SECOND EDITION

ANTIMICROBIAL THERAPY AND VACCINES

Volume II: *Antimicrobial Agents*

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Mulazimoglu, L, P. M. Tulkens & F. Van Bambeke. 2004. Macrolides. In: Anti-infective therapy, Serie Antimicrobial therapy and vaccines ((Yu,V.L.; Edwards,G.; McKinnon,P.S.; Peloquin,C.; Morse,G.D.ed.). Esun Technologies, Pittsburgh, PA, 243-280.

Macrolides

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INTRODUCTION

The story of macrolides began in 1952 at Eli Lilly Laboratories with the discovery of ilotycin (renamed thereafter erythromycin A), a natural product isolated from *Streptomyces erythreus.* It was found to inhibit Gram positive and Gram negative bacteria in concentrations of 0.007 to 6.25 µg/ml, and showed activity against *Mycobacterium tuberculosis*, *Entamoeba histolytica*, *Spirochaeta novyi*, *Trichomonas vaginalis*, oxyurids, *Rickettsiae*, and viruses of the lymphogranuloma and mouse meningopneumonitis types (278). Erythromycin was introduced to the clinical setting in the mid 1950's, and has remained the only representative of this drug class to be used on a large scale in Europe as well as in North America. Major limitations to its use appeared rapidly, namely (i) its poor and quite variable oral bioavailability, (ii) its side effects at the level of the gastrointestinal tract, and (iii) its capacity to cause major drug interactions. This stimulated the search for other compounds, as well as for semi-synthetic derivatives with improved pharmacokinetics and a better safety profile. This led first to the discovery of the naturally-occurring 16-membered macrolides (with josamycin, spiramycin and midecamycin being the most known compounds for human usage), tylosin in the United States (only used for animals), and to semi-synthetic derivatives from related compounds. In parallel, a series of semi-synthetic compounds were derived from erythromycin A (erythromycylamine [originally synthesized in the 70's, but introduced in the clinical setting much later as its prodrug dirithromycin], roxithromycin, clarithromycin, and azithromycin) which have been collectively named "neomacrolides". These semi-synthetic derivatives corrected many of the pharmacokinetic and side-effects-related difficulties of erythromycin, but did not provide an answer to the emergence of resistance to macrolides that developed in parallel to their wider use. The key pharmacophore of erythromycin and of the neomacrolides is essentially the same as far as their mode of action is concerned. Ketolides, in which the pharmacophore has been modified provide a partial answer to resistance and have integrated the other modifications that were introduced in the neomacrolides for improving bioavailability and reducing side effects. Ketolides are examined in a separate chapter.

Chemical Structure Relations to Activity and Key Pharmacokinetic Properties

All macrolides endowed with marked antibacterial activity, with the exception of the ketolides, are made of a 14-, 15-, or 16-membered lactone ring substituted by two sugars (Figure 1). The first (desosamine) bears a protonable animated function, which confers to all macrolides a cationic character responsible for their characteristic pharmacokinetic profile (see below). The second sugar (cladinose) is critical to obtain clinically-useful activity, since its removal, as in narbomycin or similar compounds, leads to only weak activity (as will be shown for ketolides, removal of the cladinose can be compensated and activity brought back to clinically useful values if an appropriate side chain is added to the molecule).

Erythromycin is unstable in acidic medium, which makes its bioavailability poor and unpredictable. This is due to the simultaneous presence of a keto-function (in position 9) and of an hydroxy-function (in position 6), which can come into close contact and react in acidic medium to generate a spiroketal (Figure 2) (231).

The understanding of the molecular mechanism of this acid-catalyzed degradation of erythromycin led to the rational synthesis of derivatives either lacking the keto-function or made incapable to form the spiroketal. Limiting the discussion to compounds brought to the clinics (which are shown in Figure 1), the first group comprises erythromycylamine (271, 272), in which the keto function is replaced by an amino function (erythromycylamine issued as its prodrug dirithromycin), roxithromycin (73), in which the same keto function is replaced by a N-oxime side chain, and azithromycin (44, 109), obtained by Beckman rearrangement of the oxime derivative of the ketone of erythromycin leading to a 15-membered macrocycle, followed by its reduction and N-alkylation (hence the name of azalide given to this class of compounds). The second group is represented by clarithromycin (128, 294) in which the 6-hydroxyfunction is methylated (the same substitution has been made in ketolides).

16-membered macrolides are intrinsically stable since they do not present a keto-function in their macrocycle. Within this class, spiramycin (226), josamycin (308) and midecamycin (221), which are natural products, and miocamycin, derived from midecamycin (223, 316), and rokitamycin, derived from leucomycin A5 (368) have been brought to the clinics.

ANTIMICROBIAL ACTIVITY

The first independent microbiological description of erythromycin (167) indicated that the drug was active against the Gram positive cocci, quite active against strains of *Neisseria*, *Diphtheria* bacteria, and *Hemophilus*, but practically inactive against most coliform and enteric bacteria, and that antibacterial action improved with

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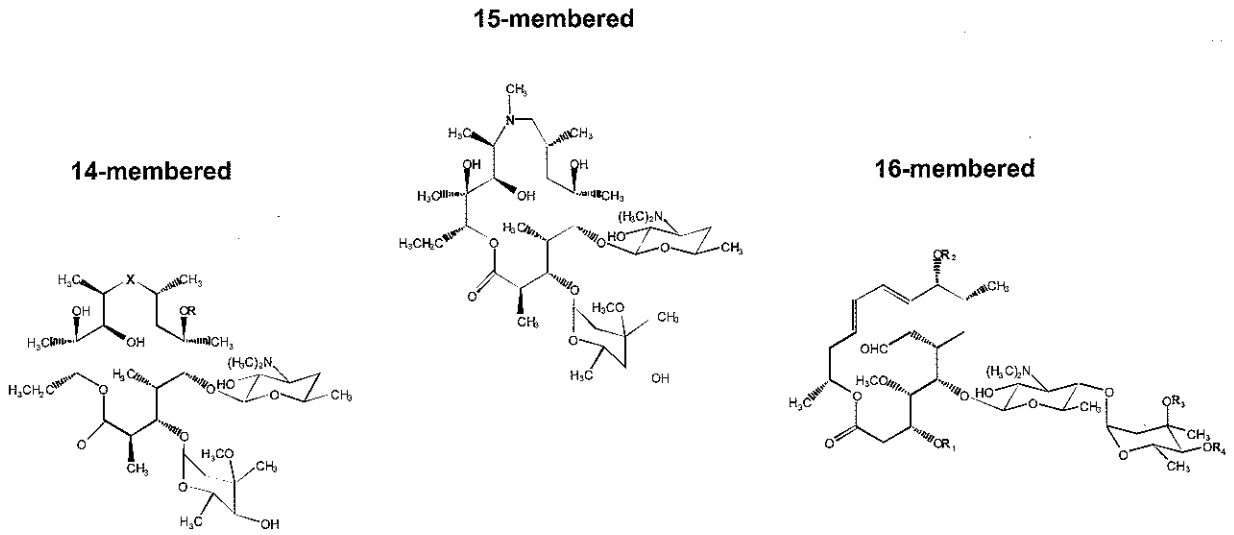

	X	R
Erythromycin	C=O	H
Roxithromycin	C=N-O-CH_2-O-CH_2-CH_2-O-CH_3	H
Clarithromycin	C=O	CH_3
Erythromycylamine	CH-NH_2	H

	R_1	R_2	R_3	R_4
Spiramycin	H	Forosamine	H	H
Josamycin	$COCH_3$	H	H	$COCH_2CH(CH_3)_2$
Miocamycin	$COCH_2CH_3$	$COCH_3$	$COCH_3$	$COCH_2CH_3$
Rokitamycin	H	H	$COCH_2CH_3$	$CO(CH_2)_2CH_3$

FIGURE 1 • Chemical structure of the macrolide antibiotics currently used in the clinics. Theses are classified according to the number of atoms in the macrocycle. All molecules possess an aminated sugar (desosamine) which confers to them a basic character responsible for their cellular accumulation (azithromycin and erythromycylamine have a second aminated function and are therefore dibasic molecules, which explains their higher level of cellular accumulation). Erythromycylamine is commercialized as a prodrug (dirithromycin) which is intrinsically inactive but regenerates erythromycylamine *in vivo* or *in vitro* (230).

increasing alkalinity within the pH range of bacterial growth. Erythromycin was also described as either bacteriostatic or bactericidal depending on the sensitivity of the organism and on the concentration (168). Table 1 lists the sensitivities observed for wild strains in studies published in the late 80's through the early 90's. Macrolides appear as having a moderately-broad spectrum of activity, which includes most Gram positive but only selected Gram negative organisms, as well as several bacteria responsible for intracellular infection such as *Mycobacteria* spp, *Chlamydia* spp, or *Legionella* spp.

Pharmacodynamic Effects

Antibiotics are now categorized as either concentration- or time-dependent drugs (10). Macrolides are considered as time-dependent antibiotics, which means that their efficacy will be related to the time interval during which their concentration at the infected site remains above the MIC of the offending organism (85). This can be easily explained on the basis of the fact that their action on bacteria is essentially bacteriostatic, and that activity can only be maintained as long as the antibiotic remains bound to the ribosome (this is similar to what is observed with β-lactams, but is in sharp contrast with aminoglycosides which impair protein synthesis as well, but also cause translation mistakes and lethal events in direct correlation to their concentration). The post-antibiotic effect of macrolides (time necessary to observe bacterial regrowth upon drug withdrawal) is short and spans between a few minutes up to a maximum of approximately 2 hours *in vitro* (361), which helps to explain why macrolides are essentially time-dependent antibiotics. This was confirmed for erythromycin in animal studies using *S. pneumoniae* and the tight infection model (310). For clarithromycin, however, the same study underlined the importance of the C_{max}/MIC ratio (310). Studies with the murine pneumonia showed that not only time during which clarithromycin concentration remains above the MIC, but also the ratio of the area under the concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) to the MIC, and the C_{max}/MIC were significantly in close correlation to antibacterial efficacy, median survival time, and total percent survival (426). Due to its particular pharmacokinetic profile, azithromycin shows prolonged persistent effects, so that its activity better correlates to the 24h-AUC/MIC ratio (440).

