103 (101)	F 375mg q12h	5-14 days	Overall 99/101 (98%) P/T 43/44 (98%) RS 39/39 (100%) OM 36/37 (97%) Sial 1/1 (100%)	90/95 (95%)
Lower respiratory tract infections (LRTIs)							
Bariffi et al.[239]	Prospective, nonblind, non-controlled, multicentre	LRTIs (bacterial acute bronchitis, pneumonia, AECB) in adults aged 18-91 years	110 (105)	F 375mg q12h	3-14 days	Overall: 86/105 (82%) CAP: 15/19 (79%) AB: 13/14 (93%) AECB: 58/77 (75%)	61/76 (80%)
Vagliasindi[234]	Prospective, randomised, double-blind, double-dummy, parallel	Acute LRTIs (bronchitis, bronchopneumonia, etc.) in patients aged 18-84 years	152 (149)	F 375mg bid C 250mg bid	4-14 days 4-14 days	69/73 (95%) 74/76 (97%)	60/72 (83%) 62/76 (82%)

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

AB = acute bronchitis; **AECB** = acute exacerbations of chronic bronchitis; **bid** = twice a day; **C** = clarithromycin; **CAP** = community-acquired pnuemonia; **OM** = otitis media; **P/T** = pharyngitis/tonsillitis; **q12h** = every 12 hours; **RS** = chronic sinusitis; **sial** = sialadenitis; **tid** = 3 times a day.

Table XIII. Results of clinical trials involving roxithromycin (R)

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Community-acquired pneumonia (CAP)							
Salvarezza et al.[240]	Prospective, randomised, nonblind, multicentre	Uncomplicated CAP in patients aged 18-60 years	60 (60)	R 300mg od Cef 400mg od	8-10 days 8-10 days	30/30 (100%) 28/30 (94%)	ND ND
Schönwald et al.[193]	Prospective, randomised, nonblind, multicentre	Atypical pneumonia (*Mycoplasma pneumoniae*, *Chlamydia* spp., and *Coxiella burnetti*) in adults aged 14-69 years	150 (142)	R 150mg bid A 500mg od	10 days 3 days	50/53 (94%) 88/89 (99%)	ND ND
Kaku et al.[241]	Prospective, non-comparative	CAP caused by *M. pneumoniae* in adults aged 17-75 years	15 (13)	R 150mg bid	>3-14 days	12/13 (92%)	4/6 (67%)
Örtqvist et al.[242]	Prospective, randomised, double-blind, multicentre	CAP in adults aged ≥18 years	304 (260)	R 150mg bid Spar 400mg od then 200mg od	10-14 days Day 1 9-13 days	106/133 (80%) 124/131 (95%)	69/73 (95%) 66/83 (80%)
Sinusitis							
Chatzimanolis et al.[243]	Prospective, randomised, nonblind	Acute or recurrent sinusitis in patients aged >18 years	60 (56)	R 150 mg bid A/C 625mg tid	≥10 days ≥10 days	27/29 (93%) 24/27 (89%)	ND ND
Kimura et al.[244]	Prospective	Chronic sinusitis in patients aged 9-80 years	30 (30)	R 150mg od	3 months	? 80%	ND
Upper respiratory tract infections (URTIs)							
Müller[218]	Prospective, randomised, nonblind, multicentre	Acute URTIs (AOM, AS, acute GABHS P/T) in adults aged >12 years	440 (431)	R 150mg bid	10 days	AOM 54/55 (98%) AS 69/73 (94%) P/T 91/92 (99%)	11/12 (92%)
				A 500mg od	3 days	AOM 51/52 (98%) AS 64/68 (94%) P/T 91/91 (100%)	18/21 (86%)
Lower respiratory tract infections (LRTIs)							
Laurent et al.[220]	Prospective, randomised, nonblind, multicentre	LRTIs (AB, AECB, CAP) in adults aged ≥18 years	204 (193)	R 150mg bid	10 days	AB 23/25 (92%) AECB 41/46 (90%) CAP 18/23 (78%)	30/37 (81%)
				A 500mg od	3 days	AB 22/23 (96%) AECB 52/57 (91%) CAP 17/19 (90%)	46/50 (92%)

Landscape table XIII to be placed here.

of erythromycin recipients compared with 22% (14 of 64) of ofloxacin recipients. This study suggests that ofloxacin is likely a superior choice in the prevention of AECB when compared with erythromycin.[172]

6.2.2 Azithromycin

A randomised, nonblind study was conducted in adults with AECB and acute tracheobronchitis in order to compare the clinical effectiveness of azithromycin and amoxicillin/clavulanic acid (table IX).[200] Azithromycin-treated patients experienced a significantly higher clinical response rate (cure plus improvement, 90%) than did those receiving amoxicillin/clavulanic acid (80%, $p = 0.011$). A similar study conducted by Beghi et al.[201] gave conflicting results with clinical cure/improvement rates of 97% with amoxicillin/clavulanic acid compared with only 68% efficacy with azithromycin in the treatment of acute purulent exacerbations of chronic bronchitis.[201] Three other studies of lower respiratory tract infections in adults report azithromycin success (cure plus improvement) of 91,[220] 94[221] and 86%.[222] The study by Laurent[220] compares azithromycin with roxithromycin (90% success), while Zachariah[221] and Gris[222] report amoxicillin/clavulanic acids success rates (cure or improvement) of 93 and 92%, respectively.

6.2.3 Clarithromycin

Clarithromycin has been compared with ciprofloxacin, ceftibuten, dirithromycin and cefaclor as therapy for adults with AECB (table X).[224-226] In the trial conducted by Chodosh et al.,[224] clinical resolution was observed in 82% of patients taking clarithromycin while 90% of ciprofloxacin recipients responded to therapy. Efficacy was measured by the infection-free interval (calculated based on the number of days to the next clinical relapse or new infection) and determined to be 52 days for clarithromycin and 142 days for ciprofloxacin based on median values. Bacterial eradication was observed in 77 and 91% of patients treated with clarithromycin and ciprofloxacin, respectively ($p = 0.01$), with the lower value observed for clarithromycin likely a result of inferior

Table XIII. Contd

Study	Design	Indication and study population	n[a]	Regimen	Duration[b]	Clinical response (cured and improved)	Bacterial eradication
Tatsis et al.[233]	Prospective, randomised, nonblind, parallel, multicentre	AECB and CAP in adults aged 18-83 years	60 (50)	R 300mg od C 500mg bid	4-17 days 4-17 days	22/25 (88%) 20/25 (80%)	60% 50%
Karalus et al.[245]	Prospective, randomised, nonblind, parallel, multicentre	Community-acquired LRTIs (bronchitis and pneumonia) in adults	242 (227)	R 150mg bid A/C 500/125mg tid	7-14 days 7-14 days	95/97 (98%) 90/95 (95%)	37/41 (90%) 12/13 (92%)

a Number of patients (number of patients with full data at the end of treatment or at follow-up if there was no evaluation at the end of treatment).

b Length of treatment.

A = azithromycin; **AB** = acute bronchitis; **A/C** = amoxcillin/clavulanic acid; **AECB** = acute exacerbations on chronic bronchitis; **AOM** = otitis media; **AS** = acute sinusitis; **bid** = twice a day; **C** = clarithromycin; **Cef** = cefixime; **GABHS** = group A β-haemolytic streptococcus; **ND** = no data available; **od** = once daily; **P/T** = pharyngitis/tonsillitis; **Spar** = sparfloxacin; **tid** = 3 times a day.

H. influenzae coverage versus ciprofloxacin. Ziering and McElvaine[225] observed similar rates of clinical and bacteriological response when comparing clarithromycin (93% clinical success and 89% bacterial eradication) with ceftibuten (91 and 85%, respectively) in an evaluator-blind trial. The 2 treatments were considered to be equally effective in this study (table X).[225]

Clinical efficacies of 95 and 90% are reported post-therapy (days 10 to 12) in a study by Hosie et al.[226] comparing clarithromycin with dirithromycin. Bacterial eradication rates were poor (72% for clarithromycin and 69% for dirithromycin) post-therapy but improve dramatically (93 and 96%, respectively) by late post-treatment (days 20 to 30). Clarithromycin and dirithromycin were considered to be equally as effective therapies. Increased compliance as a result of a shorter treatment period (once a day for 5 days) and less frequent administration may make dirithromycin a more attractive option than clarithromycin, however, group differences for compliance were not significant.[226]

Fong et al.[232] conducted a study comparing clarithromycin with cefaclor in adults with LRTIs. Of the patients with AECB and bronchiectasis, 95% of those receiving clarithromycin had favourable clinical outcomes compared with 90% of cefaclor users ($p = 0.66$) and bacteriological cure was observed in 72% of those receiving clarithromycin compared with 70% of those on cefaclor ($p = 0.28$). It was therefore concluded that clarithromycin was as effective as cefaclor with the added benefit of less frequent administration.[232] A study of LRTIs was also conducted by Tatsis et al.[233] which compared clarithromycin and roxithromycin is outlined in section 6.1.3.

6.2.4 Dirithromycin

Previously described studies by Wasilewski et al.[171] (section 6.2.1) and Hosie et al.[226] (section 6.1.3) showed that dirithromycin was equivalent to erythromycin and clarithromycin in clinical efficacy when treating AECB and may be preferred because of its more convenient administration schedule and shorter duration of therapy. A third study, conducted by Van Royen et al.,[235] details the similar rates of clinical success (cure or improvement) achieved with dirithromycin (95%) and amoxicillin/clavulanic acid (93%). No statistically significant difference in outcome was reported ($p = 0.34$), however dirithromycin may once again be of advantage because of increased compliance.[235] Dirithromycin was also found to be of value in the treatment of AECB in an nonblind, non-comparative trial conducted by Cazzola et al.[236] Clinical and bacteriological response rates were found to be 90% in patients treated with dirithromycin.

6.2.5 Flurithromycin

Bariffi et al.[239] reported that flurithromycin was 75% successful in producing favourable responses (cure plus improvement) in patients with AECB (table XII). Flurithromycin is thought to be an effective treatment in patients with LRTIs.[239] Vagliasindi[234] also found favourable results with the use of flurithromycin, although success rates specific to AECB are not provided.

6.2.6 Roxithromycin

Roxithromycin was reported to be 90% effective in the treatment of AECB when compared with azithromycin (91%) in a LRTI study conducted by Laurent[220] (table XIII). A clinical trial comparing the efficacy of roxithromycin to that of clarithromycin in the treatment of LRTIs (including AECB) found the agents to be similar.[233] The study, conducted by Tatsis et al.,[233] is summarised in section 6.1.3.

6.3 Otitis Media

6.3.1 Erythromycin

Erythromycin either alone or in combination with sulfisoxazole has been studied in the treatment of acute otitis media (AOM) in children.[248,249] In a double-blind trial conducted by Scholtz and Noack,[122] erythromycin produced success (defined as resolution of all signs and symptoms and resolution or marked improvement of otoscopy findings) in 94% of patients compared with 96% of patients treated with amoxicillin. Recurrence rates were also similar in the 2 groups. Erythromycin was concluded to be as effective as amoxicillin

in the treatment of AOM and could therefore be used as a first-line alternative, especially in patients with penicillin allergy.[122]

6.3.2 Azithromycin

Several studies evaluated the efficacy of azithromycin in the treatment of AOM (table IX).[202-209,254] One non-comparative and 3 comparative studies report clinical cure rates of up to 92% for azithromycin, with no significant differences in activity between azithromycin and amoxicillin/clavulanic acid in any of the comparative trials.[202-205] Bacterial eradication of >75% of pathogens was achieved with both agents in all trials in which they were involved. Principi[206] conducted a similar nonblind trial comparing azithromycin with amoxicillin/clavulanic acid in which satisfactory responses (cure plus improvement) were seen in 93 and 94%, respectively. Children treated with azithromycin were reported to have more rapid improvement in signs and symptoms than those treated with amoxicillin/clavulanic acid. *Haemophilus* spp. and *Streptococcus* spp. were the most commonly isolated pathogens obtained through tympanocentesis. Baseline pathogens (including *Haemophilus* spp., *Streptococcus* spp., *Enterobacter* spp., *S. aureus* and *Bacteroides assacharolyticus*) were eradicated in 94% (29 of 31) of azithromycin-treated patients and 96% (25 of 26) of patients receiving amoxicillin/clavulanic acid. The study concludes that, given as an oral suspension, azithromycin once daily for 3 days is as well tolerated and effective as amoxicillin/clavulanic acid given 3 times a day for 10 days in the treatment of AOM.[206] A study by Rodriguez[207] reported a cure or improvement (in signs and symptoms) in 98% of azithromycin recipients and in 97% of cefaclor recipients. Follow-up at approximately 1 month after treatment was completed demonstrating significantly higher cure rates ($p = 0.033$) in the azithromycin group (97%) when compared with cefaclor (86%). Azithromycin was reported to be as effective as cefaclor, and advantageous because of the less frequent administration interval and lower incidence of relapse.[207]

Antibacterial agents may have a beneficial yet limited role as prophylaxis for recurrent AOM.[251] Marchisio et al.[208] performed a study comparing the effectiveness azithromycin 5 mg/kg or 10 mg/kg once weekly and amoxicillin 20 mg/kg as prophylaxis in the prevention of recurrent AOM in children. All groups were to receive treatment for 6 months, however the azithromycin group receiving 5 mg/kg was discontinued after 8 weeks of treatment because of high failure rates (56%). Recurrence occurred in the azithromycin 10 mg/kg group in 15% of patients while 31% of amoxicillin recipients developed episodes of AOM. Azithromycin 10 mg/kg once weekly could therefore be used as an alternative to amoxicillin once daily as prophylaxis against recurrent AOM.[208]

6.3.3 Clarithromycin

Three trials have compared the clinical response rates of clarithromycin with azithromycin, cefaclor and amoxicillin/clavulanic acid in the treatment of children with AOM (table X).[209,227,228] An nonblind study conducted by Arguedas et al.[209] concluded that both clarithromycin and azithromycin are good therapeutic alternatives for AOM based on success rates of 96 and 100%, respectively. Clarithromycin was found to be comparable with cefaclor in the treatment of AOM in a study by Pavlopoulou et al.[227] Clinical response occurred in 89% by the second visit and 100% by the third visit for patients treated with clarithromycin and 87 and 95%, respectively, for cefaclor-treated patients.[227] The differences in these results were not found to be statistically significant ($p > 0.05$).[227] Similar rates of clinical efficacy were reported when clarithromycin (93%) was compared with amoxicillin/clavulanic acid (95%) in a trial conducted by Aspin et al.[228] Both of these studies cited clarithromycin as an attractive alternative therapy because of good response rates and less frequent administration.[227,228]

6.3.4 Dirithromycin

Data were not available regarding the use of dirithromycin in the treatment of otitis media.

6.3.5 Flurithromycin

A 97% rate of efficacy was reported in patients with acute and chronic otitis media after treatment with flurithromycin in a study conducted by Galioto et al.[238]

6.3.6 Roxithromycin

Roxithromycin was compared with azithromycin in the treatment of patients with otitis media in an nonblind study of patients with upper respiratory tract infections (URTIs) conducted by Müller.[218] Results of the study indicated that the 2 agents had virtually identical rates of clinical response (98% for each agent).[218]

6.4 Streptococcal Pharyngitis

6.4.1 Erythromycin

Peterson et al.[173] compared erythromycin to placebo when treating adults with non-group A streptococcal pharyngitis (table VIII). The study found that although erythromycin-treated patients had more rapid resolution of sore throat and cough, overall clinical results were not significantly different. The study concludes that although pharyngitis caused by group A β-haemolytic streptococci (GABHS) requires antibacterial treatment, the same may not hold true for other types of streptococcal pharyngitis.[173]

Three clinical trials outline the ability of erythromycin to treat pharyngitis caused by GABHS in children (table VIII).[174-176] In the first study, conducted by McCarty,[174] 10-day treatments of erythromycin ethylsuccinate and cefprozil produced clinical response rates of 91 and 95%, respectively. The author suggests that although the agents are equally effective, cefprozil may be the superior agent because it requires less frequent administration.[174] Adam et al.[175] reported clinical effectiveness of 98% for both erythromycin estolate and penicillin V (pheonxymethylpenicillin), with similar rates of bacterial eradication and recurrence also shown. Erythromycin estolate also had a significantly higher compliance rate because it requires less frequent administration and a shorter duration of therapy.[175] A statistically significant difference ($p < 0.05$) in the rate of clinical cure and bacterial eradication was shown for erythromycin (77%) compared with cefaclor (92%) and amoxicillin/clavulanic acid (91%) in a trial by Esposito et al.[176] High resistance to erythromycin (38%) may account for the poor results obtained for erythromycin and highlight the growing problem of GABHS resistance to erythromycin found in many geographical locations.[176]

6.4.2 Azithromycin

The use of azithromycin for the treatment of adults with pharyngitis was explored in 2 studies of URTIs, with clinical response rates (cure plus improvement) of 94[219] and 100%.[218] Although comparative agents reported similar levels of success, azithromycin was considered the better treatment option as it has a shorter duration of therapy and requires less frequent administration (see table IX).[218,219]

Azithromycin has also been evaluated as a treatment for children with GABHS pharyngitis in 5 trials.[210-214] Azithromycin was compared with penicillin V in 3 of these studies with varying results.[210-212] Trials by O'Doherty et al.[211] and Schaad et al.[210] found clinical response rates of 93 to 100% in patients treated with azithromycin and 89 to 97% in penicillin V-treated patients, while a study by Pacifico et al.[212] showed rates of 75 and 91%, respectively (table IX).[210-212] The study by O'Doherty[211] reports bacterial eradication rates of 98% for azithromycin and 92% for penicillin V, while the other 2 studies find azithromycin much less effective with rates of 54 to 55% compared with penicillin V rates of 80 to 86%.[210-212] A study by Cremer et al.[213] found an identical clinical response rate of 86% when comparing azithromycin with cefaclor. Very different bacterial eradication rates were reported with success in only 37% of azithromycin-treated patients compared with 74% in patients treated with cefaclor. This large difference may have been due to the presence of resistant microorganisms, inadequate duration of therapy, inadequate dose, pre-disease carriage or non-compliance.[213] Venuta et al.[214] reported high clinical and bacteriological response

rates of 99 and 95% for azithromycin and 98 and 95% for clarithromycin.

6.4.3 Clarithromycin

High rates of clinical response are reported in 2 studies in which clarithromycin is used to treat GABHS pharyngitis.[214,229] Kearsley et al.[229] compared clarithromycin with amoxicillin and found them equally effective with response rates of 98 and 97%, respectively. Bacteria were eradicated in 88% of clarithromycin-treated patients compared with 86% of patients treated with amoxicillin. Clarithromycin was suggested to be a suitable alternative therapy with the added benefit of requiring less frequent administration.[229] Clinical and bacteriological response rates of 98 and 95%, respectively, were obtained for clarithromycin recipients and 99 and 95%, respectively, for azithromycin recipients in a study conducted by Venuta et al.[214]

6.4.4 Dirithromycin

Dirithromycin was reported to be highly effective in the treatment of adults (≥12 years of age) with GAS pharyngitis in a study conducted by Watkins et al (table XI).[237] A response rate of 97% was found in the dirithromycin-treated patients compared with 94% in patients treated with penicillin VK. The 2 agents also showed similar rates of bacterial eradication (85% with dirithromycin and 83% with penicillin). Dirithromycin was reported to be an attractive alternative to penicillin therapy because of convenient once daily administration, high levels of tissue penetration, and a lack of drug-drug interactions.[237]

6.4.5 Flurithromycin

A non-comparative, prospective, nonblind trial using flurithromycin, reported a clinical efficacy rate of 98% in the treatment of adults with acute and chronic pharyngitis/tonsillitis.[238]

6.4.6 Roxithromycin

A trial by Müller[218] compared the clinical response rates of roxithromycin and azithromycin. The study reports success rates (cure or improvement) of 99% for patients treated with roxithromycin and 100% for azithromycin users.

6.5 Sinusitis

6.5.1 Erythromycin

Data on the treatment of sinusitis with erythromycin were not available based on our inclusion criteria.

6.5.2 Azithromycin

The efficacy of azithromycin in the treatment of sinusitis was examined in 3 prospective studies (table IX).[215-217] In the first study, Haye et al.[215] describe similar levels of clinical efficacy when comparing azithromycin (97%) with phenoxymethylpenicillin (penicillin V; 95%) in the treatment of acute maxillary sinusitis. The study concludes that, as no difference in efficacy is found between the 2 agents, use of azithromycin may be of advantage because of the shorter length of therapy required.[215] Clement and De Gandt.[216] drew the same conclusion on finding equivalent efficacy in their comparison of azithromycin (88%) with amoxicillin/ clavulanic acid (84%) in the treatment of acute maxillary/ethmoidal sinusitis. Bacterial eradication rates were slightly more variable with values of 90% in the azithromycin group compared with 84% for amoxicillin/clavulanic acid, however this difference was reported as statistically insignificant (p-value not reported).[216] Azithromycin was also deemed to be effective in the treatment of acute sinusitis based on a clinical cure/improvement rate of 94% in a non-comparative study by Amin and Breadon.[217]

6.5.3 Clarithromycin

Adelglass et al.[230] conducted a randomised, investigator-blind study comparing response rates of clarithromycin and levofloxacin in adults with acute bacterial sinusitis (table X). Resolution of signs and symptoms was achieved in 93 and 96% of patients receiving clarithromycin and levofloxacin, respectively. Relapse rates were 7 and 4% respectively at 1 month after therapy. It was concluded that clarithromycin and levofloxacin were comparable in terms of clinical efficacy and relapse rates.[230]

Treatment of chronic sinusitis with clarithromycin was the focus of a prospective study by

Hashiba and Baba.[231] Improvement in symptoms and rhinoscopic findings were produced in 71% of those treated with clarithromycin twice daily for up to 12 weeks. It was concluded that clarithromycin is at least as effective as the previously tested erythromycin in the treatment of chronic sinusitis.[231]

6.5.4 Dirithromycin

No clinical data were obtained regarding the efficacy of dirithromycin in the treatment of sinusitis.

6.5.5 Flurithromycin

Galioto et al.[238] report that 100% of patients with acute and chronic sinusitis showed favourable clinical outcomes (table XII).

6.5.6 Roxithromycin

Three trials reported efficacy rates for roxithromycin in the treatment of sinusitis (table XIII).[218,243,244] In a nonblind trial, Chatzimanolis et al.[243] found a clinical response in 93% of patients treated with roxithromycin compared with 89% with amoxicillin/clavulanic acid. This study of patients experiencing acute or recurrent sinusitis concluded that the 2 agents were equivalent in terms of efficacy (resolution or improvement of symptoms).[243] Kimura et al.[244] conducted a noncomparative trial to ascertain the clinical efficacy of low-dose roxithromycin in the treatment of chronic sinusitis. Symptoms were decreased or disappeared in 80% or more of the participants, suggesting that roxithromycin may be a beneficial treatment alternative.[244] High rates of success were also reported by Müller in a study of URTI in adults.[218] Responses were favourable in 94% of patients with sinusitis treated with both roxithromycin and azithromycin.

7. *In Vivo* Activity of Ketolides

Published reports regarding the use of ketolides in human trials were not available during preparatin of this review, however, use of telithromycin (HMR-3647) and ABT-773 in animal models had been evaluated (table XIV).[20,252,253,255]

Guinea pigs were used as animal models by Edelstein and Edelstein[20] for the treatment of Legionnaires' disease. Telithromycin 10 mg/kg once (n = 16) or twice (16) daily was compared with erythromycin 30 mg/kg twice daily (16) and saline (12) to determine its clinical efficacy. All animals treated with a 5-day course of telithromycin survived, regardless of dose administered, whereas 88% (14 of 16) survived after erythromycin treatment. None of the animals treated with saline survived.[20] Telithromycin was also tested against *L. pneumophila* in guinea pigs in a trial performed by Rajagopalan-Levasseur et al.[252] This study compared telithromycin with pefloxacin, erythromycin, roxithromycin and saline. At day 15, 100% of animals treated with pefloxacin were alive compared with 89% in the telithromycin group. Results for survival for the roxithromycin, erythromycin and saline groups were 75, 60 and 0%, respectively. It was concluded that the activity of telithromycin against *L. pneumophila* was comparable with that of pefloxacin. Telithromycin inhibited *L. pneumophila* serogroup 1 multiplication, and exhibited bactericidal activity in both intracellular *in vitro* and *in vivo* models.[252]

Piper et al.[253] treated immunocompetent mice with pneumonia caused by β-lactamase positive *H. influenzae* type B with telithromycin, amoxicillin, azithromycin, clarithromycin, erythromycin and pristinamycin. The data were presented in abstract form and reported that telithromycin and azithromycin demonstrated comparable efficacy (based on bacterial eradication rates). These agents demonstrated better activity than erythromycin, clarithromycin and pristinamycin ($p < 0.05$). Erythromycin and clarithromycin were more effective than either amoxicillin or no treatment ($p < 0.05$).[253]

The *in vivo* efficacy of telithromycin was tested in mice with respiratory tract infections in a study by Okamoto et al.[83] Telithromycin exhibited excellent activity in the treatment of respiratory tract infections (RTIs) caused by penicillin susceptible *S. pneumoniae*, as did azithromycin and clarithromycin. Telithromycin also demonstrated significant therapeutic effects when treating penicillin

Table XIV. Results of animal trials involving telithromycin (HMR-3647)

Study	Animal model	Dosage[a]	Duration[b]	No. of animals	Results
Edelstein & Edelstein[20]	*Legionella* pneumonia in guinea pigs	T 10 mg/kg od	5 days	16	16/16 (100%) survival
		T 10 mg/kg bid	5 days	16	16/16 (100%) survival
		E 30 mg/kg bid	5 days	16	14/16 (88%) survival
		Saline	5 days	12	0/12 (0%) survival
Rajagopalan-Levasseur et al.[252]	*Legionella* pneumonia in guinea pigs	T 30 mg/kg bid	2 days	12	89% survival
		PEF 7.5 mg/kg bid	2 days	12	100% survival
		R 30 mg/kg bid	2 days	ND	75% survival
		E 30 mg/kg bid	2 days	ND	60% survival
		Controls	NA	8	0% survival
Piper et al.[253]	*Haemophilus influenzae* pneumonia in immunocompetent mice	T 50 mg/kg q6h	4 doses	12	3/12 (25%) sterile
		Amox 25 mg/kg q6h	4 doses	15	0/15 (0%) sterile
		A 100 mg/kg q6h	4 doses	18	5/18 (28%) sterile
		C 100 mg/kg q6h	4 doses	12	0/12 (0%) sterile
		E 100 mg/kg IP q6h	4 doses	12	0/12 (0%) sterile
		PR 100 mg/kg q6h	4 doses	14	0/14 (0%) sterile
		No Treatment	NA	35	0/35 (0%) sterile
Okamoto et al.[83]	Respiratory infection in mice	T 50 or 100 mg/kg bid	3 days	ND	All agents were tested against PSSP, PRSP, and HI.
		A 50 or 100 mg/kg bid	3 days	ND	T, A, and C all reported excellent efficacy *vs* PSSP.
		C 100 mg/kg bid	3 days	ND	T was the only agent with activity *vs* PRSP. T = A >
		Cef 50 or 100 mg/kg bid	3 days	ND	C in the treatment of HI
		Levo 100 mg/kg bid	3 days	ND	
		Control	NA	ND	
Mitten et al.[254]	Respiratory infection in mice	T ND	ND	ND	PD_{50} (mg/kg): S&S = 4.5-16, P = 1-15, HI = 25-68
		A ND	ND	ND	PD_{50} (mg/kg): S&S =8->100, SP = 6->50, HI = 56-145
		C ND	ND	ND	PD_{50} (mg/kg): S&S = 6-55, SP = 7.5->50, HI = 71->300
		E ND	ND	ND	PD_{50} (mg/kg): S&S = >30-85, SP = >40->50, HI = 200->300
		J ND	ND	ND	PD_{50} (mg/kg): S&S = ND, SP= >50, HI = ND
		PR ND	ND	ND	PD_{50} (mg/kg): S&S = ≥50, SP= >50, HI = ND

a All doses given orally unless otherwise stated.

b Length of treatment.