As a consequence of these concepts, and in a context of increasing levels of resistance, it is clear that

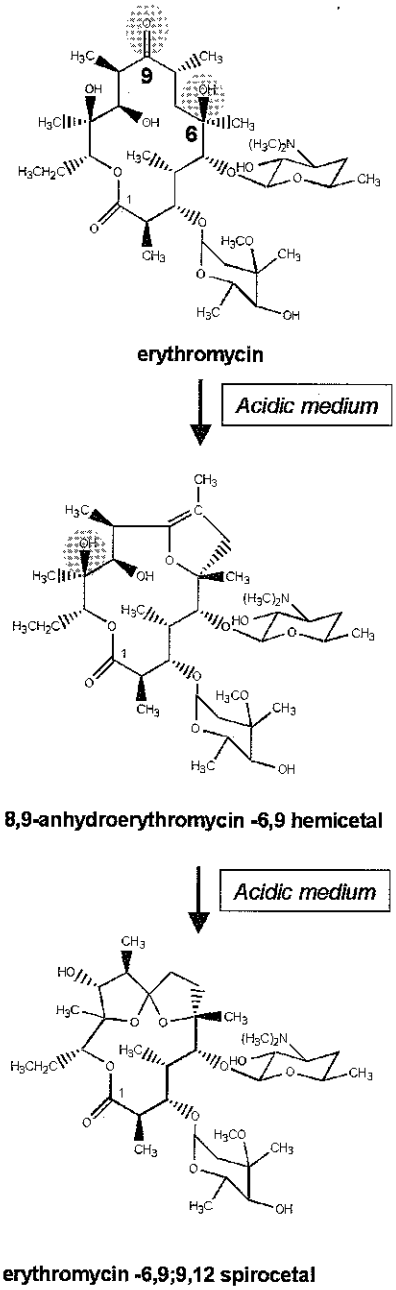

FIGURE 2 • Mechanism responsible for the inactivation of erythromycin in acidic medium. The ketone in position 9 reacts with the hydroxyl in position 6 to generate a hemiketal, which reacts again with the hydroxyl in 12 to produce a ketal. Both the hemiketal and the ketal are microbiologically inactive. Neomacrolides (see Figure 1) were made are acidostable by either removing the 9-keto function and replacing it with another function (roxithromycin, erythromycylamine, azithromycin), or by substituting the 6-hydroxyl group (clarithromycin; the same approach has been followed for telithromycin). 16-membered derivatives are intrinsically stable because of the absence of a ketone function in the cycle. Adapted from (231)

optimization of macrolide usage to eradicate less susceptible bacteria must probably imply both a reduction of the dosing interval and an increase of the unit dose (440). For example, *in vitro* studies (309) showed that a time above MIC of > or = 90% ($AUC_{0\text{-}24h}$/MIC ratio, > or = 61) will result in bacterial eradication, while values of < or = 8% ($AUC_{0\text{-}24h}$/MIC ratio, < or = 17.3) will offer only a static effect with subsequent bacterial regrowth. Applying this to the *in vivo* situation, and taking into account the concentrations achieved locally (epithelial lining fluid, e.g.), it was concluded that patients with isolates for which MICs are > or = 16 μg/ml will experience bacteriological failures because of the too short "Time above MIC" value (309). In the case of azithromycin, for which the serum levels always remain low, coverage of less susceptible organisms will require an increase of the daily dose (472),

Table I • Spectrum of Activity Of Macrolide Antibiotics (wild strains) (MIC values or ranges in µg/ml).

Bacteria	Erythromycin	Roxithromycin	Clarithromycin	Dirithromycin	Azithromycin	Miocamycin	Josamycin	Spiramycin	Rokitamycin
Staphylococcus aureus (MSSA) [a]	0.1-0.5	0.2-0.5	0.06-0.5	0.02-2	0.02-1	0.5-4	0.5-64	0.25-64	0.25-4
Streptococcus pneumoniae	0.015-1	0.05-0.2	0.015-0.5	0.06-1	0.06-2	0.12-0.5	0.03-0.12	0.015-0.03	0.12
Streptococcus pyogenes	0.03-0.06	0.03-0.06	0.015-0.015	0.03-0.12	0.03-0.12	0.25-0.5	0.06-0.25	0.06-0.12	0.12-0.25
Haemophilus influenzae	1-8	1-8	1-8	0.2-32	0.2-4	16 ->16	4-32	4-16	4-16
Chlamydia pneumoniae	0.06	0.25	0.007	0.5	< 2		4-32	4-16	
Moraxella catarrhalis	0.1-0.5	0.5-2	0.06-2	0.1-1	0.01-0.1		0.25	4	
Legionella pneumophila	0.1-1	0.06-0.5	0.1-0.5	0.5-4	0.125-0.5	0.1-0.5	0.5-1	8-64	0.12-0.25
Helicobacter pylori	0.1	0.07	0.03	0.06-0.5	0.2		0.5-1	8-64	
Chlamydia trachomatis	0.06-1	0.015-2	0.004-0.2	1	0.03-0.06	0.06			
Borrelia burgdorferi	0.03-0.12	0.015-0.12	0.015-0.12	< 0.5	0.015-0.12				
Mycobacterium avium and complex	32-64	8-32	0.5-8		8-32				

[a] MRSA are usually resistant to macrolides.
Data from (45, 174, 175, 177, 327, 345, 354, 358).

since this will prolong the time during which the antibiotic remains above a critical serum concentration treshold as well as the total 24h-AUC/MIC ratio. However, this may raise potential safety issues that have not been fully adressed so far. Moreover, pharmacodynamic studies showed that whereas the oncentration of azithromycin in serum, epithelial lining fluid and middle ear fluid rapidly eradicated macrolide-susceptible *S. pneumoniae*, they did not eradicate macrolide-resistant *S. pneumoniae* regardless of resistance phenotype (472).

Less is known about the pharmacodynamic parameters governing the intracellular activity of antibiotics (433). The high level of accumulation of macrolides inside the cells as well as their dual distribution in the lysosomes and, to a lesser extent, in the cytosol could make them drugs of choice for the treatment of various intracellular infections. Macrolides are, indeed, active *in vitro* against numerous bacteria causing intracellular infections (see above). Macrolides have, accordingly, been found most active against *Legionella* and *Chlamydia*, both in *in vitro* models (39, 200) and in patients (169, 238, 382, 405, 415). A slow killing was reported against Mycobacteria, probably favored by the prolonged exposure of the bacteria to the drug (461). Clarithromycin and azithromcyin are considered as first line therapy in AIDS patients suffering from infections by *Mycobacterium avium*, even though resistance develops (96, 233, 449, 471). In other models of infected cells, however, macrolide activity is often disappointing, with a barely static intracellular effect, as shown for example against *Listeria monocytogenes* (which infects the cytosol), and *Staphylococcus aureus* (which multiplies in lysosomes) (63, 388). It therefore appears that other parameters other than accumulation and distribution need to be taken into account in the intracellular activity of antibiotics, among which the expression of activity in the intracellular environment, the bacterial responsivness and the cooperation with cell defense mechanisms probably play a central role (62).

Anti-inflammatory Effects of Macrolides

Beside their antibacterial activity, there is now growing evidence that 14- and 15-membered macrolides may act as anti-inflammatory agents and inhibitors of bacterial virulence factors, and therefore play an adjunctive role in the management of respiratory infections with inflammatory reactions. The exact mechanisms responsible for these effects are still under investigation and are probably multifactorial. Anti-inflammatory effects are related to the ability of macrolides to inhibit the oxidative burst in macrophages and neutrophils, to decrease the adhesion of neutrophils to the epithelial surfaces, their degranulation and their death by apoptosis, and to reduce the production and/or the secretion of inflammatory cytokines by neutrophils or epithelial cells [see (87, 202) for review]. The latter effect is related to an inhibition of the activation of the transcription factor NFκB (106), which is essential

for the production of IL-8 by bronchial epithelial cells, and also induces the expression of several other chemokines, causing the migration of neutrophils in the infected region. For what concerns interference with bacterial virulence, it has been shown that azithromycin (2 mg/L) inhibits the quorum-sensing circuitry in *Pseudomonas aeruginosa*, probably by interfering with the synthesis of auto-inducers like 3-oxo-C_{12}-homoserine lactone and C_4-homoserine-lactone (419). Interestingly, these auto-inducers seem to play a major role not only in the regulation of bacterial virulence genes but also in the modulation of the host response to infection (394). In particular, 3-oxo-C_{12}-homoserine lactone activates the transcription factor NFκB (419) and upregulate the expression of the inducible cyclo-oxygenase, causing an increased production of inflammatory prostaglandins (395). Moreover it induces apoptosis in macrophages and neutrophils (420). It therefore appears that virulence factors and inflammatory response are closely linked and that the protective effect of macrolides is exerted both at the level of the host cells and of the bacteria. Further structure-activity relationship studies would be worthwhile so as to discover molecules endowed with anti-inflammatory properties but no antibiotic activity.

Mechanism of Action

Macrolides are inhibitors of protein synthesis. They impair the elongation cycle of the peptidyl chain by specifically binding to the 50 S subunit of the ribosome. Specificity towards procaryotes relies upon the absence of 50S ribosomes in eucaryotes.

The binding site of macrolides on the ribosome overlaps that of chloramphenicol or lincosamides (377), explaining pharmacological antagonism between these antibiotic classes as well as cross-resistance. Over the last 2 years the determination of the crystal structure of the ribosome in interaction with macrolides has allowed us to define the mode of action of these antibiotics in great details (376, 377). The main interaction site is located at the central loop of the domain V of the 23S rRNA, at the vicinity of the peptidyl transferase center (see Figure 3). The macrolide binding site is actually located at the entrance of the exit tunnel used by the nascent peptide chain to escape from the ribosome, at the place where the central loop of domain V interacts with finger-like β-sheet structures of r-proteins L4 and L22 and with the loop of hairpin 35 in domain II of rRNA (341). At this precise location, proteins L4 and L22 form a constriction (302), the diameter of the tunnel being reduced from 15 Å to 10 Å (145 for review). Interaction occurs via the formation of hydrogen-bounds with the reactive groups of the desosamine sugar and the lactone ring (377) (see Figure 3). The interaction between the 2'-OH group of the desosamine and of adenine residue 2058 [1] is critical. Indeed, impairment of this interaction by the dimethylation of the adenine (457) or replacement of the adenine by another base (392) leads to complete resistance. Other major interaction sites include the guanine 2505 for the 14-membered macrolides, the adenine 2059 for azithromycin, and the adenine 2062 for the 16-membered macrolides (418).

The inhibition of protein synthesis proceeds from different mechanisms. A first general consequence of the location of macrolides in the constriction of the exit tunnel is a blockage of the path of the elongating peptidyl chain through the ribosome by steric hindrance (173, 377). Since the site of binding of macrolides is quite far from the peptidyl transferase center, short polypeptide chains can be produced. The maximal length of these peptides probably depends on their sequence in amino acid as well as on the nature of the macrolide blocking the ribosome (145). Indirect consequences of macrolide binding to the ribosome may include (i) the promotion of the peptidyl tRNA dissociation form the ribosome (286), (ii) an interference with the 50S subunit assembly (70), and (iii) and inhibition of peptide bound formation (344). The latter mechanism is applicable for semi-synthetic derivatives having a long extension on the desosamine sugar (such as 16-membered macrolides) which can protrude into the peptidyl transferase center and therefore inhibit the positioning of the substrate at the P-site (173). In the case of azithromycin, it has recently been suggested that two molecules can bind at different sites of the ribosome, generating a cooperative effect which may enhance its antibacterial activity (376). One molecule is indeed located at a position similar to that of other macrolides while the second one would establish contacts with the domain II (adenine 752) of the 23S rRNA and probably also with ribosomal proteins (but this observation may be partly species-specific).