A = azithromycin; **Amox** = amoxicillin; **bid** = twice a day; **C** = clarithromycin; **Cef** = cefdinir; **E** = erythromcyin; **HI** = *Haemophilis inluenzae*; **IP** = intraperitoneal; **J** = josamycin; **Levo** = levofloxacin; **NA** = not applicable; **ND** = no data available; **od** = once daily; **PD_{50}** = protective doses; **PEF** = pefloxacin; **PR** = pristinamycin; **PRSP** = penicillin-resistant *Streptococcus pneumoniae*; **PSSP** = penicillin-sensitive *S. pneumoniae*; **q6h** = every 6 hours; **R** = roxithromycin; **S&S** = staphylococci and streptococci; **SP** = *S. pneumoniae*; **T** = telithromycin; **=** indicates equivalent efficacy; **>** indicates superior efficacy.

resistant *S. pneumoniae* whereas azithromycin, clarithromycin, cefdinir and levofloxacin showed poor activities. Treatment of *H. influenzae* infections produced similar results when comparing telithromycin and azithromycin. These agents were more efficacious than clarithromycin. Agouridas et al.[255] performed trials in mice in order to determine the protective doses (PD_{50} values) for telithromycin and other agents in the treatment of commonly occurring respiratory tract pathogens. The authors reported that telithromycin displayed high levels of efficacy against respiratory pathogens, including multidrug-resistant strains of pneumococci and concluded that future treatment of hard-to-treat respiratory pathogens with telithromycin appears promising.[244]

Recently ABT-773 and telithromycin were studied against respiratory pathogens causing acute systemic infection in mice and lung infections in rats[254] (table XIV). ABT-773 demonstrated equivalent efficacy to telithromycin against macrolide-susceptible *S. aureus* and *S. pneumoniae* in mouse protection tests and rat pulmonary infection. ABT-773 demonstrated greater effectiveness than telithromycin in rat lung infections caused by constitutively macrolide resistant *S. pneumoniae* (*erm AM*), *mefE* producing *S. pneumoniae* and *H. influenzae*.[254] ABT-773 was also compared with azithromycin against experimental rat lung infections caused by *S. pneumoniae*.[256] ABT-773 was as efficacious as azithromycin against macrolide susceptible *S. pneumoniae* infections and significantly better (>5 fold) than azithromycin against *mefE* producing and *ermAM* producing *S. pneumoniae* infections.[256]

8. Overall Evaluation

Choosing an appropriate antibacterial for specific respiratory tract infections should be based on several factors, including susceptibility of suspected pathogens, the tolerbility profile, convenience of administration and the cost of the drug.[2,257] The clinical trials reviewed in section 6 show that macrolides exhibit similar bacterial eradication and clinical cure rates for several types of respiratory tract infections. However, some specific comments and recommendations can be made for individual agents.

8.1 CAP

The choice of empirical treatment for CAP is based on many host specific and pharmacological specific factors which include severity of the illness, comorbidity and bacterial resistance.[246,258] The previously published Canadian guidelines for non-severe CAP in patients previously well and/or <65 years of age suggested the use of macrolides as first-line monotherapy, while macrolides were recommended in combination with a second or third generation cephalosporin ± rifampin if the infection was serious in nature.[246] The elderly and those with underlying disease were considered to be at a greater risk for morbidity and mortality and likely to be infected with a wider range of organisms, leading to the use of a more broad spectrum antibacterials as empirical therapy.[246,258] In patients with non-severe CAP, macrolides were recommended to be added to an empirical regimen of either a second generation cephalosporin, cotrimoxazole (trimethoprim/sulphamethoxazole) or penicillin plus a β-lactamase inhibitor if infection with *Legionella* spp. was a concern.[246] In severe CAP, a macrolide ± rifampin and a third generation cephalosporin is one of the options used as empirical treatment.[246]

The recently published Infectious Diseases Society of America (IDSA) guidelines for CAP recommend macrolides (azithromycin, clarithromycin or erythromycin) or a respiratory fluorquinolone (grepafloxacin, levofloxacin, sparfloxacin, trovafloxacin) or doxycycline for the empirical outpatient treatment of CAP.[259] The authors state that within the macrolide class that azithromycin and clarithromycin are preferred to erythromycin when *H. influenzae* is suspected.[259] If a pathogen is identified then therapy is targeted specifically at that organism.[259] The new Canadian guidelines for the empirical treatment of outpatient CAP again recommend macrolides (azithromycin or clarithromycin if *H. influenzae* is suspected) as first-

line treatment and doxycycline as second-line.[260] For patients at risk to fail first-line treatment with macrolides (i.e. patients who received antibacterials or oral corticosteroids within the last 3 months), are empirically treated with either amoxicillin/clavulanate or a second general cephalosporin (e.g. cefuroxime axetil or cefprozil) with or without a macrolide or a respiratory fluoroquinolone.[260] We know of no data to suggest that azithromycin and clarithromycin are different from each other in terms of bacteriological or clinical efficacy in CAP. The ketolides have exhibited good activity against *L. pneumophila* pneumonia in guinea pigs and the majority of pathogens known to cause pneumonia, making them potential future agents for use in CAP pending positive results in clinical trials.[20,255]

8.2 AECB

Antibacterial therapy of patients with AECB presenting with increased sputum production and sputum purulence along with dyspnea provides cure rates greater than placebo.[2] Although *M. catarrhalis*, *S. pneumoniae* and *H. parainfluenzae* cause AECB, *H. influenzae* is the most common cause of bacterial exacerbations and should be included in the spectrum of any antibacterial agent chosen as therapy. The suboptimal activity of erythromycin against *H. influenzae* makes it a less likely candidate for treatment. Other macrolides, however, such as azithromycin and clarithromycin, display greater activity against this organism and are considered to be useful and very well tolerated alternatives to second generation cephalosporins such as cefuroxime axetil or cefprozil.[2] Other than erythromycin, because of its poor activity versus *H. influenzae*, we know of no data to suggest that any of the macrolides is superior to another either bacteriologically or clinically in patients with AECB. In animal models the ketolides exhibit therapeutic efficacy equivalent to or better than that of azithromycin in the treatment of mice infected with *H. influenzae* and appear to be promising future treatments for patients with bacterial AECB.[255,261]

8.3 Otitis Media

Amoxicillin is recommended as first-line therapy for treatment for AOM.[262] Because of the increasing numbers of β-lactamase producing *M. catarrhalis* and *H. influenzae* as well as the rising prevalence of penicillin-resistant strains of *S. pneumoniae*, however, alternative treatment options are being considered.[2,48,49,262,263] Erythromycin is not the preferred treatment of otitis media because the marginal activity against *H. influenzae*.[264] Newer macrolides, such as azithromycin and clarithromycin, achieve high concentrations in the middle ear fluid are clinically effective and very well tolerated agents to use in patients with otitis media.[2,235,264] Whether the growing resistance to these agents, especially by penicillin-intermediate or penicillin-resistant *S. pneumoniae*, will limit the effective use of macrolides is unclear.[264] The ketolides have been shown to be effective against these resistant pathogens in animal models and their use in treatment of penicillin- and/or macrolide-resistant *S. pneumoniae* infections appears promising.[255]

8.4 Pharyngitis

The effectiveness of standard treatment of GABHS pharyngitis with penicillin is becoming of limited value because of the increasingly prevalent problem of bacteriological treatment failure (which may occur in up to 30% of patients) which may put patients at risk of sequelae and recurrence of infection.[265] Penicillin has also an inconvenient administration schedule as treatment requires multiple daily doses for an average of 10 days. Treatment alternatives such as erythromycin, clindamycin and cephalosporins (e.g. cefaclor) are also less convenient as they require multiple doses over 10 days. Newer macrolides such as azithromycin and clarithromycin are attractive options for pharyngitis treatment because of high therapeutic efficacy, safety and convenient administration regimens (once or twice daily, respectively).[265,266] We know do not know of any data to suggest that any of the new macrolides are different from each

Landscape table XV to be placed here.

other in terms of bacteriological or clinical efficacy.

8.5 Sinusitis

First-line therapy for patients with acute bacterial sinusitis is amoxicillin; however, increasing numbers of β-lactamase positive *H. influenzae* and *M. catarrhalis* and a rising prevalence of penicillin-resistant *S. pneumoniae* have created a need for alternative treatment options.[48,49,250,267] Newer macrolides such as azithromycin, clarithromycin and erythromycin-sulfisoxazole are all options approved for use in Canada. We know do not know of any data to suggest that any of the new macrolides are different from each other in terms of bacteriological or clinical efficacy. These agents are used for patients intolerant to β-lactams or as first-line treatment.[267,268] The ketolides appear to be promising future agents in the management of difficult to treat respiratory tract infections.[255]

9. Adverse Effects

Macrolides generally have a low adverse effect profile and are considered to be one of the safest classes of antibacterials currently available.[16,54,269] Adverse effects including GI disorders, allergic reactions, hepatotoxicity, ototoxicity and local irritation have been reported (table XV).[16,19,24,53,61,67,269-275] Unusual adverse effects include psychiatric complications, haemolytic anaemia, asthma, pancreatitis, infantile hypertrophic pyloric stenosis, exacerbation of myasthenia gravis, proarrhythmogenic effect and pseudomembranous colitis.[269] These adverse effects have been rarely reported and are not be discussed in this review.

Macrolide-associated GI intolerance is the most common adverse effect and is dose related.[269] Symptoms included abdominal pain, occasional cramping, flatulence, diarrhoea, nausea and vomiting.[269] The GI discomfort associated with the macrolides occurs through stimulation of GI contractility and the endogenous release of motilin.[269] Although the mechanism of action is unknown, it has been suggested that macrolides may bind to a motilin receptor, thus stimulating gut mo-

Table XV. Frequently occurring adverse effects of the macrolides (adapted from references[16,19,24,52,53,61,67,269-275])

Adverse effects	Erythromycin	Azithromycin	Clarithromycin	Dirithromycin	Roxithromycin	Spiramycin
Gastrointestinal						
abdominal pain	x	x	x	xx	x	x
nausea	xxx	x	x	x	x	x
vomiting	x	x/–	x/–	ND	x/–	x
diarrhoea	x	x	x	x	x/–	x
overall	xxx	x	x	xxx	x	x
allergic reactions	x	x/–	x/–	x/–	x/–	–
Hepatic function abnormality	xxx	x	x	ND	x	ND
Ototoxicity						
tinnitus	x	–	x/–	ND	x/–	ND
hearing loss	x	ND	ND	ND	ND	ND
Taste perversion	–/x	–/x	–/x	–	–	–
Central nervous system						
headache	x	x	x	x	x/–	ND
dizziness	x	x	x/–	ND	x/–	x

ND = no data available; **–** indicates adverse effect has not been observed; **x/–** indicates adverse effect occurs in <1% of patients; **x** indicates adverse effect occurs in 1-5% of patients; **xx** indicates adverse effect occurs in 5-10% of patients; **xxx** indicates adverse effect occurs in >10% of patients; **x/ND** indicates adverse effect is known to occur; however, no percentages were found.

tility.[53] The presence of the dimethylamino group and neutral sugar at C-3 of the lactone ring appear necessary for stimulation and is present only on 14- and 15-membered macrolides.[53,269] GI intolerance has been reported to occur in 20 to 50% of patients receiving erythromycin but occurs much less frequently with the newer macrolides (e.g. azithromycin, clarithromycin, roxithromycin) [table XV].[53,269,270] Intravenous erythromycin is associated with a higher incidence of GI intolerance compared with oral erythromycin.[270] A recent review of intravenous erythromycin use reported GI adverse effects were the most common reactions compared with matched cohorts.[270]

Hepatic effects reported with the macrolides may range from minor elevations of hepatic enzymes to hepatotoxicity (e.g. cholestatic jaundice) or rarely hepatic failure (table XV). Hepatic enzyme elevations have been reported for most macrolides, although hepatotoxicity has been associated with erythromycin estolate and also reported with troleandomycin.[24,269] Although the mechanism of action of hepatotoxicity is poorly understood, it is thought to involve a combination of hypersensitivity and toxic reaction.[269] These reactions appear to require a hydrophobic agent and the presence of an unhindered, readily accessible N-dimethylamino group.[269] Agents such as clarithromycin, flurithromycin, roxithromycin, miokamycin, josamycin and midecamycin have low hepatotoxic potentials, whereas those of azithromycin, dirithromycin, rokitamycin and spiramycin are almost negligible.[269,276]

Ototoxicity is a rare complication of erythromycin therapy but has generally occurred in patients receiving large dosages of erythromycin (≥4 g/day) in the presence of hepatic or renal impairment.[271] Symptoms include deafness or decreased hearing, tinnitus and vertigo.[271] The erythromycins appear to cause low tonal tinnitus or sensorineural hearing loss, particularly at frequencies above 4000Hz.[269] Risk factors include hepatic and/or renal dysfunction, age, female gender and dosages of erythromycin of 4 g/day or greater.[269,271] Although elevated serum erythromycin concentrations are causally related, the mechanism of injury has not been elucidated. In most cases, hearing loss is reversible returning to normal within a few days after discontinuation of the macrolide.[269] However, rare reports of prolonged or irreversible hearing loss have occurred.[269] Recently, a case of azithromycin associated ototoxicity (hearing loss, tinnitus) was reported.[271]

Local irritation or phlebitis is a common occurrence with the parenteral administration of erythromycin,[269,270] however, it is much less common with parenteral azithromycin.[277] Intravenous injections cause phlebitis, whereas intramuscular injections result in local pain.[269] Hypersensitivity or allergic reactions rarely occur in patients receiving macrolides.[67,269] Reactions may include erythema, maculopapular rash, urticarial eruptions, eczema, fixed drug eruption and toxic epidermal necrolysis.[269]

10. Drug Interactions

Macrolides are involved in drug interactions with many commonly administered agents (table XVI). Drug interactions with the macrolides may occur as a result of altered gastric emptying time or by alteration of GI flora or more commonly through inhibition of hepatic metabolism of the concomitant agent. A wide range of drug interactions are known to occur with the concomitant administration of erythromycin and specific therapeutic agents.[279] Only clinically significant drug interactions with selected agents (e.g. carbamazepine, cyclosporine, theophylline, antihistamines, digoxin, warfarin and benzodiazepines) are discussed in this section. These interactions occur as a result of complex formation and inactivation of the isoenzyme CYP3A4 by erythromycin in the liver resulting in the accumulation of the inhibited agent.[276,281]

The macrolides can be divided into 3 groups based on their level of interaction with liver enzymes. Group 1 consists of agents with strong microsomal interaction potential that are involved in numerous drug interactions (e.g. erythromycin, troleandomycin). Group 2 includes agents with

Table XVI. Drug interactions involving the macrolides (adapted from[13,53,276-285]). If no indication of interaction is provided then no data were available

Drug	Effect	Interaction	No interaction	Suspected[a]	Not suspected[b]
Alfentanil and sufentanil	Inhibition of alfentanil/sufentanil metabolism and results in decreased clearance	Erythromycin, troleandomycin, clarithromycin			
Oral anticoagulants	Inhibition of warfarin metabolism causes increases in the hypothrombinaemic effect of warfarin thus increasing prothrombin time and the probability of haemorrhage	Erythromycin, troleandomycin, clarithromycin	Roxithromycin, azithromycin		
Astemizole and terfenadine	Metabolic changes cause increased potential for QT interval prolongation, Torsade de Pointes, or ventricular arrhythmias therefore coadministration is contraindicated	Erythromycin, troleandomycin, clarithromycin			
Carbamazepine	Inhibition of carbamazepine hepatic metabolism causes an increase in carbamazepine serum concentration and a decrease in its clearance; macrolide effectiveness is decreased by its enhanced metabolism by carbamazepine induced CYP3A4	Erythromycin, troleandomycin, clarithromycin, flurithromycin, josamycin, miokamycin	Roxithromycin, azithromycin		Dirithromycin, rokitamycin, spiramycin
Cisapride	Cisapride is not recommended for use with erythromycin or clarithromycin due to potential for QT interval prolongation, Torsade de Pointes, or ventricular arrhythmias therefore coadministration is contraindicated	Erythromycin, clarithromycin		Troleandomycin	
Clozapine	Metabolism by CYP3A4 is slowed and therefore serum concentrations of clozapine increase which may lead to increased pharmacologic effect	Erythromycin		Troleandomycin, clarithromycin	
Cyclosporin	Inhibition of CYP3A4 metabolism and increased absorption/decreased metabolism of cyclosporin causes increases in blood levels, area under the curve, and decreases in drug clearance	Erythromycin, clarithromycin, josamycin, miokamycin	Azithromycin, spiramycin	Troleandomycin	Dirithromycin, rokitamycin, roxithromycin

Table XVI. Contd

Drug	Effect	Interaction	No interaction	Suspected[a]	Not suspected[b]
Digoxin	Increased concentrations of digoxin in the serum are caused by increased digoxin related products due to alterations in gastrointestinal flora	Erythromycin, clarithromycin, azithromycin		Troleandomycin, flurithromycin, josamycin, midecamycin, miokamycin, roxithromycin, dirithromycin, rokitamycin, spiramycin	
Disopyramide	Reduced clearance of disopyramide	Erythromycin, troleandomycin		Clarithromycin	
Ergot alkaloids	Inhibition of ergot metabolism may lead to ergotism	Erythromycin, troleandomycin, clarithromycin		Flurithromycin, josamycin, midecamycin, miokamycin, roxithromycin, azithromycin, dirithromycin, rokitamycin, spiramycin	
Felodipine	Inhibition of CYP3A4 metabolism leads to increases in felodipine serum concentrations and adverse effects	Erythromycin		Troleandomycin, clarithromycin	
Lovastatin	Cases of rhabdomyolysis have been reported	Erythromycin		Troleandomycin, clarithromycin	
Methylprednisone	Increased serum concentrations and decreased clearance of the agent is observed due to inhibition of its metabolism	Erythromycin, troleandomycin, clarithromycin			
Theophylline	Inhibition of CYP3A4 metabolism causes increased half-life and decreased clearance of theophylline	Erythromycin, troleandomycin, clarithromycin, roxithromycin	Josamycin, midecamycin, miokamycin, azithromycin, dirithromycin[c], rokitamycin, spiramycin		
Triazolam and midazolam	Inhibition of metabolism causes increased serum levels and effects	Erythromycin, troleandomycin, clarithromycin, roxithromycin	Azithromycin		
Valproic acid	Inhibition of metabolism by macrolides may cause increased serum valproate concentrations	Erythromycin, clarithromycin			

a No data available, however, a drug-drug interaction is suspected.

b No data available and no drug-drug interaction is suspected.

c Dirithromycin causes an increase in the clearance and a decrease in the steady state plasma concentrations and maximum serum concentrations of oral doses of theophylline.[269]

CYP = cytochrome P450.

lower affinity for CYP3A4 and hence less involvement in drug interactions (e.g. clarithromycin, flurithromycin, josamycin, midecamycin, miokamycin, roxithromycin). Group 3 agents have virtually no effect on hepatic metabolism and are not able to alter the pharmacokinetics of other agents (e.g. azithromycin, dirithromycin, rokitamycin, spiramycin).[276,281]

The clearance of carbamazepine is decreased by inhibition of hepatic metabolism by macrolides resulting in increased serum concentrations (table XVI).[279,281] Concomitant use of these agents should be avoided if possible. However, if coadministration is necessary, monitoring of serum carbamazepine concentrations should be performed as well as monitoring for signs and symptoms of toxicity (e.g. confusion, somnolence, ataxia, nausea and vomiting, vertigo).[279,281] There is no interaction between carbamazepine and azithromycin.[272]

Coadministration of macrolides with cyclosporin may interfere with the metabolism of cyclosporin and/or increase the rate and extent of absorption of cyclosporin resulting in substantial increases in cyclosporin concentrations and subsequent toxicity.[281] If concomitant administration is unavoidable, blood cyclosporin concentrations and serum creatinine levels should be monitored. In addition, cyclosporin dosage may be empirically decreased by 30 to 50% and adjusted based on desired cyclosporin concentrations. Azithromycin has not been reported to interact with cyclosporin.[272,279]

Serious cardiotoxic reactions have been associated with the combination of nonsedating histamine H_1 receptor antagonists (e.g. terfenadine, astemizole) and macrolides. These toxic reactions have resulted in the withdrawal of terfenidine and astemizole from the market. The inhibition of CYP3A4 metabolism may result in high concentrations of the aforementioned antihistamines resulting in potentially serious prolongation of the QT interval, torsades de pointes and ventricular arrhythmias.[272,279] Similar cardiac events have been associated with the concomitant use of cisapride and macrolides.[280] Hence, coadministration of these agents is contraindicated.

The interaction between erythromycin and theophylline has been well described. The clearance of theophylline may be decreased through concomitant administration of erythromycin usually occurring in patients receiving erythromycin for longer than 7 to 10 days.[279,281] Significant variability is observed in the impact that macrolides have on theophylline clearance.[279,281] This appears to be correlated with the duration of macrolide treatment, while the multiple sites of theophylline metabolism may also cause variability.[279] Careful monitoring should be undertaken as the narrow therapeutic index of theophylline may lead to concentration-dependent adverse effects.[279] There is interaction between theophylline and azithromycin.[279]

Interactions between macrolides and digoxin may lead to high serum digoxin concentrations.[281,284] This may occur as a result of an increase in digoxin bioavailability as a result enhanced gastric emptying induced by the macrolides, as well as by decreased metabolism of digoxin by *Eubacterium lentum* through elimination of this organism in the GI tract.[281,284] Although only erythromycin and clarithromycin have been proven to exert this effect, it is likely to be caused by other macrolides because of this unique mechanism of action.[284,285] If used concomitantly, digoxin concentrations should be monitored and the patient observed for signs of digoxin toxicity.

Initiation of erythromycin therapy in patients stabilised on oral anticoagulants such as warfarin may result in prolongation of prothrombin time and potential bleeding. Close monitoring of the prothrombin time or international normalised ratio is encouraged. Erythromycin may also result in the decreased clearance of midazolam and triazolam resulting in increased pharmacological effects of the benzodiazepine.[281] Macrolides inhibit this metabolism resulting in decreased clearance and increased serum concentrations. Coadministration of these agents should be avoided if possible, or the dose of the benzodiazepine should be decreased by

50% or the dose of midazolam is titrated to effect.[281,282]

11. Pharmacoeconomic Considerations

There is a paucity of pharmacoeconomic studies pertaining to the macrolides in North America. The majority of economic analyses in the literature have evaluated the oral macrolide formulations such as roxithromycin. Considerations in pharmacoeconomic evaluations of macrolides include acquisition cost, adverse effect profile, drug interaction potential, activity, frequency of administration (patient compliance), monitoring, cost of treatment failure (readmission, alternate antibacterials, secondary physician visit), morbidity, lost income/productivity and quality of life.[257]

In an nonblind study comparing oral roxithromycin (10 days) versus oral azithromycin (3 and 5 days) for pharyngitis, Carbon et al.[286] found similar clinical response rates between the 2 regimens. However, the total cost of care (4-week evaluation period) was higher (US$202.10) for roxithromycin compared with 3- and 5-day courses of azithromycin (US$193.60 and US$195.30, respectively. 1995 values).[286] In addition, patient compliance was noted to be significantly higher ($p < 0.01$) in the azithromycin study arm. in addition, there was a marked reduction in time absent from work with azithromycin compared with roxithromycin.[286] In studies comparing roxithromycin with erythromycin or amoxicillin/clavulanate, similar cost-effectiveness/cost-benefit trends in favour of roxithromycin have been reported.[287,288]

As with oral macrolides, there is also a paucity of economic data evaluating parenteral macrolides. A cost-minimisation study by Howard and colleagues[277] compared intravenous erythromycin and azithromycin for the treatment of patients with CAP over a 3-month period. Demographic and microbiological data were similar between the 2 groups of patients ($n = 25$ per arm). Phlebitis occurred in 9 patients in the erythromycin arm compared to none in the azithromycin arm ($p < 0.05$). The mean duration of therapy was 5.1 days for azithromycin and 5.6 for erythromycin.[277] The total cost of macrolide therapy including cost of complications (phlebitis) was $US66.46 for azithromycin versus $US96.56 in the erythromycin group (1998 values).[277] The authors concluded that there was no significant difference in costs between azithromycin or erythromycin in the intravenous treatment of CAP.[277]

Classen and colleagues[270] retrospectively evaluated the resource utilisation and cost impact of intravenous erythromycin use compared with newer macrolides in a matched group of hospitalised patients from 1990 to 1994. The attributable length of stay and cost of hospitalisation was 2.14 days and $US6061, respectively, in patients receiving erythromycin. Based on a linear regression model, patients receiving intravenous erythromycin had an increased cost of hospitalisation ($US1198) and increased length of stay (0.751).[270] The increase in costs and hospital stay was attributed to the prevalence of GI tolerance in patients receiving intravenous erythromycin. The authors hypothesised that if the newer macrolides were more tolerable, cost saving and decreased length of stay may occur from decreased GI adverse effects when compared with intravenous erythromycin.[270]

Further pharmacoeconomic studies evaluating the role of the oral and parenteral macrolides are essential to a balanced health economic assessment of these agents.

12. Formulary Considerations

With the availability of intravenous and oral macrolides, the conversion of therapy from parenteral to oral therapy is desirable. Significant cost reduction is observed as a result of decreased length of hospitalisation, decreased drug cost, and a decreased chance of secondary bacteraemias and phlebitis as intravenous lines are removed earlier in treatment.[289]

Factors that should be considered for using a macrolide include local/regional epidemiology, bacterial resistance, patterns of prescribing, severity of illness, tolerability profiles, drug interaction profiles, availability of other antibacterial regimens, patient considerations (compliance, administration

convenience) and patient/payer economic considerations.[183,290] Considerations in the paediatric use of oral macrolides include the taste and palatability of the formulation, abbreviated treatment duration, daily versus intermittent administration, administration with/without meals and the absence of having to administer a dose when the child is at school are factors which lead to increased compliance.[257] Other ancillary costs such as intravenous admixture costs (materials, labour, nursing time) may also need to be considered. All of these factors must be taken into consideration when a macrolide is reviewed for addition to a government, health organisation or hospital formulary.

13. Potential Use of Ketolides

The increasing prevalence of resistance is a growing problem. The prevalence of penicillin resistance in *S. pneumoniae* in Canada doubled between 1994-1995 and 1997-1998, and remains at about half of the level reported in the US.[48,107] The high incidence of penicillin resistance in *S. pneumoniae* has created a need for alternative clinical agents, and macrolides have increasingly been used to treat bacterial infections no longer susceptible to penicillins.[291,292] However, resistance to macrolides is also on the rise and studies have shown that penicillin-resistant strains of *S. pneumoniae* are more likely to be resistant to macrolides as well.[291-293] Resistance to antibacterials has also become a problem in other common respiratory pathogens. Production of β-lactamase in isolates of both *M. catarrhalis* and *H. influenzae* may be leveling off,[49] however the high levels now observed are also creating a requirement for alternative antibacterial therapy. No resistance to macrolides has been reported in *M. catarrhalis* but a low level of resistance to macrolides has been reported in *H. influenzae*.[49,294,295] Resistance to macrolides has also been reported in GABHS.[296]

The ketolides are being developed in an attempt to address the increasingly prevalent problem of macrolide-resistant and multiresistant organisms.[47] Ketolides may represent the future of macrolide treatment as resistance to macrolides is likely to continue to increase. The excellent activity of ketolides against resistant organisms will probably make them an ideal replacement for currently used macrolides. However, proper control of ketolide use will have to be maintained in order to prevent resistance to these agents developing.