The interactions of the cladinose with the ribosomal target of the macrolides have not yet been studied in detail. As explained earlier, macrolides devoid of cladinose show only a poor activity (unless they also carry a side chain that allows them to bind simultaneously to domain II of the 23S rRNA, as in telithromycin and related ketolides). Yet, these derivatives are insensitive to the mechanisms of resistance involving dimethylation of adenine 2058. This would suggest that the cladinose is essentially to increase the tightness of the binding to this adenine, unless it is modified by dimethylation.

MECHANISM OF RESISTANCE

Following what is now recognized as a general rule for all antibiotics, resistance to erythromycin was

[1] *E.coli* numbering system. Being an established model of studying bacterial protein synthesis, *E. coli* ribosomes have been used for most of the original research on the mode of action of macrolides (the lack of activity of macrolides against this species is due to lack of penetration, not lack of intrinsic activity). *E. coli* numbering has, therefore, been kept even for other species to keep the nomenclature uniform.

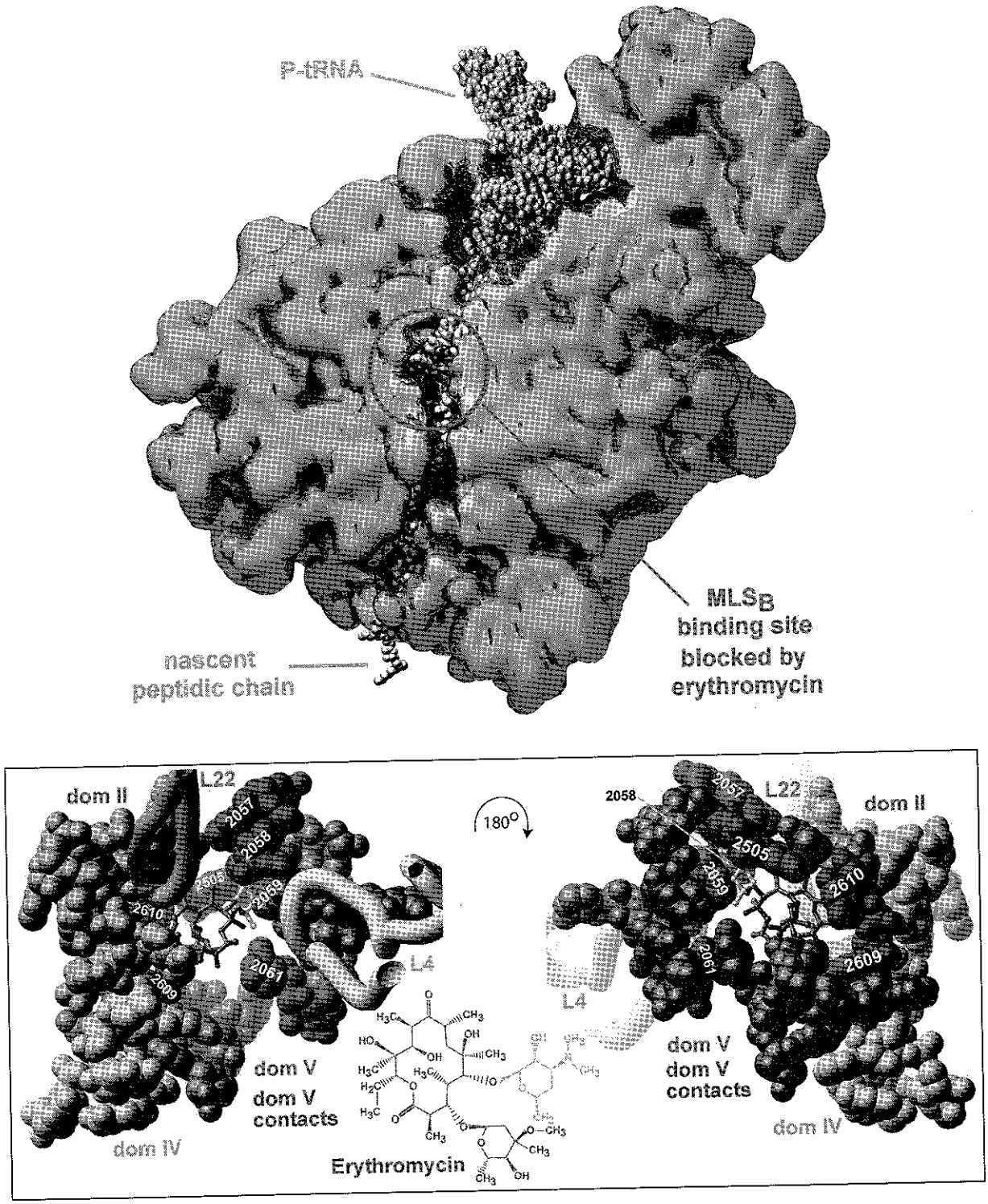

FIGURE 3 • Macrolides in interaction with their ribosomal target. Upper panel: 50S ribosomal subunit of *Deinococcus radiodurans* in cross section, showing the path of the peptide through the tunnel from the peptidyl -transferase site to emerge of the subunit. The elongating peptide is shown in light blue, the macrolide bound to the ribosome in red, and tRNA in green. Lower panel: erythromycin in interaction with the ribosome, with the desosamine interacts with adenine 2058 shown in grey. Color codes: dark blue: domain V; dark mauve: contacts between erythromycin and domain V, violet: domain II, light blue: domain IV; yellow ribbon; L4 protein; green ribbon, L22 protein. The left panel is a view from the tunnel to erythromycin and the peptidyl transferase site; the right panel is a view from the peptidyl transferase site to the tunnel. The figure also shows the position of the bases involved in the interaction with the antibiotic. Figure prepared by J.M. Harms, Max-Planck-Research Unit for Ribosomal Structure, Hamburg, Germany.

Table 2 • Clinically Relevant Mechanisms of Resistance to Macrolide Antibiotics, Phenotype and Frequency of the Resistant Strains.

Bacterial Species	% Resistance	Mechanism	Genetic Support	Phenotype	Frequency	References
S. aureus	> 80 % MRSA ~ 40 % MSSA	Ribosomal methylation	*erm*(A), (C)	MLS_B	> 80%	(378, 378, 379, 379)
		efflux	*msr*(A)	MS_B	< 10 %	
		Antibiotic inactivation			rare	
S. pneumoniae	~ 30 %	Ribosomal methylation	*erm*(B)	MLS_B	~ 65 %	(126)
		23S rRNA mutation		ML	Rare	
		r-protein mutation		MS_B	Rare	
		Efflux	*mef*(A)- *mef*(E)	M	~ 35 %	
S. pyogenes	~ 10 %	Ribosomal methylation	*erm*(A), (B)	MLS_B	~ 50 %	(126)
		Efflux	*mef*(A)	M	~ 50 %	
Haemophilus influenzae	rare	Ribosomal methylation		MLS_B		(331)
		23S rRNA mutation		ML	~ 10 %	
		r-protein mutation		MS_B	~ 65 %	
		Efflux		M	~ 100 %	
Helicobacter pylori	~ 10 %	23S rRNA mutation		ML		(282)
Mycoplasma		Ribosomal methylation		MLS_B		(59)
		23S rRNA mutation		ML		(249)
Mycobacteria		23S rRNA mutation		ML		(249)
Enterobacteriaceae		Antibiotic inactivation	*ere*	M		(249)

both easy and quickly obtained by serial transfer in the laboratory (252, 351). In the clinical setting, however, resistance was considered unimportant for many years (and was still mentioned as such in the 1991 edition of Harrison's Principles of Internal Medicine), and concerned only *Staphylococcus aureus* and coagulase-negative staphylococci. Yet, the latter organism was recognized as constituting a large reservoir of the ermA and ermC class of resistance determinants, with clear potential for interspecies spread (427). Not surprisingly, massive utilization of macrolides made resistance widespread and affected many of the other species for which macrolides were recommended; specifically, *Streptococcus* spp., *Bacteroides* spp., *Enterococcus* spp., *Clostridium* spp., *Bacillus* spp., *Lactobacillus* spp., *M. pneumoniae*, *Campylobacter* spp., *Corynebacterium diphteriae*, and *Propionobacterium*, as well as many members of the *Enterobacteriaceae* (250). It has now become a worrisome problem, which seriously compromises their use in several indications, as will be discussed later. Table 2 shows the mechanisms and frequencies of resistance and corresponding phenotypes conferred.

Modification of the Target

Methylation of rRNA: This mechanism of resistance, which was first described in terms of specific modification of the target of macrolides (241), is currently the most prevalent in pathogenic bacteria (126). It is mediated by the acquisition of an erm gene, encoding for a methyltransferase which methylates the N(6) position of adenine 2058 in 23S rRNA (457). More than 30 erm genes from a variety of sources have been described but they all show large similarities suggesting that they all derive from a common ancestor (250, 359, 457). The physiological function of this methylase is unknown. Monomethylation confers high level of resistance to lincosamides and streptogramins and lower level of resistance to macrolides, while dimethylation confers high levels of resistance to the three classes of drugs, conferring the MLS_B phenotype of cross resistance (250). Resistance is most likely due to the steric hindrance created by the methyl(s) into the macrolide binding site, which prevents the correct positioning of the amino-sugar, thanks to a modification of the binding site conformation (341). The free rotation of the methyls around the C(6)-N(6) bond explains why a dimethylation

is required for more effective blocking of the macrolide access to its binding site. Different molecular determinants have been described: *erm(A)* is mostly found in Staphylococci and in *Streptococcus pyogenes* but is rare in *Streptococcus pneumoniae*; conversely, *erm(B)* is the major determinant found in *S. pneumoniae* and also in other streptococci and in enterococci. Other determinants have been found in specific organisms, like *erm(C)* (389) which is found in *S. aureus* ((257, 378), *erm(D)* and *erm(G)* in *Bacillus spp* (164, 293), and *erm(F)* in *Bacteroides fragilis* (355). Focusing on pneumococci, the *erm(B)* gene is located on conjugative and transferable transposons (431), which allows for its easy dissemination. The expression of the methylase is either constitutive or inducible. In the later case, inducers include the 14-, 15-, and 16-membered macrolides, lincosamides and streptogramins (250) but not the ketolides (42, 248). The mechanism of induction is not yet clearly established. It has been proposed that, in the presence of macrolide, the ribosome is stalled by the leader peptide open reading frame that precedes the erm mRNA and represses its translation. This would induce a conformational change of the erm ribosome binding site which activates the *erm* translation (165). Because macrolides inhibit protein synthesis, this mechanism implies that the efficiency of induction is critically dependent on the macrolide concentration. If the concentration is low, too few ribosomes will be occupied to allow for sufficient *erm* synthesis. Conversely, if the concentration is too high, the antibiotic will rather inhibit the translation of the *erm* mRNA (145). An adequate equilibrium between drug binding and dissociation from the ribosome should thus be reached, which may explain why ketolides, which are characterized by a tighter binding, are poor inducers (474). It may also explain why ketolides are poorly active against strains in which the expression of *erm(B)* is constitutive, or in which two successive methylations take place efficiently (56, 112). In clinical practice, the *erm(B)* phenotype confers resistance to ketolides in *S. pyogenes*, but to a lesser extent in *S. pneumoniae* (213).