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References

1. Shah F. Erythromycin. Pediatr Rev 1998; 19: 140-1
2. Charles L, Segreti J. Choosing the right macrolide antibiotic: a guide to selection. Drugs 1997; 53: 349-57
3. Cornish P, Tailor SAN. The new macrolides: azithromycin and clarithromycin. Metro Toronto Hospitals Drug Information Service 1994; 13: 20-41
4. Ballow CH, Amsden GW. Azithromycin: the first azalide antibiotic. Ann Pharmacother 1992; 26: 1253-61
5. Carbon C. Clinical relevance of intracellular and extracellular concentrations of macrolides. Infection 1995; 23 Suppl. 1: S10-4
6. Bryskier A. Novelties of the field of anti-infectives in 1997. Clin Infect Dis 1998; 27: 865-83
7. Mazzei T, Mini E, Novelli A, et al. Chemistry and mode of action of macrolides. J Antimicrob Chemother 1993; 31 Suppl. C: 1-9
8. Van KZ, Majer J. Macrolide antibiotics. In: Gottlieb D, Shaw PD, editors. Antibiotics. Vol. II: Biosynthesis. New York: Springer-Verlag, 1967: 154-88
9. Vazifeh D, Abdelghaffar H, Labro MT. Cellular accumulation of the new ketolide RU 64004 by human neutrophils: comparison with that of azithromycin and roxithromycin. Antimicrob Agents Chemother 1997; 41: 2099-107
10. Ma Z, Clark RF, Wong S, et al. Design synthesis and characterization of ABT-773: a novel ketolide highly active against multidrug resistant pathogens. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
11. Zhong P, Hammond R, Cao Z, et al. Molecular basis of ABT 773 activity against *erm*-containing macrolide resistant *S. pneumoniae*. Proceedings of the 39th Interscience Conference on Antimicrobial Agents Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
12. Carbon C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. Clin Infect Dis 1998; 27: 28-32
13. Gillis MC, editor. Compendium of pharmaceuticals and specialties, 34th ed. Ottawa: Canadian Pharmaceutical Association, 1999
14. Kirst HA, Sides GD. New directions for macrolide antibiotics: pharmacokinetics and clinical efficacy. Antimicrob Agents Chemother 1989; 33: 1419-22

15. Kirst HA. New macrolides: expanded horizons for an old class of antibiotics. J Antimicrob Chemother 1991; 28: 787-90
16. Bahal N, Nahata MC. The new macrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. Ann Pharmacother 1992; 26: 46-55
17. Kirst HA, Sides GD. New directions for macrolide antibiotics: structural modifications and *in vitro* activity. Antimicrob Agents Chemother 1989; 33: 1413-8
18. Piscitelli SC, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. Clin Pharm 1992; 11: 137-52
19. Sturgill MG, Rapp RP. Clarithromycin: review of a new macrolide antibiotic with improved microbiologic spectrum and favorable pharmacokinetic and adverse effect profiles. Ann Pharmacother 1992; 26: 1099-108
20. Edelstein PH, Edelstein MAC. *In vitro* activity of the ketolide HMR 3647 (RU 6647) for *Legionella* spp.; its pharmacokinetics in guinea pigs, and use of the drug to treat guinea pigs with *Legionella pneumophila* pneumonia. Antimicrob Agents Chemother 1999; 43: 90-5
21. Agouridas C, Bonnefoy A, Chantot JF. *In vitro* antibacterial activity of RU 004, a novel ketolide highly active against respiratory pathogens. Proceedings of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-20: San Francisco. Washington, DC: American Society for Microbiology, 1995
22. Shortridge D, Ramer NC, Beyer J, et al. The *in vitro* activity of ABT 773 against Gram-positive and Gram-negative pathogens. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
23. Brisson-Noël A, Trieu-Cuot P, Courvalin P. Mechanism of action of spiramycin and other macrolides. J Antimicrob Ther 1998; 22 Suppl. B: 13-23
24. Kucers A, Bennett NMcK. Erythromycin. In: Kucers A, Bennett NMcK, editors. The use of antibiotics: a comprehensive review with clinical emphasis, 4th ed. Philidelphia (PA): J.B. Lippincott Co., 1987: 851-77
25. Monro RE, Vazquez D. Ribosome-catalysed peptidyl transfer: effects of some inhibitors of protein synthesis. J Mol Biol 1967; 28: 161-5
26. Menninger JR, Otto DP. Erythromycin, carbomycin, and spiramycin inhibit protein synthesis by stimulating the dissociation of peptidyl-tRNA from ribosomes. Antimicrob Agents Chemother 1982; 21: 811-8
27. Menninger JR. Functional consequences of binding macrolides to ribosomes. J Antimicrob Chemother 1985; 16 Suppl. A: 23-4
28. Champney WS, Burdine R. Macrolide antibiotics inhibit 50S ribosomal subunit assembly in *Bacillus subtilis* and *Staphylococcus aureus*. Antimicrob Agents Chemother 1995; 39: 2141-4
29. Jamjian C, Biedenbach DJ, Jones RN. *In vitro* evaluation of a novel ketolide antimicrobial agent, RU-64004. Antimicrob Agents Chemother 1997; 41: 454-9
30. Agouridas C, Collette P, Mauvais P, et al. RU 004: preliminary studies on the mechanism of action. Proceedings of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-20: San Francisco. Washington, DC: American Society for Microbiology, 1995
31. Cao Z, Hammond R, Pratt S, et al. Mechanism of action for novel ketolide ABT 773. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
32. Xiong L, Shah S, Mauvais P, et al. Interaction of macrolides and ketolides with the ribosome. Mol Microbiol 1999; 31: 633-9
33. Leclercq R, Courvalin P. Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. Antimicrob Agents Chemother 1991; 35: 1267-72
34. Weisblum B. Erythromycin resistance by ribosome modification. Antimicrob Agents Chemother 1995; 39: 577-85
35. Roberts MC, Sutcliffe J, Courvalin P, et al. Nomenclature for macrolide and macrolide-lincosamide-streptogramin B resistance determinants. Antimicrob Agents Chemother 1999; 43: 2823-30
36. Cocito C, Di Giambattista M, Nyssen E, et al. Inhibition of protein synthesis by streptogramins and related antibiotics. J Antimicrob Chemother 1997; 39 Suppl. A: 7-13
37. Hummel H, Böck A. Ribosomal changes resulting in antimicrobial resistance. In: Bryan LE. Handbook of experimental pharmacology – microbial resistance to drugs. Vol. 91. New York (NY): Springer-Verlag, 1989: 43-64
38. Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. Antimicrob Agents Chemother 1991; 35: 1273-6
39. Nikaido H. Prevention of drug access to bacterial targets: permeability barriers and active efflux. Science 1994; 264: 382-8
40. Sutcliffe J, Tait-Kamradt A, Wondrack L. *Streptococcus pneumoniae* and *Streptococcus pyogenes* resistant to macrolides but sensitive to clindamycin: a common resistance pattern mediated by an efflux system. Antimicrob Agents Chemother 1996; 40: 1817-24
41. Johnston NJ, de Azavedo JC, Kellner JD, et al. Prevalence and characterization of the mechanisms of macrolide, lincosamide, and streptogramin resistance in isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother 1998; 42: 2425-6
42. Clancy J, Dib-Hajj F, Petitpas J, et al. Cloning and characterization of a novel macrolide efflux gene, mreA, from *Streptococcus agalactiae*. Antimicrob Agents Chemother 1997; 41: 2719-23
43. Goldman RC, Capobianco JO. Role of an energy-dependent efflux pump in plasmid pNE24-mediated resistance to 14- and 15-membered macrolides in *Staphylococcus epidermidis*. Antimicrob Agents Chemother 1990; 34: 1973-80
44. Shortridge VD, Flamm RK, Ramer N, et al. Novel mechanism of macrolide resistance in *Streptococcus pneumoniae*. Diagn Micro Infect Dis 1996; 26: 73-8
45. Bonnefoy A, Girard AM, Agouridas C, et al. Ketolides lack inducibility properties of MLS_B resistance phenotype. J Antimicrob Chemother 1997; 40: 85-90
46. Rosato A, Vicarini H, Bonnefoy A, et al. A new ketolide, HMR 3004, active against streptococci inducibly resistant to erythromycin. Antimicrob Agents Chemother 1998; 42: 1392-6
47. Agouridas C, Bonnefoy A, Chantot JF. Antibacterial activity of RU 64004 (HMR 3004), a novel ketolide derivative active against respiratory pathogens. Antimicrob Agents Chemother 1997; 41: 2149-58
48. Zhanel GG, Karlowsky JA, Palatnick L, et al. Prevalence of antimicrobial resistance in respiratory tract isolates of *Streptococcus pneumoniae*: results of a Canadian national surveillance study. Antimicrob Agents Chemother 1999; 43: 2504-9
49. Zhanel GG, Karlowsky JA, Low DE, et al. Antibiotic resistance in respiratory tract isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* collected from across Canada in 1997-1998. J Antimicrob Chemother 2000; 45: 655-62

50. Hardy DJ, Hensey DM, Beyer JM, et al. Comparative *in vitro* activities of new 14-, 15-, and 16-membered macrolides. Antimicrob Agents Chemother 1988; 32: 1710-9
51. Dunn CJ, Barradell LB. Azithromycin: a review of its pharmacological properties and use as 3-day therapy in respiratory tract infections. Drugs 1996; 51: 483-505
52. Langtry HD, Brogden RN. Clarithromycin: a review of its efficacy in the treatment of respiratory tract infections in immunocompetent patients. Drugs 1997; 53: 973-1004
53. Williams JD, Sefton AM. Comparison of macrolide antibiotics. J Antimicrob Chemother 1993; 31 Suppl. C: 11-26
54. Peters DH, Friedel HA, McTavish D. Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs 1992; 44: 750-99
55. Hoepelman IM, Schneider ME. Azithromycin: the first of the tissue-selective azalides. Int J Antimicrob Agents 1995; 5: 145-67
56. Schülin T, Wennersten CB, Moellering Jr RC, et al. *In vitro* activity of RU 64004, a ketolide antibiotic, against Gram-positive bacteria. Antimicrob Agents Chemother 1997; 41: 1196-202
57. Barry AL, Fuchs PC, Brown SD. *In vitro* activities of the ketolide HMR 3647 against recent Gram-positive clinical isolates and *Haemophilus influenzae*. Antimicrob Agents Chemother 1998; 42: 2138-40
58. Hoban DJ, Karlowsky JA, Palatnick L, et al. Telithromycin (HMR 3647) is highly active against Canadian pharyngeal isolates of *Streptococcus pyogenes*. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
59. Mandell LA. The renaissance of the macrolides: new and changing roles in infectious diseases. Can J Infect Dis 1993; 4 Suppl. A: 1A-4A
60. Fong IW. An overview of the activity of clarithromycin against *H. influenzae*. Infect Med 1993 Dec; Suppl.: 41-6
61. Lonks JR, Medieros AA. Activity of clarithromycin compared to erythromcyin against *Streptococcus pneumoniae* isolated from blood cultures. Proceedings of the 1st International Conference on the Macrolides, Azalides and Streptogramins; 1992 Jan 21-24: Santa Fe
62. Hoban DJ, Zhanel GG, Karlowsky JA. *In vitro* activity of the novel ketolide HMR 3647 and comparative oral antibiotics against Canadian respiratory tract isolates of *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. Diagn Microbiol Infect Dis 1999; 35: 37-44
63. Pankuch GA, Hoellman DB, Lin G, et al. Activity of HMR 3647 compared to those of five agents against *Haemophilus influenzae* and *Moraxella catarrhalis* by MIC determination and time-kill assay. Antimicrob Agents Chemother 1998; 42: 3032-4
64. Bauerfeind A. *In-vitro* activity of dirithromycin in comparison with other new and established macrolides. J Antimicrob Chemother 1993; 31 Suppl. C: 39-49
65. Reinert RR, Bryskier A, Lütticken R. *In vitro* activities of the new ketolide antibiotics HMR 3004 and HMR 3647 against *Streptococcus pneumoniae* in Germany. Antimicrob Agents Chemother 1998; 42: 1509-11
66. Pankuch GA, Visalli MA, Jacobs MR, et al. Susceptibilities of penicillin- and erythromycin-susceptible and -resistant pneumococci to HMR 3647 (RU 66647), a new ketolide, compared with susceptibilities to 17 other agents. Antimicrob Agents Chemother 1998; 42: 624-30
67. McConnell SA, Amsden GW. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. Pharmacotherapy 1999; 19: 404-15
68. Hamilton-Miller JM, Shah S. Comparative *in-vitro* activity of ketolide HMR 3647 and four macrolides against Gram-positive cocci of known erythromycin susceptibility status. J Antimicrob Chemother 1998; 41: 649-53
69. Karlowsky JA, Zhanel GG, Hoban DJ. Activity of the ketolide telithromycin (HMR 3647) against erythromycin-resistant isolates of *S. pneumoniae*. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
70. Barry AL, Fuchs PC, Brown SD. *In vitro* activity of the new ketolide HMR 3004 compared to an azalide and macrolides against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Eur J Clin Microbiol Infect Dis 1997; 16: 767-9
71. Ednie LM, Spangler SK, Jacobs MR, et al. Susceptibilities of 228 penicillin- and erythromycin-susceptible and -resistant pneumococci to RU-64004, a new ketolide, compared with susceptibilities to 16 other agents. Antimicrob Agents Chemother 1997; 41: 1033-6
72. Hoban DJ, Zhanel GG, Bellyou T, et al. Telithromycin (HMR 3647) demonstrates axcellent activity against clinical isolates of *Streptococcus pyogenes* and *Streptococcus pneumoniae* with M and MLS_B resistance phenotypes. Proceedings of the 5th International Conference on Macrolides Azalides Streptogramins Ketolides and Oxazolidinones; 2000 Jan 26-28: Seville
73. Shortridge D, Ramer NC, Beyer J, et al. The *in vitro* activity of ABT-773 against Gram-positive respiratory pathogens. Proceedings of the 5th International Conference on Macrolides Azalides Streptogramins Ketolides and Oxazolidinones; 2000 Jan 26-28: Seville
74. Neu HC. Clinical microbiology of azithromycin. Am J Med 1991; 91 Suppl. 3A: 12S-8S
75. Drew RH, Gallis HA. Azithromycin-spectrum of activity, pharmacokinetics, and clinical applications. Pharmacother 1992; 12: 161-73
76. Schülin T, Wennersten CB, Moellering Jr RC, et al. *In-vitro* activity of the new ketolide antibiotic HMR 3647 against Gram-positive bacteria. J Antimicrob Chemother 1998; 42: 297-301
77. Hoelleman DB, Bajaksouzian S, Jacobs MR, et al. Activity of HMR 3647 compared to 4-macrolides and pristinamycin against *H. influenzae* and *M. catarrhalis* by MIC. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington (DC): American Society for Microbiology, 1998
78. Hoban D, Karlowsky J, Worobec E, et al. *In vitro* activity of the ketolide HMR 3647 and comparative macrolides against *Streptococcus pneumonaie, Haemophilus influenzae* and *Moraxella catarrhalis* isolated from 18 medical centres across Canada. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
79. Inoue M, Sato Y, Kuga A, et al. The novel ketolide HMR 3647 shows high activity against Gram-positive cocci. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
80. MacGowan AP, Wootton M, Janowska A, et al. *In vitro* activity of HMR 3647 against *S. pneumoniae* and *H. influenzae* an-

alysed on the basis of erythromycin or cefuroxime susceptibility. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998

81. Otsuki M, Harada H, Nishino T. *In vitro* antibacterial activity of HMR 3647, a new ketolide antibiotic. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
82. Verhaegen J, Verbist L. *In vitro* activity of the new ketolide HMR 3647 against Gram-positive cocci either suceptible or resistant to erythromcyin. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
83. Okamoto H, Miyazaki S, Ishii Y, et al. *In vitro* and *in vivo* antibacterial activities of HMR 3647 against penicillin-susceptible and -resistant *Streptococcus pneumoniae*. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
84. Coccuzza CE, Tomasini A, Renzetti D, et al. Ketolide (HMR 3647) *in vitro* activity on 4000 strains of *Streptococcus pyogenes* isolated in northern Italy. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
85. Hoban D, Palatnick L, Weshnowski B, et al. The novel ketolide HMR 3647 is highly active against worldwide isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
86. Ednie L, Jacobs M, Appelbaum P. Antianaerobic activity of the ketolide HMR 3647 compared to 12 other compounds. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
87. Agouridas C, Bonnefoy A, Chantot JF. *In vitro* antibacterial activity of HMR 3647, a novel ketolide highly active against respiratory pathogens. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
88. Felmingham D, Robbins MJ, Clark S, et al. The comparative *in vitro* activity of HMR 3647 against speciated coagulase-negative *Stapyhylococcus* spp. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
89. Roblin PM, Hammerschlag MR. *In vitro* activity of a new ketolide antibiotic, HMR 3647, against *Chlamydia pneumoniae*. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
90. Hoban D, Palatnick L, Balko TV, et al. *In vitro* activity of a novel ketolide HMR 3647 and comparative macrolides against worldwide *Haemophilus influenzae* (HI) isolates. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
91. Torres C, Zarazaga M, Tenorio C, et al. *In vitro* activity of the new ketolide HMR3647 in comparison with those of macrolides and pristinamycins against *Enterococcus* spp. Antimicrob Agents Chemother 1998; 42: 3279-81
92. Lin G, Bajaksouzian S, Jacobs MR, et al. Activity of ABT 773 (a new ketolide) compared with 11 agents against *H. influenzae* and *M. catarrhalis* by MIC. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sept 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
93. Barry AL, Fuchs PC, Brown SD. Comparative *in vitro* antimicrobial activity of ABT 773 and tentative disk test interpretive criteria. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
94. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, fourth edition. Approved M7-A4. Villanova (PA): National Committee for Clinical Laboratory Standards, 1997
95. Ednie LM, Jacobs MR, Appelbaum PC. Comparative antianaerobic activities of the ketolides HMR 3647 (RU 66674) and HMR 3004 (RU 64004). Antimicrob Agents Chemother 1997; 41: 2019-22
96. Ednie LM, Spangler SK, Jacobs MR, et al. Antianaerobic activity of the ketolide RU 64004 compared to activities of four macrolides, five β-lactams, clindamycin, and metronidazole. Antimicrob Agents Chemother 1997; 41: 1037-41
97. Bryskier A. Roxithromycin: review of its antimicrobial activity. J Antimicrob Chemother 1998; 41 Suppl. B : 1-21
98. Citron DM, Kwok YY, Appleman MD. *In vitro* activity of ABT-773 against 362 clinical isolates of anaerobic bacteria. Proceedings of the 5th International Conference on Macrolides Azalides Streptogramins Ketolides and Oxazolidinones; 2000 Jan 26-28: Seville
99. Roblin PM, Hammerschlag MR. *In vitro* activity of a new ketolide antibiotic, HMR 3647, against *Chlamydia pneumoniae*. Antimicrob Agents Chemotherapy 1998; 42: 1515-6
100. Soriano F, Fernández-Roblas R, Calvo R, et al. *In vitro* susceptibilities of aerobic and facultative non-spore-forming Gram-positive bacilli to HMR 3647 (RU 66647) and 14 other antimicrobials. Antimicrob Agents Chemother 1998; 42: 1028-33
101. Schülin T, Wennersten CB, Ferraro MJ, et al. Susceptibilities of *Legionella* spp. to newer antimicrobials *in vitro*. Antimicrob Agents Chemother 1998; 42: 1520-3
102. Bébéar CM, Renaudin H, Aydin MD, et al. *In vitro* activity of ketolides against mycoplasmas. J Antimicrob Chemother 1997; 39: 669-70
103. Bébéar CM, Renaudin H, Bryskier A, et al. Activity of telithromycin (HMR 3647) a new ketolide antimicrobial against human mycoplasmas. Proceedings of the 5th International Conference on Macrolides Azalides Streptogramins Ketolides and Oxazolidinones; 2000 Jan 26-28: Seville
104. Jung R, Li DH, Pendland SL, et al. Intracellular activity of ABT 773 and other antimicrobial agents against *Legionella pneumophila* isolates. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
105. Strige S, Roblin PM, Reznik T, et al. In vitro activity of ABT-773 a new ketolide antibiotic against *Chlamydia pneumoniae*. Proceedings of the 5th International Conference on Macrolides Azalides Streptogramins Ketolides and Oxazolidinones; 2000 Jan 26-28: Seville
106. Anderson DM, editor. Dorland's illustrated medical dictionary. 28th ed. Toronto: WB Saunders Co., 1994

107. Doern GV, Pfaller MA, Kugler K, et al. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial program. Clin Infect Dis 1998; 27: 764-70
108. Felmingham D, Washington J, Alexander Project. Trends in the antimicrobial susceptibility of bacterial respiratory tract pathogens: findings of the Alexander Project 1992-1996. J Chemother 1999; 11: 5-21
109. Zhanel G, Laing N, Karlowsky J, et al. *In vitro* pharmacodynamic modelling of clarithromycin versus *mef*A and *erm*B macrolide resistant *Streptococcus pneumoniae*. Proceedings of the 26th International Congress of Chemotherapy (ICC); 2001: Amsterdam
110. Lambert HP, O'Grady FW. Macrolides. In: Lambert HP, O'Grady FW, editors. Antibiotics and chemotherapy. 6th ed. New York (NY): Churchill Livingstone, 1992: 168-79
111. Berry V, Thorburn CE, Knott SJ, et al. Bacteriological efficacies of three macrolides compared with those of amoxicillin-clavulanate against *Streptococcus pneumoniae* and *Haemophilus influenzae*. Antimicrob Agents Chemother 1998; 42: 3193-9
112. Bergogne-Bérézin E. Tissue distribution of dirithromycin: comparison with erythromycin. J Antimicrob Chemother 1993; 31 Suppl. C: 77-87
113. Geerdes-Fenge HF, Goetschi B, Rau M, et al. Comparative pharmacokinetics of dirithromycin and erythromycin in normal volunteers with special regard to accumulation in polymorphonuclear leukocytes and in saliva. Eur J Clin Pharmacol 1997; 53: 127-33
114. Nilsen OG. Comparative pharmacokinetics of macrolides. J Antimicrob Chemother 1987; 20 Suppl. B: 81-8
115. Drusano GL, Goldstein FW. Relevance of the Alexander Project: pharmacodynamic considerations. J Antimicrob Chemother 1996; 38 Suppl. A: 141-54
116. Nightingale CH. Pharmacokinetics and pharmacodynamics of newer macrolides. Pediatr Infect Dis 1997; 16: 438-43
117. Puri SK, Lassman HB. Roxithromycin: a pharmacokinetic review of a macrolide. J Antimicrob Chemother 1987; 20 Suppl. B: 89-100
118. Young RA, Gonzalez JP, Sorkin EM. Roxithromycin: a review of its activity, pharmacokinetic properties and clinical efficacy. Drugs 1989; 37: 8-41
119. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990; 25 Suppl. A: 73-82
120. Rapp RP. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. Ann Pharmacother 1998; 32: 785-93
121. Langtry HD, Balfour JA. Azithromycin: a review of its use in paediatric infectious diseases. Drugs 1998; 56: 273-97
122. Scholz H, Noack R. Multicenter, randomized, double-blind comparison of erythromycin estolate versus amoxicillin for the treatment of acute otitis media in children. Eur J Clin Microbiol Infect Dis 1998; 17: 470-8
123. Powers JL. Properties of azithromycin that enhance the potential for compliance in children with upper respiratory tract infections. Pediatr Infect Dis J 1996; 15: S30-7
124. Kucers A, Bennett NMcK. Spiramycin, josamycin and rosaramicin. In: Kucers A, Bennett NMcK, editors. The use of antibiotics: a comprehensive review with clinical emphasis, 4th ed. Philidelphia (PA): J.B. Lippincott Co., 1987: 883-92
125. Rubenstein E, Keller N. Spiramycin renaissance. J Antimicrob Chemother 1998; 42: 572-6
126. Strausbaugh L, Bolton K, Dilworth J. Comparative pharmacology of josamycin and erythromycin stearate. Antimicrob Agents Chemother 1976; 10: 450-6
127. Lenfant B, Sultan E, Wable C, et al. Pharmacokinetics of 800 mg once-daily oral dosing of the ketolide, HMR 3647, in healthy young volunteers. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
128. Gemmell CG. Macrolides and host defences to respiratory tract pathogens. J Hosp Infect 1991; 19 Suppl. A: 11-9
129. McDonald PJ, Pruul H. Phagocyte uptake and transport of azithromycin. Eur J Clin Microbiol Infect Dis 1991; 10: 828-33
130. Honeybourne D, Baldwin DR. The site concentrations of antimicrobial agents in the lung. J Antimicrob Chemother 1992; 30: 249-60
131. Bergogne-Bérézin E. Predicting the efficacy of antimicrobial agents in respiratory infections: is tissue concentration a valid measure? J Antimicrob Chemother 1995; 35: 363-71
132. Scaglione F, Fraschini F. Distribution of clarithromycin and its metabolite (14-OH) in therapeutically relevant respiratory tract tissues and fluids. Proceedings of the 1st International Conference on the Macrolides, Azalides and Streptogramins; 1992 Jan 21-24: Santa Fe
133. Fraschini F, Scaglione F, Pintucci G, et al. The diffusion of clarithromycin and roxithromycin into nasal mucosa, tonsil and lung in humans. J Antimicrob Chemother 1991; 27 Suppl. A: 61-5
134. Serieys CM, Cantalloube C, Soler P, et al. The ketolide antimicrobial, HMR 3647, achieves high and sustained concentrations in broncho-pulmonary tissues [abstract]. Proceedings of the International Congress of Chemotherapy; 1999 Jul 4-7: Birmingham. J Antimicrob Chemother 1999; 44 Suppl. A: 78
135. Pierre J, Bergogne-Bérézin E, Kafe H, et al. The penetration of macrolides into bronchial secretions. J Antimicrob Chemother 1985; 16 Suppl. A: 217-20
136. Fietta A, Boeri P, Colombo ML, et al. Uptake of flurithromycin by human polymorphonuclear phagocytes: partial characterization of the entry mechanism. Chemother 1992; 38: 433-40
137. Rimoldi R, Mangiarotti P, de Rose V, et al. Penetration of roxithromycin into bronchial secretions. Br J Clin Pract 1987; Suppl. 55 : 74-7
138. Bergogne-Bérézin E. Tissue distribution of roxithromycin. J Antimicrob Chemother 1987; 20 Suppl. B: 113-20
139. Baldwin DR, Ashby JP, Andrews JM, et al. Pulmonary disposition of azithromycin following a single 500 mg oral dose. Thorax 1990; 45: 324P
140. Olsen KM, San Pedro GS, Gann LP, et al. Intrapulmonary pharmacokinetics of azithromycin in healthy volunteers given five oral doses. Antimicrob Agents Chemother 1996; 40: 2582-5
141. Conte Jr JE, Golden J, Duncan S, et al. Single-dose intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin, and cefuroxime in volunteer subjects. Antimicrob Agents Chemother 1996; 40: 1617-22
142. Chastre J, Brun P, Fourtillan JB, et al. Pulmonary disposition of roxithromycin (RU 28965), a new macrolide antibiotic. Antimicob Agents Chemother 1987; 31: 1312-6
143. Brun Y, Forey F, Gamondes JP, et al. Levels of erythromycin in pulmonary tissue and bronchial mucus compared to those of amoxicillin. J Antimicrob Chemother 1981; 8: 459-66
144. Bergogne-Bérézin E. Azithromycine: pharmacologie tissulaire. Pathol Biol 1995; 43: 498-504
145. Tsang KWT, Roberts P, Read RC, et al. The concentrations of clarithromycin and its 14-hydroxy metabolite in sputum of