Mutation of 23S rRNA: Among the mutations detected in the binding site of macrolides, substitution of adenine 2058 with a guanine is the most common one in bacterial pathogens (341, 445). This simple substitution is sufficient to disrupt the hydrogen bond with the amino sugar carried by the desosamine and also to create a hydrophilic patch in the tunnel wall which perturb the positioning of the hydrophobic macrocycle (341). It usually defines an ML phenotype of resistance, with high MICs for erythromycin, azithromycin, the 16-membered macrolides, and the lincosamides, a slightly reduced susceptibility to clarithromycin, but no influence on streptogramins and ketolides (56). This mechanism is mainly found in *Helicobacter pylori*, *Mycoplasma* and *Mycobacterium* spp, probably because these bacteria possess only one or two copies of the rRNA operons (445). A new gene [*erm(38)*] has been recently described as conferring intrinsic ML phenotype resistance of *M. smegmatis*. This gene is similar to *erm(37)* (Rv1988) observed in the *M. tuberculosis* complex, suggesting that such genes are widespread in mycobacteria with intrinsic macrolide resistance (304).

Detectable resistance by this mechanism is less probable in species like *S. pneumoniae* which possess four copies of this operon, that need to be mutated on a step-wise fashion, but strains carrying these mutations have been isolated from patients in Eastern Europe and North America (417). A recent analysis of resistance mechanisms in clinical isolates of *S pneumoniae* has accordingly demonstrated its implication in only 1.5 % of the strains (125).

Mutation of r-Proteins: Mutations in the proteins L4 and L22 have also been recently associated with the appearance of resistance to macrolides in clinical strains of streptococci (125, 356, 417). Mutations in the L4 protein are located in a conserved motif which interacts with the rRNA (417) and perturb the binding of the macrolide to its target (160); they confer a MS_B resistance phenotype, with MIC remaining low (56). Mutations in the L22 protein are localized on a β-sheet making part of the exit tunnel (57). They cause a wider opening of the tunnel, allowing the nascent peptide to slip by the macrolide (140). These mutations confer a low level of resistance to macrolides (including telithromycin for which MIC remains < 0.25 mg/L) and clindamycin and a higher level of resistance to streptogramins (57).

Small Peptides: This mechanism has been described fortuitously in *E. coli* while searching for small rRNA fragments able to bind antibiotics. It was found thereafter that deletion of some of these small fragments render cells resistant to erythromycin but that translation of these fragments was sufficient to confer resistance, indicating that it was the encoded peptide rather than the RNA which was the resistance determinant (422, 423). These peptides act in *cis*, so that they confer resistance only to the ribosome on which they were translated and their sequence defines the macrolides to which they confer resistance.Thus, E-peptides conferring resistance to erythromycin are characterized by the consensus sequence M-(L)-L/I-(F)-V, while K-peptides conferring high resistance to ketolides have the consensus sequence M-K/R-(F/L/V)-X-X (425, 432). The strong correlation between the peptide sequence and the affected macrolide suggests a direct interaction between the peptide and the macrolide in the ribosome, which is quite reminiscent of what has been proposed to explain the induction of *erm* genes. Interestingly enough, indeed, the amino acid sequence suspected to play a role in interaction with macrolide have similar physico-chemical properties in both cases (424). The mechanism of resistance proposed here is that of a "bottle brush", where the ribosome produces a short peptide (which remains possible even in the presence of a macrolide as explained above) that binds to the macrolide, kicks it out of its bind-

ing site on the ribosome, and thereby, makes the ribosome available for protein synthesis (424, 444). These observations open interesting perspectives in the understanding of the ribosome functioning, but the spontaneous emergence of this resistance mechanism in clinical isolates has, to our knowledge, not been described so far.

Antibiotic Inactivation: Unlike target modification, this mechanism confers resistance to structurally-related antibiotics only, which means that it affects macrolides but not lincosamides or streptogramins (249, 301). At the present time, phosphorylases and esterases conferring resistance to 14-, 15- and 16-membered macrolides have been mainly reported in enterobacteriaceae. Enterobacteria are intrinsically resistant to high levels of erythromycin and two types of erythromycin-inactivating esterases have been identified in *E. coli* strains. These esterases are encoded by two genes, *ere(A)* (*ereA* from pIP1100) and *ere(B)*, the first of which has been shown recently to be organized as an integron gene cassette, the mobility of which has been demonstrated (36). The clinical significance of this resistance remains minor since these bacteria are not the primary target of macrolides (although the WHO still includes oral erythromycin as a treatment of severe cases of cholera [http://www.who.int/mediacentre/factsheets/fs107/en/inf-fs/en/]). Yet, a few strains of *S. aureus* producing phosphotransferases have already been reported (274, 465), which suggests that this mechanism may become more significant in the future. Interestingly, the *mph(C)* gene encoding for this enzyme is located downstream of the *msrA* gene encoding for an efflux pump extruding macrolide and is expressed only in the presence of the later gene, indicating a common mechanism of regulation (275).

Efflux: Expression of efflux pumps is now recognized as a general mechanism developed by cells to protect themselves against invasion by diffusible, foreign substances. In this respect, constitutively expressed pumps able to transport macrolides are probably responsible for the poor susceptibility of several gram-negative to macrolides (249, 438). Moreover, these pumps have a wide spectrum of substrates, and are therefore often involved in multi-resistant phenotypes (438). In Gram positive bacteria, the expression of efflux pumps conferring resistance to macrolides is induced by the exposure of the bacteria to the antibiotic. Two main classes of pumps have been described so far. In contrast with what is described in Gram negative, these efflux pumps have a narrow spectrum. Thus, the Msr(A) pump of Staphylococci species and which is inducible by 14- and 15-macrolides, confers resistance to these macrolides and to streptogramins, but not to lincosamides (MS_B phenotype) (362). This pump belongs to the super family of ABC transporters (ATP-binding cassette) (438) which require ATP hydrolysis as an energy source. Interestingly, the *msr(A)* gene is frequently found in strains carrying the *erm* determinant or the *mph(C)* determinant, suggesting additional roles for this protein (357). The *Mef(A)* and *Mef(E)* efflux systems of streptococci, described in several species of streptococci including *S. pneumoniae* and *S. pyogenes* as well as in enterococci, are inducible and confer resistance only to 14- and 15-membered macrolides (M phenotype of resistance) (79, 249, 416). They belong to the MFS (major facilitator super family) of transporters (438) driven by proton-gradient motive force. The *mef(A)* gene is located on a conjugative transposon, and can therefore easily spread between bacteria or even between streptococci species (78, 151, 215, 250, 370, 411) .

Epidemiology of Resistance and Consequences for the Use of Macrolides

Resistance towards Gram positive cocci is now widespread. For *S. pyogenes*, the global incidence (as determined in worldwide surveillance studies) has reached an average of about 10 % (with figures varying from undetectable levels in some countries up to >40% in others [like Poland]). Efflux and ribosome methylation are found in similar proportions (126). Resistance of *S. pneumoniae* to macrolides reaches about 30% (again with a large heterogenity among countries, some of them showing rates >40% [France, Hungary, Spain] and even >80% [South Korea]). On a worldwide basis, the most frequent mechanism of resistance is due to ribosome methylation followed by overexpression of efflux pumps, but some strains harbor both mechanisms (126). Ribosome methylation, however (giving rise to cross resistance with clindamycin and streptogramins), is predominant in Europe whereas efflux is the major mechanism in the United States (110, 190), and about equal numbers in Japan (but where the combination of both mechanisms reach about 16% (307)). About half of these macrolide-resistant *S. pneumoniae* are also resistant (or show a decreased susceptibility) to penicillin and cotrimoxazole (55). Most strains of *S. aureus* are resistant to macrolides. Ribosomal methylation is more frequent in methicillin resistant organisms (>60%), while efflux is more often observed in methicillin-sensitive organisms (378, 379, 384). From a global perspective, 14- or 15-membered macrolides can no longer be considered as first choice antibiotics for infections caused by *Staphylococcus* and Streptococcal species in the absence of information concerning bacterial susceptibilities (as available from surveillance data in a given geographic region or, ideally, in the individual patient to be treated). The 16 membered-macrolides are not highly active against *S. aureus* and are, therefore not recommended in for *S. aureus* infections. Concerning *S. pneumoniae,* the fact that the 16-membered macrolides are not inducers of the erm-mediated resistance has erroneously led to the conclusion that they could be potentially useful in an environment where this mechanism of resistance is predominant. Inducible resistance, however, occurs only in a minority of *S. pneumoniae* isolates and the advantage of the 16-membered over the 14/15-mem-

TABLE 3 • Main Pharmacokinetic Properties of Macrolide Antibiotics

Pharmacokinetic parameter	*Erythromycin* (500 mg bid) (45)	Roxithromycin (150 mg qd) (349)	Clarithromycin (250 mg qd) (338, 339, 410)	Dirithromycin (500 mg qd) (45, 463)	Azithromycin (500 mg qd) (136, 338, 339)	Miocamycin (600 mg qd) (52)	Josamycin (500 mg) (59)	Spiramycin (6 Mio U.I.) (59)
Cmax (mg/l)	3	6.8	6.8	0.2-0.6	0.4	2-3	1.2	1.2
Tmax (h)	1.9-4.4	2	2.7	3-5	2.5	2	1	2
T ½ (h)	2	8-13	4.4	42	35-40	1	2	8
Vd (l/kg)	0.64		3-4	11	23-31			
Bioavailability	25-60 %	72-85 %	55 %	6-14%	37%			
Protein binding	65-90	73-96	40-70	15-30	12-40		10	12
Tissue/serum concentration	0.5	1-2	3-8	20-30	50-1150		2-20 [b]	1-30
AUC (mg.h/l)	4.4-14	70	4.1	3.8	2-3.4	3	7.9	8.5

bered macrolides in this context is therefore quite marginal. Indeed, in the case of *S. aureus*, most clinical strains are poorly sensitive, whereas inducible resistance makes only a minor proportion of the *S. pneumoniae* isolates. The only place for 16-membered macrolides against the 14-membered macrolides is therefore in infections caused by strains resistant by efflux.

The situation appears more favorable for those Gram negative organisms that are susceptible to macrolides, since only a small proportion of *H. influenzae* has been found resistant to macrolides so far (156, 189). But it must be remembered that macrolides are intrinsically poorly active against *H. influenzae* and resistance is actually a shift of the population across an arbitrary limit.