patients with bronchiectasis following single dose oral administration. J Antimicrob Chemother 1994; 33: 289-97
146. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 1996; 15: 255-9
147. Pukander J, Rautianen M. Penetration of azithromycin into middle ear effusions in acute and secretory otitis media in children. J Antimicrob Chemother 1996; 37 Suppl. C: 53-61
148. Gan VN, McCarty JM, Chu SY, et al. Penetration of clarithromycin into middle ear fluid of children with acute otitis media. Pediatr Infect Dis J 1997; 16: 39-43
149. Falchi M, Teodori F, Carraro A, et al. Penetration of erythromycin into tonsillar tissue. Curr Med Res Opin 1985; 9: 611-5
150. Begue P, Lacombe H, Cotin G, et al. Diffusion of roxithromycin into tonsillar tissue in children. Br J Clin Pract 1987; Suppl. 55: 78-9
151. Giamarellou H, Petrikkos G, Moschovakis E, et al. Clarithromycin pharmacokinetics in sinus secretions of patients suffering from chronic maxillary sinusitis. Proceedings of the 1st International Conference on the Macrolides, Azalides and Streptogramins; 1992 Jan 21-24: Santa Fe
152. Wise R. The pharmacokinetics of azithromycin. Rev Contemp Pharmacother 1994; 5: 329-40
153. Schentag JJ, Ballow CH. Tissue-directed pharmacokinetics. Am J Med 1991; 91 Suppl. 3A: 5S-11S
154. Ishiguro M, Koga H, Kohno S, et al. Penetration of the macrolides into human polymorphonuclear leukocytes. J Antimicrob Chemother 1989; 24: 719-29
155. Vazifeh D, Preira A, Bryskier A, et al. Interactions between HMR 3647, a new ketolide, and human polymorphonuclear neutrophils. Antimicrob Agents Chemother 1998; 42: 1944-51
156. Garcia I, Pascual A, Ballesta S, et al. Uptake and intracellular activity of HMR 3647 in human phagocytic and non-phagocytic cells. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
157. Mtairag EM, Abdelghaffar H, Douhet C, et al. Intraphagocytic location of macrolides. Antimicrob Agents Chemother 1995; 39: 1676-82
158. Lenfant B, Perret C, Pascual MH. The bioavailability of HMR 3647, a new once-daily ketolide antimicrobial, is unaffected by food [abstract]. Proceedings of the International Congress of Chemotherapy; 1999 Jul 4-7: Birmingham. J Antimicrob Chemother 1999; 44 Suppl. A: 69
159. Hernandez L, Sadrzadeh N, Krill S, et al. Preclinical pharmacokinetic profile of ABT 773 in mouse, rat, monkey and dog. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
160. Schwab JC, Mandell GL. The importance of penetration of antimicrobial agents into cells. Infect Dis Clin North Am 1989; 3: 461-7
161. Rakita RM. Intracellular activity, potential clinical uses of antibiotics: several newer macrolides and quinolones that reach high levels in host cells are effective against intracellular pathogens. ASM News 1998; 64: 570-5
162. Mtairag EM, Abdelghaffar H, Labro MT. Investigation of dirithromycin and erythromycylamineerythromycylamine uptake by human neutrophils *in vitro*. J Antimicrob Chemother 1994; 33: 523-36
163. Gladue RP, Bright GM, Isaacson RE, et al. *In vitro* and *in vivo* uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrob Agents Chemother 1989; 33: 277-82
164. Tulkens, PM. Intracellular distribution and activity of antibiotics. Eur J Clin Microbiol Infect Dis 1991; 10: 100-6
165. Bohte R, van't Wout JW, Lobatto S, et al. Efficacy and safety of azithromycin versus benzylpenicillin or erythromycin in community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 1995; 14: 182-7
166. Lode H, Garau J, Grassi C, et al. Treatment of community-acquired pneumonia: a randomized comparison of sparfloxacin, amoxycillin-clavulanic acid and erythromycin. Eur Respir J 1995; 8: 1999-2007
167. Liippo K, Tala E, Puolijoki H, et al. A comparative study of dirithromycin and erythromycin in bacterial pneumonia. J Infect 1994; 28: 131-9
168. Hernández JM, Sides GD, Conforti PM, et al. Clinical efficacy of dirithromycin in patients with bacteremic pneumonia. Clin Ther 1996; 18: 1128-38
169. Jang TN, Lui CY, Wang FD, et al. A randomized comparative study on the safety and efficacy of clarithromycin and erythromycin in treating community-acquired pneumonia. Chin Med J 1995; 55: 302-6
170. Block S, Hedrick J, Hammerschlag MR, et al. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatr Infect Dis J 1995; 14: 471-7
171. Wasilewski MM, Johns D, Sides GD. Five-day dirithromycin therapy is as effective as seven-day erythromycin therapy for acute exacerbations of chronic bronchitis. J Antimicrob Chemother 1999; 43: 541-8
172. Kawahara S, Watanabe Y, Matsuka Y, et al. Inhibitory effect of ofloxacin on acute exacerbations of chronic respiratory tract infections in comparison with erythromycin. Drugs 1995; 49 Suppl. 2: 414-5
173. Peterson K, Phillips RS, Soukups J, et al. The effect of erythromycin on resolution of symptoms among adults with pharyngitis not caused by Group A Streptococcus. J Gen Intern Med 1997; 12: 95-101
174. McCarty JM. Comparative efficacy and safety of cefprozil versus penicillin, cefaclor and erythromycin in the treatment of streptococcal pharyngitis and tonsillitis. Eur J Microbiol Infect Dis 1994; 13: 846-50
175. Adam D, Scholz H, Pharyngitis Study Group. Five days of erythromycin estolate versus ten days of penicillin V in the treatment of Group A streptococcal tonsillopharyngitis in children. Eur J Clin Microbiol Infect Dis 1996; 15: 712-7
176. Esposito S, De Ritis G, D'Errico G, et al. Clinical comparison of cefaclor twice daily versus amoxicillin-clavulanate or erythromycin three times daily in the treatment of patients with streptococcal pharyngitis. Clin Ther 1998; 20: 72-9
177. Roord JJ, Wolf BHM, Goossens MMHT, et al. Prospective open randomized study comparing efficacies and safeties of a 3-day course of azithromycin and a 10-day course of erythromycin in children with community-acquired acute respiratory tract infections. Antimicrob Agents Chemother 1996; 40: 2765-8
178. Cars O, Nyström T, Engstrand L. Pharmacodynamic studies of the ketolides HMR 3647 and 3004 on extracellular and intracellular *Heliobacter pylori*. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
179. Gia HP, Roeder V, Namour F, et al. The new ketolide, HMR 3647, achieves high and sustained concentrations in white

blood cells in man [abstract]. Proceedings of the International Congress of Chemotherapy; 1999 Jul 4-7: Birmingham. J Antimicrob Chemother 1999; 44 Suppl. A: 79
180. Craig WA. Choosing an antibiotic on the basis of pharmacodynamics. Ear Nose Throat J 1998; 77 Suppl. 6: 7-11
181. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998; 26: 1-10
182. Zhanel GG, Craig WA. Pharmacokinetic contributions to postantibiotic effects: focus on aminoglycosides. Clin Pharmacokinet 1994; 27: 377-92
183. Zhanel GG, Walkty A, Vercaigne L, et al. The new fluoroquinolones: a critical review. Can J Infect Dis 1999; 10: 1-33
184. Zhanel GG, Ennis K, Vercaigne L, et al. The new fluoroquinolones: focus on respiratory infections. Drugs. In press
185. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993; 37: 1073-81
186. Thomas JK, Forrest A, Bhaunani SM, et al. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. Antimicrob Agents Chemother 1998; 42: 521-7
187. Zhanel GG, Hoban DJ, Harding GKM. Postantibiotic effect: a review of *in vitro* and *in vivo* data. Ann Pharmacother 1991; 25: 478-84
188. Odenholt-Tornqvist I, Löwdin E, Cars O. Postantibiotic effects and postantibiotic sub-MIC effects of roxithromycin, clarithromycin, and azithromycin on respiratory tract infections. Antimicrob Agents Chemother 1995; 39: 221-6
189. Boswell FJ, Andrews JM, Wise R. Pharmacodynamic properties of HMR 3647, a novel ketolide, on respiratory pathogens, enterococci and *Bacteroides fragilis* demonstrated by studies of time-kill kinetics and postantibiotic effect. J Antimicrob Chemother 1998; 41: 149-53
190. Neuhauser MM, Prause JL, Li DH, et al. *In vitro* bactericidal activity of ABT 773 a new ketolide versus clarithromycin, azithromycin, ciprofloxacin, amoxicillin/clavulanate against penicillin/erythromycin sensitive and resistant *S. pneumoniae* and *H. influenzae*. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
191. Odenholt I, Lowdin E, Cars O. Pharmacodynamic studies of HMR 3646 *in vitro* against respiratory tract pathogens. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
192. Dubois J, St. Pierre C. Post antibiotic effect (PAE) and bactericidal activity of HMR 3647 and other antimicrobial agents against respiratory pathogens. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
193. Schönwald S, Barsi B, Klinar I, et al. Three-day azithromycin compared with ten-day roxithromycin treatment of atypical pneumonia. Scand J Infect Dis 1994; 26: 706-10
194. Rizzato G, Montemurro L, Montanari G, et al. Efficacy of a three day course of azithromycin in moderately severe community-acquired pneumonia. Eur Respir J 1995; 8: 398-402
195. Roblin PM, Hammerschlag MR. Microbiological efficacy of azithromycin and susceptibilities to azithromycin of isolates of *Chlamydia pneumoniae* from adults and children with community-acquired pneumonia. Antimicrob Agents Chemother 1998; 42: 194-6
196. Harris JAS, Kolokathis A, Campbell M, et al. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J 1998; 17: 865-71
197. Wubbel L, Muniz L, Ahmed A, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. Pediatr Infect Dis J 1999; 18: 98-104
198. Kuzman I, Soldo I, Schönwald S, et al. Azithromycin for treatment of community acquired pneumonia caused by *Legionella pneumophila*: a retrospective study. Scand J Infect Dis 1995; 27: 503-5
199. Socan M. Treatment of atypical pneumonia with azithromycin: comparison of a 5-day and a 3-day course. J Chemother 1998; 10: 64-8
200. Biebuyck XA, Azithromycin Study Group. Comparison of azithromycin and co-amoxiclav in the treatment of acute tracheobronchitis and acute infectious exacerbations of chronic bronchitis in adults. J Int Med Res 1996; 24: 407-18
201. Beghi G, Berni F, Carratù L, et al. Efficacy and tolerability of azithromycin versus amoxicillin/clavulanic acid in acute purulent exacerbation of chronic bronchitis. J Chemother 1995; 7: 146-52
202. Khurana CM. A multicenter, randomized, open label comparison of azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school. Pediatr Infect Dis J 1996; 15 (9 Suppl.): S24-S9
203. Aronovitz G. A multicenter, open label trial of azithromycin vs. amoxicillin/clavulanate for the management of acute otitis media in children. Pediatr Infect Dis J 1996; 15: S15-S9
204. McCarty J. A multicenter, open label trial of azithromycin for the treatment of children with acute otitis media. Pediatr Infect Dis J 1996; 15 (9 Suppl.): S10-S4
205. McLinn S. A multicenter, double blind comparison of azithromycin and amoxicillin/clavulanate for the treatment of acute otitis media in children. Pediatr Infect Dis J 1996; 15: S20-S3
206. Principi N. Multicentre comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of paediatric patients with otitis media. Eur J Clin Microbiol Infect Dis 1995; 14: 669-76
207. Rodriguez AF. An open study to compare azithromycin with cefaclor in the treatment of children with acute otitis media. J Antimicrob Chemother 1996; 37 Suppl. C: 63-9
208. Marchisio P, Principi N, Sala E, et al. Comparative study of once-weekly azithromycin and once-daily amoxicillin in prevention of recurrent acute otitis media in children. Antimicrob Agents Chemother 1996; 40: 2732-6
209. Arguedas A, Loaiza C, Rodriguez F, et al. Comparative trial of 3 days of azithromycin versus 10 days of clarithromycin in the treatment of children with acute otitis media with effusion. J Chemother 1997; 9: 44-50
210. Schaad UB, Heynen G, Swiss Tonsillopharyngitis Study Group. Evaluation of the efficacy, safety and toleration of azithromycin vs. penicillin V in the treatment of acute streptococcal pharyngitis in children: results of a multicenter, open comparative study. Pediatr Infect Dis J 1996; 15: 791-5
211. O'Doherty B, Paediatric Azithromycin Study Group. Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. Eur J Clin Microbiol Infect Dis 1996; 15: 718-24
212. Pacifico L, Scopetti F, Ranucci A, et al. Comparative efficacy and safety of 3-day azithromycin and 10-day penicillin V