The overall result of this situation is that, today and in many European countries, macrolides are no longer indicated as first line antibiotics in most respiratory tract infections in which *S. pneumoniae* or *S. aureus* is considered as a likely causative organism. An important conclusion of an European Conference on Antibiotic Use in Europe (15-17 November 2001, Brussels, Belgium) was that (i) for each indication, local contemporary susceptibility data should be available to guide empirical prescribing for common target pathogens, and (ii) a 10% prevalence resistance rate for key pathogens was a reasonable threshold above which indications for using macrolides should be reconsidered (although in specific indications where no alternative treatment is available, a higher threshold could be acceptable)[2]. In the United States, macrolide resistance among *Streptococcus pneumoniae* is a growing global concern, although its specific impact on public health is not currently well defined. A consensus Working Group convened in March 2001 to address whether credible, scientific data substantiate macrolide resistance in *S. pneumoniae* as: (i) producing significant morbidity; (ii) creating attendant health and economic burdens; (iii) constituting a public health threat; and (iv) warranting intervention, including development of new antibiotics with efficacy against these strains. Despite the limitations of available clinical data, concern about the possibility of treatment failure with macrolides was expressed in clinical practice and translated in formal treatment guidelines, questioning the future of these agents in the treatment of respiratory tract infections (291). Because activity against *Haemophilus* also remains problematic, many European guidelines tend to discourage the use of macrolides for serious infections involving this organism. Conversely, the use of macrolides in infections caused by *Mycoplasma* (except *Mycoplasma hominis*), *Chlamydia*, or *Legionella*, for which activity remains excellent, remains fully supported.

[2] see *http://www.md.ucl.ac.be/facm/esac/* (the conclusions of all other workshops of this Conference are available for download at *http://www.ua.ac.be/main.asp?c=*ESAC&n=515&ct=ESACCONF03&e=o725*

TABLE 4 • Dosages of Macrolides.

	adult	child
Erythromycin	500 mg 4 X/day	12.5 mg/kg 4 X/day
Roxithromycin	150 mg 2 X/day	3 mg/kg 2 X/ day
Clarithromycin [a]	250 mg-1000 mg 2 X/day	7.5 mg/kg 2 X/day
Dirithromycin	500 mg 1 X/day	-
Azithromycin	500 mg 1 X/day or 500 mg on day 1 and 250 mg on days 2-5	10 mg/kg on day 1 and 5 mg/kg on days 2-5
Miocamycin [a]	600 mg 2 X/day	25 mg/kg 2 X/day
Spiramycin	3 Mio U 2-3 X/day	0.075-0.1 Mio U/kg 2-3 X/day
Josamycin [a]	500 mg – 1000 mg 2 X/day	10-20 mg/kg 2-3 X/day

[a] a 3 X/day administration should be preferred to an increase of the dose given 2 X/day in case of less susceptible organism, based on pharmacodynamic considerations (time above MIC).

PHARMACOKINETICS

Absorption

The main pharmacokinetic data of macrolides are summarized in Table 3. Due to their amphiphilic character, macrolides are diffusible molecules, which are well absorbed by oral route (bioavailability 30-50%, and up to 80% for roxithromycin). The implication of efflux transporters, like P-glycoprotein, capable to extrude them from enterocytes to the intestinal lumen has been examined, but does not seem to play a clinically significant role (321). Only erythromycylamine has been commercialized as a prodrug (dirithromycin) because preclinical animal studies revealed a poor oral bioavailability (83). The effect of food on macrolide absorption depends on the formulation (473). In particular, some formulations of azithromycin (capsule and powdered suspension) and erythromycin (base or stearate) need to be taken 1 hour before or 2 hours after meals. In the other cases, macrolides are best taken during the meal to improve the digestive tolerance. The serum peak is usually reached within 2 hours.

Distribution

Probably the most striking pharmacokinetic property of macrolides is their large volume of distribution (21, 306), which is related to their exceptional ability to accumulate inside eukaryotic cells. The mechanism of this accumulation consists most probably in the diffusion of the non-protonated form through the membranes and the trapping of the less diffusible protonated form in the acidic compartments of the cells (lysosomes) (60, 61), as proposed for other cationic amphiphiles (100). This mechanism also explains why a dibasic molecule like azithromycin accumulates to a still larger extent. The consequences of this large volume of distribution is that the serum level of macrolide (and of azithromycin, in particular) is low which may limit their efficacy, while their tissular and cellular concentrations are high, which may be an advantage for the treatment of infections localized in these compartments (374, 473). Penetration in the CNS is, however, limited (225), and only subtherapeutic levels can be reached in this compartment.

Routes of Elimination

Macrolide elimination mainly occurs by metabolization through the cytochrome P450, which explains the numerous drug interactions they can induce (see below). Macrolides are primarily eliminated through the bile, with the exception of clarithromycin which shows significant elimination in the urine (306, 462). The half-life of the neomacrolides is longer than that of erythromycin (and the derivatives that were selected for commercialization were largely selected on that basis), so that less frequent administrations are required. Azithromycin elimination is extremely slow (136), probably because of its prolonged retention in cells and/or tight binding to phospholipids (437). It can be administered once-daily and for much shorter periods (3 to 5 days) than other macrolides.

DOSAGE

Adults and Children

Dosages for macrolides are given in Table 4.

Renal Failure

Dosage reduction (50-75%) is only required for erythromycin and clarithromycin (and possibly for dirithromycin) in case of severe renal failure.

Hepatic Failure

The degree of modification of macrolide pharmacokinetics by renal insufficiency or hepatic disease is usually not considered clinically relevant, and no recom-

mendation for dose modification is necessary in these patients (332). A 50% reduction in daily roxithromycin dosage has, however, been recommended for patients with liver cirrhosis, even though C_{max}, T_{max}, and AUCs are not affected in these patients (349). The pharmacokinetics of macrolides is modified in elderly patients.

Elderly

Dosage adjustment is usually not required in the elderly with conventional dose, although the pharmacokinetics of macrolides is modified in these patients. Closer than usual clinical monitoring of the older patient has therefore been advocated (332).

Body Composition

Since macrolides are concentrated in extravascular tissues rather than plasma, dosage adjustment is not required in patients with ascites or with edema as well as in obesity.

ADVERSE EFFECTS

For many years, macrolides were considered as safe antibiotics even though specific adverse effects were recognized early on. Serious untoward effects were rare with erythromycin with the exception of cholestatic hepatitis that can be striking. Allergic reactions, including eosinophilia, fever, and skin eruptions usually disappeared upon treatment cessation. Over the years, however, more attention was paid to other side effects since these tended to limit the use of erythromycin. More recently, regulatory authorities were made also made alert of possible cardiac complications related to the prolongation of the Q-T interval. The overall toxicity profile of macrolides appears, therefore, less favorable today than originally considered.

Gastrointestinal Adverse Effects

These are the most common side effects and easily observed by patients. Abdominal pain (16%), nausea and vomiting (14%), and diarrhea are reported with an overall incidence 30% for erythromycin (123). Erythromycin, actually, acts as a motilin receptor agonist in the gastrointestinal tract (328) and stimulates stomach and gut motility (208, 234). 14-membered macrolides and oleandomycin, but not 16-membered macrolides, are active in inducing interdigestive migrating contractions (MIC) in the stomach in association with the endogenous release of motilin, which suggests specific structure-activity relationships (209). Accordingly, erythromycin is now used as a therapeutic agent for some motility disorders due this adverse effect. An intense search for more specific and active derivatives has, nevertheless, been quite active and has recently led to the discovery of GM-611 (mitemcinal), an acido-stable derivative of erythromycin devoid of antibacterial activity but endowed with a marked gastrokinetic activity (329, 469). Macrolide-induced emesis may be partially due to 5-hydroxytriptamine receptors. This adverse effect is dose-dependent and probably structure-related (317). Gastrointestinal adverse effects of macrolides are largely independent from the route of administration since they relate to receptor occupancy by the circulating antibiotic (385).

Efforts have been spent to try to decrease the severity and incidence of the gastrointestinal side effects of erythromycin. Various salts and galenic formulations have been tested without reproducible results. One of these salts, erythromycin acistrate, was claimed to be better tolerated (36% of the patients with gastrointestinal side effects versus 50 to 54% for erythromycin base) (468). With respect to the neomacrolides, dirithromycin, which acts as erythromycylamine and therefore resembles erythromycin the most, still causes discomfort in up to 22% of patients (104). Lower figures have been reported for the newer molecules and ranging from 3% for roxithromycin (40), 9% for clarithromycin (176), and 10% for azithromycin (198).

Hepatotoxicity

Hepatotoxicity is a rare but serious adverse effect of erythromycin. The incidence of patients developing acute symptomatic liver disease resulting in hospitalization after treatment with a 10-day course of erythromycin was estimated at 2.3 per million patients (64). The risk of cholestatic jaundice was estimated at 0.4 per million patients (102). Hepatotoxicity occurs most commonly in adults and usually after 1 to 2 weeks of drug administration. Nausea and abdominal pain are initial symptoms followed by fever (50%). Patients (75%) show eosinophilia (> 500 cells/mm^3) and uniformly elevated transaminase levels. Liver function tests reverted to normal within days after discontinuation of drug but may occur after rechallenge (122). Hepatotoxicity can occur with any erythromycin formulation (108, 319), although most of the initial reports implicated the estolate formulation (122). The mechanism of this toxicity may represent a hypersensitivity and toxic reactions resulting formation of nitrosoalkanes (336). Troleandomycin, erythromycin and its prodrugs form nitrosoalkanes. The semisynthetic macrolides rarely or never form nitrosoalkanes and therefore are unlikely to cause hepatotoxicity (334). Elevated liver enzymes has been reported with high dose clarithromycin (2000 mg/day) in elderly patients (46).

Ototoxicity

The incidence of ototoxicity is uncertain but it is likely underestimated. A prospective case-control study found evidence of ototoxicity in 21% of patients receiving

a 4 g/day erythromycin, when audiograms were performed and patients were closely monitored (413). Subjective symptoms begin within the first week of drug administration (366, 413), but are usually reversible within 1 to 30 days upon discontinuation of the drug (51). However, irreversible tinnitus unilaterally (254) and irreversible hearing loss (6) has been reported with intravenous administration of erythromycin lactobionate 4 gr/day and 2 gr/day respectively. Ototoxicity has also been reported with clarithromycin (97) and azithromycin (448). The mechanism of erythromycin ototoxicity is not known, but it may occur by an effect on the central auditory pathway (51) and its probably dose-dependent (413, 421). While auditory dysfunction is most common, vestibular dysfunction may also occur (350). Erythromycin causes low local tinnitus, and hearing loss ranges from bilateral flat to high frequency sensorineural loss, which can be detected on audiograms at both conventional (0.25 - 8.0 kHz) and extended high frequencies (8 - 14 kHz). Ototoxicity can occur with all formulations, including lactobionate and stearate (121, 366). Preexisting hepatic or renal abnormalities, advanced age, high dosages and concurrent ototoxic medications are predisposing factors (181, 435, 443). Ototoxicity has also been reported in patients without predisposing factors (6, 366).