treatment of Group A beta-hemolytic streptococcal pharyngitis in children. Antimicrob Agents Chemother 1996; 40: 1005-8
213. Cremer J, Wallrauch C, Milatovic D, et al. Azithromycin versus cefaclor in the treatment of pediatric patients with acute Group A beta-hemolytic streptococcal tonsillopharyngitis. Eur J Clin Microbiol Infect Dis 1998; 17: 235-9
214. Venuta A, Laudizi L, Beverelli A, et al. Azithromycin compared with clarithromycin for the treatment of streptococcal pharyngitis in children. J Int Med Res 1998; 26: 152-8
215. Haye R, Lingaas E, Høivik HO, et al. Efficacy and safety of azithromycin versus phenoxymethylpenicillin in the treatment of acute maxillary sinusitis. Eur J Clin Microbiol Infect Dis 1996; 15: 849-53
216. Clement PAR, De Gandt JB. A comparison of the efficacy, tolerability and safety of azithromycin and co-amoxiclav in the treatment of sinusitis in adults. J Int Med Res 1998; 26: 66-75
217. Amin NM, Breadon G. An open-label, noncomparative study to evaluate the efficacy, safety, and tolerability of azithromycin in the treatment of patients with acute sinusitis. Clin Ther 1995; 17: 701-7
218. Müller O. An open comparative study of azithromycin and roxithromycin in the treatment of acute upper respiratory tract infections. J Antimicrob Chemother 1996; 37 Suppl. C: 83-92
219. O'Doherty B. An open comparative study of azithromycin versus cefaclor in the treatment of patients with upper respiratory tract infections. J Antimicrob Chemother 1996; 37 Suppl. C: 71-81
220. Laurent K. Efficacy, safety and tolerability of azithromycin versus roxithromycin in the treatment of acute lower respiratory tract infections. J Antimicrob Chemother 1996; 37 Suppl. B: 115-24
221. Zachariah J. A randomized, comparative study to evaluate the efficacy and tolerability of a 3-day course of azithromycin versus a 10-day course of co-amoxiclav as treatment of adult patients with lower respiratory tract infections. J Antimicrob Chemother 1996; 37 Suppl. C: 103-13
222. Gris P. Once-daily, 3-day azithromycin versus a three-times-daily, 10-day course of co-amoxiclav in the treatment of adults with lower respiratory tract infections: results of a randomized, double-blind comparative study. J Antimicrob Chemother 1996; 37 Suppl. C: 93-101
223. Genné D, Siegrist HH, Humair L, et al. Clarithromycin versus amoxycillin-clavulanic acid in the treatment of community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 1997; 16: 783-8
224. Chodosh S, Schreurs A, Siami G, et al. Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. Clin Infect Dis 1998; 27: 730-8
225. Ziering W, McElvaine P. Randomized comparison of once-daily ceftibuten and twice-daily clarithromycin in the treatment of acute exacerbations of chronic bronchitis. Infection 1998; 26: 68-75
226. Hosie J, Quinn P, Smits P, et al. A comparison of 5 days of dirithromycin and 7 days of clarithromycin in acute bacterial exacerbation of chronic bronchitis. J Antimicrob Chemother 1995; 36: 173-83
227. Pavlopoulou L, Leotsacos P, Sereti E, et al. Randomized controlled study of clarithromycin versus cefaclor suspensions in the treatment of acute otitis media in children. J Chemother 1995; 7 Suppl. 4: 150-3
228. Aspin MM, Hoberman A, McCarty J, et al. Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media in children. J Pediatr 1994; 125: 136-41
229. Kearsley NL, Campbell A, Sanderson AAF, et al. Comparison of clarithromycin suspension and amoxycillin syrup for the treatment of children with pharyngitis and/or tonsillitis. Br J Clin Pract 1997; 51: 133-7
230. Adelglass J, Jones TM, Ruoff G, et al. A multicenter, investigator-blinded, randomized comparison of oral levofloxacin and oral clarithromycin in the treatment of acute bacterial sinusitis. Pharmacother 1998; 18: 1255-63
231. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. Acta Otolaryngol 1996; Suppl. 525: 73-8
232. Fong IW, Laforge J, Dubois J, et al. Clarithromycin versus cefaclor in lower respiratory tract infections. Clin Invest Med 1995; 18: 131-8
233. Tatsis G, Tsoukalas G, Boulbasakos G, et al. Efficacy and tolerance of roxithromycin versus clarithromycin in the treatment of lower respiratory tract infections. J Antimicrob Chemother 1998; 41 Suppl. B: 69-73
234. Vagliasindi M. Use of flurithromycin ethylsuccinate in infections of the lower airways due to sensitive germs: multicenter comparative study with clarithromycin. Int J Clin Pharmacol Ther 1997; 35: 245-9
235. Van Royen P, Betz W, Heyrman J, et al. Dirithromycin versus amoxiclav in the treatment of acute exacerbations of chronic bronchitis. J Int Med Res 1997; 25: 33-40
236. Cazzola M, Caputi M, Santangelo G, et al. A five-day course of dirithromycin in the treatment of acute exacerbation of severe chronic obstructive pulmonary disease. J Chemother 1997; 9: 279-84
237. Watkins VS, Smietana M, Conforti PM, et al. Comparison of dirithromycin and penicillin for treatment of streptococcal pharyngitis. Antimicrob Agents Chemother 1997; 41: 72-5
238. Galioto GB, Passali D, Catalano GB, et al. Oral therapy with flurithromycin in ear, nose and throat infections. Int J Clin Pharmacol Ther 1995; 33: 204-7
239. Bariffi F, Clini V, Ginesu F, et al. Flurithromycin ethylsuccinate in the treatment of lower respiratory tract bacterial infections. Infection 1994; 22: 226-30
240. Salvarezza CR, Mingrone H, Fachinelli H, et al. Comparison of roxithromycin with cefixime in the treatment of adults with community-acquired pneumonia. J Antimicrob Chemother 1998; 41 Suppl. B: 75-80
241. Kaku M, Kohno S, Koga H, et al. Efficacy of roxithromycin in the treatment of mycoplasma pneumonia. Chemother 1995; 41: 149-52
242. Örtqvist Å, Valtonen M, Cars O, et al. Oral empiric treatment of community-acquired pneumonia: a multicenter, double-blind, randomized study comparing sparfloxacin with roxithromycin. Chest 1996; 110: 1499-506
243. Chatzimanolis E, Marsan N, Lefatzis D, et al. Comparison of roxithromycin with co-amoxiclav in patients with sinusitis. J Antimicrob Chemother 1998; 41 Suppl. B: 81-4
244. Kimura N, Nishioka K, Nishizaki K, et al. Clinical effect of low-dose, long-term roxithromycin chemotherapy in patients with chronic sinusitis. Acta Med Okayama 1997 51: 33-7
245. Karalus NC, Garrett JE, Lang SDR, et al. Roxithromycin 150mg b.i.d. versus amoxycillin 500mg/clavulanic acid 125mg t.i.d. for the treatment of lower respiratory tract infections in general practice. Infection 1995; 23 Suppl. 1: S15-S20
246. Mandell LA, Niederman M, Canadian Community Acquired Pneumonia Consensus Conference Group. Antimicrobial

treatment of community acquired pneumonia in adults: a conference report. Can J Infect Dis 1993; 4: 25-8
247. Klugman KP, Feldman C. Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. Emerging treatment for an emerging problem. Drugs 1999; 58: 1-4
248. Bergeron MG, Ahronheim G, Richard JE, et al. Comparative efficacies of erythromycin-sulfisoxazole and cefaclor in acute otitis media: a double blind randomized trial. Pediatr Infect Dis J 1987; 6: 654-60
249. Mandel EM, Rockette HE, Paradise JL, et al. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion in children. Pediatr Infect Dis J 1991; 10: 899-906
250. Williams JW, Holleman DR, Samsa GP, et al. Randomized controlled trial of 3 versus 10 days of trimethoprim/sulfamethoxazole for acute maxillary sinusitis. JAMA 1995; 173: 1015-21
251. Williams RL, Chalmers TC, Stange KC, et al. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: a meta-analytic attempt to resolve the brouhaha. JAMA 1993; 270: 1344-51
252. Rajagopalan-Levasseur P, Vallèe E, Bonnefoy A, et al. HMR 3647: activity against *L. pneumophila* serogroup 1 (LP) in monocyte-derived macrophages and in experimental guinea pig infection models. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
253. Piper KE, Rouse MS, Patel R, et al. HMR 3647 Treatment of β-lactamase positive *Haemophilus influenzae* Type B experimental pneumonia in immunocompetent mice. Proceedings of the 38th International Conference on Antimicrobial Agents and Chemotherapy; 1998 Sep 24-27: San Diego. Washington, DC: American Society for Microbiology, 1998
254. Mitten M, Meulbroek J, Paige L, et al. Efficacies of ABT 773 and HMR 3647 against respiratory pathogens causing acute systemic infections in mice and lung infections in rats. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
255. Agouridas C, Bonnefoy A, Chantot JF. *In vivo* activity of HMR 3647, a novel ketolide highly active against respiratory pathogens [abstract]. Abstracts of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides: 1998 Jan 21-23; Barcelona, 23
256. Muelbroek J, Mitten M, Mollison KW, et al. Efficacies of ABT 773 and azithromycin against experimental rat lung infections caused by *Streptococcus pneumoniae*. Proceedings of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29: San Francisco. Washington, DC: American Society for Microbiology, 1999
257. Pichichero ME. Empiric antibiotic selection criteria for respiratory infections in pediatric practice. Pediatr Infect Dis J 1997; 16: S60-S64
258. Finch RG, Woodhead MA. Practical considerations and guidelines for the management of community-acquired pneumonia. Drugs 1998; 55: 31-45
259. Bartlett JG, Breiman RF, Mandell LA, et al. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis 1998; 26: 811-38
260. Mandell LA, Marrie TJ, Grossman RF, et al. Summary of Canadian guidelines for the initial management of community acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. Can Respir J 2000; 7 (5): 731-82
261. Visalli MA, Jacobs MR, Appelbaum PC. Antipneumococcal activity of HMR 3647, a new ketolide, compared to other drugs, by time-kill. Proceedings of the Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides; 1998 Jan 21-23: Barcelona
262. Dowell SF, Butler JC, Giebink S, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance. Drug-resistant *Streptococcus pneumoniae* therapeutic working group. Pediatr Infect Dis 1999; 18: 1-9
263. Paradise JL. Managing otitis media: a time for change. Pediatr 1995; 96: 712-6
264. Chartrand S, Pong A. Acute otitis media in the 1990s: the impact of antibiotic resistance. Pediatr Ann 1998; 27: 86-95
265. Still JG. Management of pediatric patients with Group A beta-hemolytic *Streptococcus* pharyngitis: treatment options. Pediatr Infect Dis J 1995; 14: S57-S61
266. Scaglione F, Demartini G, Arcidiacono MM, et al. Optimum treatment of streptococcal pharyngitis. Drugs 1997; 53: 86-97
267. Noyek A, Brodovsky D, Coyle S, et al. Classification, diagnosis and treatment of sinusitis: evidence-based clinical practice guidelines. Can J Infect Dis 1998; 9 Suppl. B: 3B-24B
268. Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. Can Med Assoc J 1997; 156: S1-S14
269. Periti P, Mazzei T, Mini E, et al. Adverse effects of macrolide antibacterials. Drug Saf 1993; 9: 346-64
270. Classen DC, Burke JP, Pestonik SL, et al. Clinical and financial impact of intravenous erythromycin therapy in hospitalized patients. Ann Pharmacother 1999; 33: 669-73
271. Bizjak ED, Haug III MT, Schilz RJ, et al. Intravenous azithromycin-induced ototoxicity. Pharmacother 1999; 19: 245-8
272. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med 1991; 91 Suppl. 3A: 40S-5S
273. Pillans P. Drug associated hepatic reactions in New Zealand: 21 years experience. N Z Med J 1996; 109: 315-9
274. Blanc F, D'Enfert J, Fiessinger S, et al. An evaluation of tolerance of roxithromycin in adults. J Antimicrob Chemother 1987; 20 Suppl. B: 179-83
275. De Cock L, Poels R. Comparison of spiramycin with erythromycin for lower respiratory tract infections. J Antimicrob Chemother 1998; 22 Suppl. B: 159-63
276. Periti P, Mazzei T, Mini E, et al. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinet 1992; 23: 106-31
277. Howard KB, Blumenschein K, Rapp RP. Azithromycin versus erythromycin for community-acquired pneumonia: a cost minimization analysis. Am J Health Syst Pharm 1999; 56: 1521-4
278. Boucher FD. The new macrolide antibiotics: use them carefully. Pediatr Child Heal 1997; 2: 385-6
279. Nahata M. Drug interactions with azithromycin and the macrolides: an overview. J Antimicrob Chemother 1996; 37 Suppl. C: 133-42
280. van Haarst AD, van 't Kloster GA, Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 1998; 64: 542-6
281. von Rosensteil NA, Adam D. Macrolide antibacterials: drug interactions of clinical significance. Drug Saf 1995; 13: 105-22
282. Amsden GW. Macrolides versus azalides: a drug interaction update. Ann Pharmacother 1995; 29: 906-17
283. Gurevitz SL. Erythromycin: drug interactions. J Dent Hyg 1997; 71: 159-61

284. Thalhammer F, Hollenstein UM, Locker GJ, et al. Azithromycin-related toxin effects of digitoxin. Br J Pharmacol 1998; 45: 91-2
285. Felsted S. Azithromycin drug interactions. Pathol Biol 1995; 43: 512-4
286. Carbon C, Hotton JM, Pépin LF, et al. Economic analysis of antibiotic regimens used in the treatment of pharyngitis: a prospective comparison of azithromycin versus roxithromycin. J Antimicrob Chemother 1996; 37 Suppl. C: 151-61
287. Norinder A, Paulsen O, Hjorstberg C. Economic analysis of treatment with roxithromycin in comparison with erythromycin patients with lower respiratory tract infections. Scand J Infect Dis 1997; 29: 83-6
288. Scott WG, Cooper BC, Scott HM. Pharmacoeconomic evaluation of roxithromycin versus amoxycillin/clavulanic acid in a community-acquired lower respiratory tract infection study. Infection 1995; 23 Suppl. 1: S21-S4
289. Hitt CM, Nightingale CH, Quintiliani R, et al. Streamlining antimicrobial therapy for lower respiratory tract infections. Clin Infect Dis 1997; 24 Suppl. 2: S231-7
290. Wandstrat TL, Kaplan B. Pharmacoeconomic impact of factors affecting compliance with antibiotic regimens in the treatment of acute otitis media. Pediatr Infect Dis J 1997; 16: S27-S9
291. Barry AL, Fuchs PC, Brown SD. Macrolide resistance among *Streptococcus pneumoniae* and *Streptococcus pyogenes* isolates from out-patients in the USA. J Antimicrob Chemother 1997; 40: 139-40
292. McLinn S, Williams D. Incidence of antibiotic-resistant *Streptococcus pneumoniae* and beta-lactamase-positive *Haemophilus influenzae* in clinical isolates from patients with otitis media. Pediatr Infect Dis J 1996; 15: S3-S9
293. Simor AE, Louie M, Canadian Bacterial Surveillance Network, et al. Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother 1996; 40: 2190-3
294. Doern GV, Jones RN, Pfaller MA, et al. *Haemophilus influenzae* and *Moraxella catarrhalis* from patients with community-acquired respiratory tract infections: antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program (United States and Canada, 1997). Antimicrob Agents Chemother 1999; 43: 385-9
295. Davidson RJ, Canadian Bacterial Surveillance Network, Low DE. A cross-Canada surveillance of antimicrobial resistance in respiratory tract pathogens. Can J Infect Dis 1999; 10: 128-33
296. Seppälä H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in Group A streptococci in Finland. N Engl J Med 1997; 337: 441-6

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