Other Adverse Reactions

Allergic reactions are rarely reported for all macrolides (334), although skin rashes are not exceptional. Erythromycin administered intramuscularly can cause pain at the injection site, when administered intravenously, causes thrombophlebitis (4 %) (413).

Macrolides, like ketolides, certain fluoroquinolones, and other classes of antimicrobial agents have been associated with prolongation of cardiac repolarization (prolongation of the QT interval). According to a recent review (203), this effect is most notable with erythromycin, clarithromycin, and telithromycin. The molecular mechanism appears to be a blockade of the HERG channel-dependent potassium current in myocyte membranes (446). Clarithromycin (3-100 μM) has also been shown to exert concentration-dependent lengthening effects on action potential with higher efficacy and reverse frequency-dependence in Purkinje fibers (150). These interactions may give rise to polymorphic ventricular tachycardia, "*Torsades de Pointes*" or ventricular fibrillation. There is, however, no simple correlation between the prolongation of repolarization and the proarrhythmic potential (erythromycin > clarithromycin > azithromycin) in the rabbit experimental model, which suggests other interactions of the drugs with the myocardial cells (288). In any case, the risk of malignant arrhythmias is increased by concomitant usage with Type Ia or III anti-arrhythmic agents, with other drugs that prolong the QTc interval such as cisapride (239, 442) or terfenadine, or drugs that compete for the same metabolic routes as macrolides (116).

Risk For Pregnancy

Erythromycin and azithromycin are in category B, like penicillins and cephalosporins, in FDA pregnancy categories, while clarithromycin is in category C.[3]

MONITORING REQUIREMENTS

Therapeutic drug monitoring for macrolide antimicrobials is not required. Patients with preexisting hepatic or renal abnormalities, at advanced age, on high dosages of macrolides and on concurrent ototoxic medications need, however, to be followed for ototoxicity (181, 435, 443), especially in case of predisposing factors (6, 443).

DRUG INTERACTIONS

Drug interactions with macrolides are a non-negligible problem, which seriously limits their use in high risk patients. The main mechanism involved in these interactions is the ability of macrolides to bind to cytochrome P_{450} (group 3A4). As shown in Figure 4, the metabolization of erythromycin leads to the formation of an oxidized derivative able to bind to this enzyme with a high affinity, impairing thereby the subsequent metabolization of other substrates of the same cytochrome (333). The elimination of these co-administered drugs is therefore reduced, causing a potential risk of toxicity (333, 447).

The main clinically-relevant interactions related with the inhibitory effect of macrolides on cytochrome P450 are summarized in Table 5. Macrolide differ by their ability to induce such interactions, depending on the tightness of their binding to the ribosome, which varies in function of the steric hindrance around the tertiary amine of the desosamine and of their degree of lipophilicity. In this respect, erythromycin is characterized by the strongest, and azithromycin and erythromycylamine by the lowest binding, the other molecules having an intermediate behavior (333, 447). On a practical point of view,

[3] Definitions of categories are (according to the section "Current Categories for Drug Use in Pregnancy" available on the FDA Website at http://www.fda.gov/fdac/features/2001/301_preg.html):
B: Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus; C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women, or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.

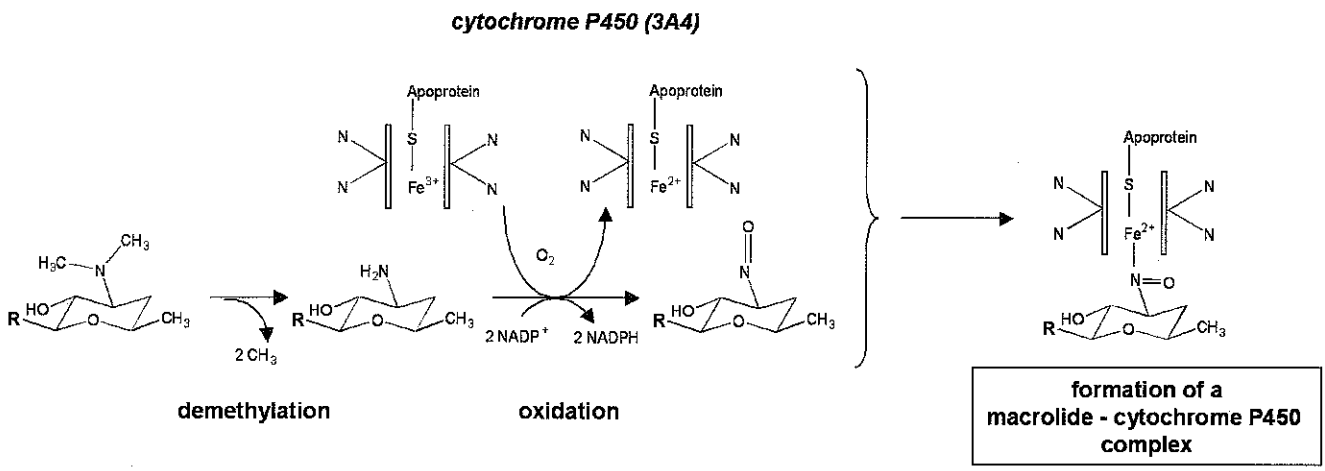

FIGURE 4 • Metabolization of erythromycin by cytochrome P_{450} and formation of an inactive complex. The tertiary amine of the desosamine is metabolized in nitroso-alkane, which forms a stable, inactive complex with the ion Fe^{2+} of the cytochrome. This mechanism is responsible for the inhibition by macrolides of the metabolization of other drugs. Adapted from (333).

this means that azithromycin and erythromycylamine are the safest macrolides to use when risks of drug interactions are suspected; erythromycin should be avoided, and clarithromycin, roxithromycin, ketolides or 16-membered molecules must be used with caution, in particular in the case of co-administration of drugs for which an overdosing may have toxicological consequences (322, 458). The use of any macrolide should be contraindicated when the interaction may have a life-threatening risk. This is the case for ergotamine (risk of ergotism) or for drugs able to prolong the QT-interval and to increase the risk of "Torsade de pointes" due to the macrolides (88), as discussed above. The risk is even larger if these drugs themselves prolong the QT interval, which is the case of tamoxifen, fluoxetine, salmoterol, cisapride, astemizole, terfenadine, or grepafloxacin (note that the last 4 drugs have been withdrawn from the market because of their excessive risk). Coadministration of inducers of the cytochrome P_{450} 3A4, such as rifampin or rifabutin, or of other macrolides can reduce macrolide plasma levels, which can lead to therapeutic failure or to selection of resistant strains.

Finally, it is also important to note that macrolides are inhibitors of P-glycoprotein, an eukaryotic efflux pump which is now considered as playing a limiting role in the intestinal reabsorption of several drugs (436, 439). This mechanism has been evoked for example to explain why macrolides may increase the serum level of digoxin (237). This new mechanism of interaction could come in complement with another one, consisting in an inhibition by macrolides of the intestinal metabolization by the gastrointestinal flora of digoxin in less active compounds (295). In any case, this increase oral bioavailability may cause an overdosing in about 10% of the patients (38).

CLINICAL INDICATIONS

Respiratory Tract Infections

Antibiotic use for respiratory tract infections represents a major portion of all consumption in humans, a large proportion of which seems irrational (154). Yet, most national and international guidelines (among those from the Centers for Disease Control and Prevention) underscore that antibiotic treatment, at least in adults without comorbidity, does not enhance illness resolution of minor upper respiratory tract infections and is therefore not recommended (152, 397). Similar conclusions have been reached for children (114). Because the prevalence of oral antibiotic treatment for patients diagnosed with nonspecific upper respiratory infections (colds, pharyngitis, bronchitis, influenza, ...) is high (47, 197), and because of the increasing rate of resistance of most pathogens (see above), interventions to reduce antibiotic prescribing are needed. Macrolide use in respiratory tract infections should therefore be revisited in such a context (132, 134, 210, 291).

Pharyngitis: Erythromycin is one of the most effective antimicrobial agents for treatment of nonstreptococcal pharyngitis due to *Chlamydia pneumoniae and Mycoplasma pneumoniae* (159, 277). It is very effective in pertussis infection as well as for decreasing transmission during pertussis outbreaks (404). For diphtheria and for carrier state with *Corynebacterium diphtheriae*, erythromycin is the drug of choice.

Erythromycin is the alternative therapy of choice for penicillin allergic patients with Group A beta hemolytic streptococcal pharyngitis (127), the most common bacterial cause of pharyngitis (232). The increasing resistance of these organisms to erythromycin and macrolides in general [up to 25-30% in some countries of Eastern

TABLE 5 • Drug Interactions of Macrolides and Therapeutic Attitudes.

Macrolide	totally contra-indicated drugs	Drugs to use with caution (requiring a dose reduction and/or a therapeutic monitoring)
Erythromycin	astemizole cisapride ergotamine terfenadine	oral anticoagulants benzodiazepines bromocriptine carbamazepine cyclosporin clozapine digoxin felodipine lovastatin sildenafil theophylline
Roxithromycin	astemizole cisapride ergotamine terfenadine	benzodiazepines bromocriptine theophylline
Clarithromycin	astemizole cisapride ergotamine terfenadine	oral anticoagulants bromocriptine carbamazepine cyclosporine clozapine digoxin theophylline
Dirithromycin	astemizole cisapride ergotamine terfenadine	
Azithromycin	astemizole cisapride ergotamine terfenadine	
Miocamycin	astemizole cisapride ergotamine terfenadine	carbamazepine cyclosporine
Josamycin	astemizole cisapride ergotamine terfenadine	benzodiazepines bromocriptine carbamazepine cyclosporine theophylline
Spiramycin	astemizole cisapride ergotamine terfenadine	
Rokitamycin	astemizole cisapride ergotamine terfenadine	

(based on demonstration of increase in serum level by coadministration with macrolides [interaction with cytochrome P450]) (11, 333, 473).

Europe (43) or in Greece (207)] is, however, of concern.

A series of studies have examined the other macrolides, sometimes in comparison between them and/or with other antibiotics [see also (473) for review]. The efficacy of roxithromycin for streptococcal pharyngitis seems satisfactory, although this has been subject to controversies. One open-label, randomized study with 300 mg once daily for 9 days (200 patients) found a clinical efficacy of 100% (99), and a large international trial (32; 405 patients) using a dose of 150 mg twice a day for 7-14 days obtained a 97% clinical success rate (267). Yet, one study with 31 available patients showed a comparable clinical response (83% for 300 mg daily for 10 days and 100% for 150 mg twice a day for 10 days) but an unacceptable bacteriological cure rate (33%) for both regimens (284). This study excluded patients considered to be carriers rather than infected. Tonsil concentrations of roxithromycin are somewhat lower compared to the other macrolides (137, 142). Comparative studies with clarithromycin (250 mg twice a day for 10 days) versus penicillin V (19, 253) or versus erythromycin (500 mg twice daily for 10 days) (371) in adults showed clinical

and bacteriological cure rates at about 90% without significant differences between the two drugs. In children with streptococcal pharyngitis, clarithromycin (7.5 mg/kg twice a day for 10 days) was significantly more likely to produce bacteriological cure than penicillin V (92 % versus 81 %, $p < 0.004$) although clinical cure rates were identical (96 % versus 94 %) (406). The gastrointestinal adverse effects were greater for clarithromycin (14%) as compared to penicillin V (5 %) ($p < 0.001$). In adults with streptococcal pharyngitis, dirithromycin (500 mg once daily for 10 days) had comparable clinical and bacteriological response to erythromycin (250 mg four times daily for 10 days) (104, 298). Cure rates were more than 79% for both macrolides; gastrointestinal adverse effects were significantly more frequent for erythromycin in the first study (54 % vs. 44 %, $p < 0.01$). Comparative studies of azithromycin (10-12 mg/kg/day for 3 days for children or 500 mg initially, then 250 mg a day for 5 days for adults), penicillin V (125 mg or 250 mg three or four times a day for 10 days), or erythromycin (30-50mg/kg/day for 10 days) in adults and children with streptococcal pharyngitis showed similar efficacies (about 90%, both clinically and bacteriologically) for all drugs (170, 196, 312, 456). Adverse effects, mainly gastrointestinal, were significantly more frequent for azithromycin than penicillin V in one study in adults (17% versus 2 %, $p < 0.001$) (196). However, azithromycin (12 mg/(kg x day) for 5 days) was statistically superior to penicillin V, both clinically (97% versus 82%, $p < 0.001$) and bacteriologically (95% versus 69%, $p < 0.001$) in a study of children (406), while another study found azithromycin (10 mg/kg once daily for 3 days) clinically as effective as penicillin V (100000 IU/(kg x day) in three doses for 10 days), but inferior in eliminating group A beta hemolytic streptococci from the throat (372).

It is important however to keep in mind that only 5-15% of pharyngitis cases in adults and 30% in children are caused by Group A beta-hemolytic streptococci and that the main goal of antibiotic treatment in these patients is the prevention of rare complications (82). Guidelines from the Centers for Disease Control and Prevention (for adults) and of the Infectious Diseases Society of America are: (1) to offer analgesic, antipyretic and supportive care to all patients with pharyngitis and (2) to limit antibiotic administration to those patients with a high likelihood of GABHS, based on appropriate differential diagnostic (Center criteria, and, in a second instance, on rapid antigen detection testing), and to consider penicillin as first choice, with erythromycin as alternative in allergic patients only (37, 82, 396). These guidelines, however, do not apply to patients at risk (chronic lung or heart disease; history of rheumatic fever, recurrent pharyngitis, immunosuppression) or during an epidemic of acute rheumatic fever of streptococcal pharyngitis (82).

Otitis Media: Erythromycin in co-administration with a sulfonamide (most often sulfisoxazole, which has a half-life of about 5-6 hours) has long remained the treatment of choice for otitis media (147, 451). Long term erythromycin treatment (erythromycin base at 600 mg/day for more than 4 months) was effective for the treatment of sinobronchial syndrome-associated otitis media with effusion (204).

As for pharyngitis, other macrolides have been more or less systematically compared to erythromycin, but most often in acute forms of the disease only. Clarithromycin (7.5 mg/kg twice a day for 10 days) compared with amoxicillin in the treatment of acute otitis media in children showed clinical success rates above 90% for both drugs without any significant differences between the two drugs (347). Clarithromycin (7.5 mg/kg twice a day for 10 days) and amoxicillin/clavulanate showed clinical response rates above 90% in two comparative studies (18, 276), but diarrhea (32% versus 12%, $p < 0.001$ and 40% versus 12%, $p < 0.001$), and diaper rash (12% versus 1%, $p < 0.004$) were significantly more common for patients treated with amoxicillin/clavulanate. Azithromycin (10-15mg/day for 3-5 days) compared to amoxicillin (292) or amoxicillin/clavulanate (16, 94, 228, 279, 337, 346, 372) or cefaclor (40mg/kg daily in three divided doses for 10 days) (314, 360) showed comparable clinical success of approximately 90%. However, a significantly higher incidence of side effects were found in the amoxicillin/clavulanate group in four studies (16% versus 2.5%, 30.8 vs.8.8, 31.0% vs.3.5%, 17.1% vs.7.2% $p<0.001$) (16, 228, 279, 372) in contrast to the low incidence of adverse effects for the other mentioned studies. Azithromycin (10mg/kg initially, than 5 mg/kg for 4 days) was comparable to amoxicillin/clavulanate in another study with 61% and 65% clinical response respectively. Side effects, mostly diarrhea, were more common in the amoxicillin/clavulanate group (17% versus 7%, $p<0.001$) (228). Azithromycin (10mg/kg once daily for 6 months) was found as a valid alternative to amoxicillin (20mg/kg once daily for 6 months) in prevention of recurrent acute otitis media in children, without substantial modifications of the nasopharyngeal flora (266).

This accumulation of positive evaluations should, however, be examined with caution. First, acute otitis media is largely a self-limiting disease in which the role of antibiotics in improving the clinical symptoms may often be marginal. The microbiologic results indicate indeed that approximately one quarter of children have acute otitis media due to a viral pathogen and that many episodes of bacterial otitis media resolve without antibacterial drugs (441), prompting European physicians to withhold antibiotic therapy from children with acute ear infections (49). In parallel, representatives of the US Centers for Disease Control and Prevention and the American Academy of Pediatrics concluded that physicians should make an appropriate distinction between acute otitis media and otitis media with effusion, use shorter courses of antibiotic therapy in uncomplicated cases of otitis media and limit prophylaxis to recurrence as defined strictly by number of

episodes (115). Second, most of the studies summarized above were performed in the early 90's, when resistance of *S. pneumoniae* towards macrolides was low. More recent evaluations have concluded that macrolides may no longer be indicated as first line therapy in otitis media in regions where resistance has become important, and that oral amoxicillin should remain the first line antimicrobial agent, with higher dosages when needed in view of the presence of *S. pneumoniae* with decreased susceptibility to β-lactams (113). In regions where resistant pneumococci are prevalent, it has also been shown that antibiotics with insufficient activity may not only fail to eradicate the organisms, but they may often induce middle ear superinfection with resistant pneumococci initially carried in the nasopharynx (89). Finally, studies using the double tympanocentesis approach, have shown that macrolides, and especially azithromycin, often fail to achieve eradication most likely because of the insufficient concentrations in the middle ear fluid, leading to suboptimal effects especially with respect to *S. pneumoniae* (90). This may have immediate consequences, since the same approach showed that clinical failures are significantly associated with inability to eradicate the causative organisms from the middle ear fluid within 3 to 4 days after initiation of antibiotic therapy (91). This topic, as well as the significance of the resistance, remains, however, a field of hot debate. A recent trial of single-dose azithromycin (30 mg/kg) in treatment of acute otitis media in children after a baseline tympanocentesis (120) showed clinical cure rates for patients infected with *Streptococcus pneumoniae* (88%) and with *Haemophilus influenzae* (64%) that were considered consistent with historical rates for the 5-day dosing regimen underlined above. Similarly, a very recent study comparing so-called high doses of azithromycin (20 mg/kg once a day for 3 days) and of amoxicillin-clavulanate (90 mg/6.4 mg/kg divided in two doses per day and given for 10 days) showed very similar high rates of success at short term (86 versus 84% at days 12 to 16, respectively) and a superiority of azithromycin in the long term (72 versus 61%, $p = 0.047$, at days 28 to 32), with an even larger difference for patients of less than 2 years (68 versus 51%, $P = 0.017$). These results, however, may be specific of the environment in which they were performed (US, Costa Rica and Chile) since resistance of *S. pneumoniae* in these patients was primarily linked to efflux mechanisms, with high-level azithromycin resistance (MIC ≥ 64 μg/ml) mediated by the *ermB* gene noted in only 15% of azithromycin-resistant isolates.

Sinusitis: Sinusitis refers to an inflammation of the sinuses that is most often accompanied by an inflammation of the nasal mucosa, so that the term 'rhinosinusitis' is more appropriate. Although physicians prescribe antibiotics in 85 to 98% of cases, sinusitis is often viral and frequently resolves spontaneously, even when of bacterial origin (398). In such a context, results of clinical studies comparing macrolides with placebo or with other antibiotic classes need to be considered with caution.

Roxithromycin at low dose (150 mg/day for 3 months) was thus found successful to reduce the symptoms of chronic sinusitis, probably due to a conjunction of antibiotic and anti-inflammatory activity (229). In open, randomized trials, a twice daily administration of 150mg for 10 days was as efficient as amoxicillin/clavulanate or azithromycin (75, 297). Similarly, clarithromycin (400 mg for 12 weeks) proved efficient in chronic sinusitis (178) and showed an efficacy comparable to levofloxacin, ciprofloxacin, amoxicillin/clavulanate or cefuroxime axetil in acute sinusitis when 250 or 500 mg are administered twice a day for 10 to 14 days (3, 80, 118, 401). A meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections including acute sinusitis (11 comparisons including 1742 patients) showed that azithromycin had similar clinical failure rates to the other antibiotics and there were no significant differences in bacteriological outcomes (206). A 3- or 6-day regimen with azithromycin led to an equivalent success rate (186).

Despite these quite positive results, macrolides are currently not considered as recommendable antibiotics in guidelines from the CDC, and the Sinus and Allergy Health Partnership (188, 393, 398). The reason for this is the high rate of resistance of *S. pneumoniae* to macrolides and to their insufficient activity against *H. influenzae* in several countries (188, 343). Based on pharmacokinetic/pharmacodynamic breakpoints, macrolides now appear to be inactive against one-third of the *S. pneumoniae* isolates and all *H. influenzae* isolates (343). A mathematical model was elaborated to predict the response to antimicrobial therapy and establish guidelines, taking into account the proportion of patients with bacterial infection, the rate of resolution of disease in culture-negative patients, the distribution of causative pathogens, the rate of spontaneous resolution for each pathogen, and the susceptibility of these pathogens at PK/PD breakpoint (343, 393). Using this model, a response rate of 80-90% was calculated with macrolides against > 90% with amoxicillin/clavulanate in children. In such a context, macrolides appear, today, only as alternatives in β-lactam allergic patients. It must also be reminded that the usefulness of antibiotics in sinusitis is still a matter of debate (4, 30, 185, 428). Accordingly, current guidelines do not recommend the systematic administration of antibiotics in this indication, either in children or in adults (81, 188). In particular, waiting 48-72 hours before prescribing antibiotics is recommended (30).

Bronchitis: The vast majority of uncomplicated acute bronchitis have a nonbacterial cause, so that routine antibiotic treatment is not recommended, regardless the duration of cough (153). The CDC guideline is based on meta-analyses which fail to show an impact of antibiotic treatment on duration of illness, limitation of activity, or

loss of work, regardless of erythromycin, doxycycline or sulfamethoxazole use. The only patients who could benefit from antibiotic treatment, and macrolides in particular, are those infected by *Mycoplasma*, but differential diagnosis is difficult.

In contrast, antibacterial therapy seems beneficial in patients suffering from exacerbation of chronic obstructive pulmonary disease (COPD). *H. influenzae* is the most frequent bacteria isolated, and should therefore be included in the spectrum of the chosen antibiotic (473). Among macrolides, clarithromycin and azithromycin appear the most active ones (74), but there is no clear data showing superiority as compared to other neomacrolides. Indeed a clinical and bacteriological efficacy above 80% was reported with dirithromycin (500 mg once a day for 5-7 days) as compared to erythromycin (250 mg qid for 7 days), clarithromycin (250 mg twice daily) or azithromycin (500 mg qd on day 1 and 250 mg qd on days 2 to 5) (67, 141, 201, 391). Macrolides are also equivalent to other antibiotic classes. Thus, roxithromycin (300 mg once daily for 10 days) was comparable (cure rates of 90%) to amoxicillin (500 mg three times a day for 10 days)(199); clarithromycin (250 mg twice a day for 7-14 days) was comparable (clinical success, 90%) to ampicillin (250 mg qid for 7-14 days) (8, 20); azithromycin (500 mg once a day for 3 days) was found as effective as amoxicillin/clavulanate (625 mg tid for 10 days) or as amoxicillin (500 mg tid for 5 days) or levofloxacin (500 mg q24h for 7 days) (12, 24, 35, 191, 287).

Pneumonia: In contrast to other respiratory tract infections, pneumonia is often caused by bacteria and clearly requires antibiotic administration. Surveys in North America indicate that the major pathogens associated with community acquired pneumonia are *Streptococcus pneumoniae* (20-60%), *Haemophilus influenzae* (3-10%), *Staphylococcus aureus* (3-5%), and organisms associated with the so-called atypical forms of pneumonia [*Mycoplasma pneumoniae* (1-6%), *Chlamydia pneumoniae* (4-6%), and *Legionella pneumophila* (2-8%)] (25). Nosocomial pneumonia, in contrast, is mainly caused by Gram negative organisms that are out of the spectrum of macrolides.

A large number of clinical studies have accordingly been conducted to evaluate the efficacy of macrolides in community-acquired pneumonia [see (133) for review]. These studies demonstrate equivalency to beta-lactams or fluoroquinolones, but they rarely include severely-ill patients. In combination with beta-lactams, macrolides are likely to reduce the duration of hospitalization and mortality rate, as suggested from the results of two studies examining more than 60,000 medical records collectively (48, 149). No difference in efficacy could be evidenced between macrolides, but erythromycin was more prone to induce side effects (13). Thus, a comparable success rate was obtained with clarithromycin (250 mg bid for 14 days for adults and 15mg/kg/day bid for 10 days for children) versus erythromycin (500 mg qid for 14 days and 40 mg/kg/day bid or tid for 10 days) (13, 41), dirithromycin (500 mg once daily for 10-14 days) versus erythromycin (250 mg qid for 10-14 days) (212, 255), or azithromycin (500 mg once daily for 3 days) versus clarithromycin (250 mg bid for 10 days) (313). Azithromycin (250 mg bid on day one followed 250 mg once daily for totally 5 days) was found as effective as erythromycin (500 mg qid for 10 days) or roxithromycin (150 mg bid for 10 days) in the treatment of atypical pneumonias where causative pathogens were identified by serological methods (380, 381). Intravenous route is considered in hospitalized patients. The lactobionate formulations of erythromycin have been used for a long time but clarithromycin or azithromycin are preferred because of their more convenient administration, the easy switch to oral forms while maintaining adequate efficacy (243, 296).

Many guidelines have been proposed to rationalize the antibiotic choice in community-acquired pneumonia [see (93, 133) for reviews] as well as in nosocomial pneumonia [see (264) for review]. In particular, the role of macrolides in community-acquired pneumonia has been extensively reviewed recently (133). In a nutshell, macrolides offer an adequate coverage of these bacteria, which is why they are recommended as empiric first line therapy in the guidelines of North America Societies for patients with no modifying factors (see the guidelines of the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, the American Thoracic Society, the Canadian Infectious Diseases Society, and the Canadian Thoracic Society) (9, 26, 183, 265). Guidelines from South America, Australia, Africa, and some Asian countries follow the same rules, considering macrolides as one of the antibiotic classes of first choice (15, 163, 290, 340, 467). The European Respiratory Society also proposes macrolides as a potential empiric choice, ranking it at the same level as β-lactams, fluoroquinolones, or tetracyclines (124). Guidelines from individual European countries and from some Asian countries, however, adopt another position, in which the coverage of atypical pathogens is not considered as a priority in empirical treatment. They rather put the emphasis on the optimization of the therapy towards *S. pneumoniae,* and, accordingly, recommend high doses of β-lactams as first line treatment (53, 111, 166, 325, 470). In these cases, macrolides are presented either as alternative, or as first choice when atypical pathogens are strongly suspected, or most often as combination with β-lactams. This type of combination is also recommended for elderly patients or patients with comorbidity, with the aim to insure optimal coverage of both pneumococci and atypical pathogens.In patients requiring hospitalization, intravenous administration of both macrolides and beta-lactams are recommended for the same reasons.

Discrepancies between guidelines may appear surprising at first glance, but they mainly stem from differences in perception of the implication and the risk

associated with *Legionella* spp. (out of an epidemiological context and in immunocompetent patients), *Chlamydia* spp. and *Mycoplasma* in pneumonia, and of the importance of the resistance problems for *S. pneumoniae*. First, the true role of organisms causing so-called atypical pneumonia remains controversial in most cases of the community-acquired forms of the disease because the etiological diagnostic is difficult and because these often present as mixed infections. Second, most of the studies evaluating macrolide efficacy in pneumonia have been performed when resistance of *S. pneumoniae* was still low, and their conclusions tend not to be questioned in many countries in the absence of clear evidence of clinical failures due to resistance. Moreover, in areas where efflux-mediated resistance is predominant (mainly North America), macrolides have been maintained because this mechanism confers low resistance level only. Conversely, in areas in which resistance is predominantly mediated by target modification and is therefore of high level (Europe, Asia), there is clearly little advantage and rather a significant risk at maintaining macrolides as first line antibiotics in monotherapy. Yet, translating this evidence into clinical guidelines remains slow because of the lack of studies specifically designed to evaluate the impact of resistance on outcome. Yet, documented case reports of failure due to resistant pneumococci exist (135, 453), and selection of macrolide-resistant pneumococci in patients receiving a macrolide has been evidenced (261, 300). Recent leading papers, including those by North-American experts, point to the fact that increasing resistance can be a cause of treatment failure and that new definitions of susceptibility criteria and treatment options are warranted (28, 93, 291, 318, 452).[4]

Use of Macrolides as Antiinflammatory Agents in Respiratory Tract Infections: Based on these considerations developed in the Adverse Effects section, administration of macrolides at low dose and long term is now proposed as adjuvant therapy for chronic respiratory tract infections, such as diffuse panbronchiolitis (a pathology which is frequent in Japan), chronic sinusitis, asthma, bronchestiestasis, and pulmonary infections in cystic fibrosis patients, even if the causative organisms are not susceptible to their antibiotic activity (143, 202). Thus, a prospective open trial evaluating the efficacy and safety of 200 mg once-a-day clarithromycin for 4 years in patients with diffuse panbronchiolitis showed a stable improvement in the pulmonary function in most patients and a sterilization of sputum specimens within 6 months, with no side effects (219). Similarly, a double-blind placebo-controlled study including 60 adults suffering from cystic fibrosis demonstrated that the administration of azithromycin (250 mg/day for 3 months) significantly improved the quality of life, reduced the CRP levels, the number of exacerbations and the decline of lung function (464). A multicenter, randomised, double-blind, placebo-controlled trial including 251 patients evaluated the interest of larger doses (250 mg [weight < 40 kg]; 500 mg [weight > 40 kg]) 3 days a week for 168 days (367). Treated patients again showed an improvement of their respiratory function, a gain of weight, and a reduced risk of exacerbations but experienced more frequent side effects (nausea, diarrhea, and wheezing). These encouraging results suggest the interest of this approach but also indicate that optimal dosing and duration of therapy needs to be better defined. The prolonged administration of low doses of macrolides in these indications also raises the issue of the potential selection of resistance in other pathogenic bacteria.

Sexually Transmitted Diseases

In vitro erythromycin, roxithromycin, clarithromycin, dirithromycin and azithromycin are active against commonly isolated pathogens of sexually transmitted diseases, namely *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma* spp. and *Ureaplasma urealyticum*. Thus, roxithromycin (150 mg twice daily for 10 days) was found effective in eradicating 97% of the isolates of *Chlamydia trachomatis*, 88% of *Ureaplasma urealyticum* and 73% of *Mycoplasma hominis* in patients with non-gonococcal urethritis (245). Azithromycin (with a conventional scheme of administration or with 1 g given as a single dose) was found as effective as doxycycline (100 mg bid for 7 days) in the treatment of sexually transmitted diseases including pelvic inflammatory diseases caused by *C. trachomatis, N. gonorrhoeae and U. urealyticum* (34, 246, 402, 403, 460) or cervical infections caused by *C. trachomatis* in adults (268, 320) and in adolescents (171). Similarly, azithromycin (2 g single dose) was found as effective as ceftriaxone (250 mg single dose) in the treatment of uncomplicated gonorrhea (172) while a 1 g single dose was as effective as doxycycline (100 mg twice daily for 7 days) in patients with non-gonococcal urethritis (247, 399).

On this basis, the current guidelines of the Centers for Disease Control and Prevention (68) recommend erythromycin 500 mg 4 times a day for 21 days as first choice or azithromycin 1g weekly for 3 weeks for the treatment of lymphogranuloma venereum caused by *C. trachomatis*, azithromycin 1g single dose in non-gonococcal urethritis, and erythromycin 500 mg 4 times a day for 7 days combined with metronidazole 2 g single dose for recurrent urethritis. As an alternative, they also recommend erythromycin 500 mg 4 times a day for 7 days for non-gonococcal urethritis or granuloma inguinale (donovanosis). The main indication of macrolides is without doubt infection by *Chlamydia trachomatis*. Antibiotic administration should be considered in

[4] see also footnote 2 above.

sexual partners and also in pregnant women to prevent transmission. Antibiotics are also warranted in patients with gonococcal infection because of the high risk of co-infection. The first choice in these indications is azithromycin, 1 g single dose, or erythromycin 500 mg 4 times a day for 7 days, or a fluoroquinolone for 7 days as an alternative. Erythromycin was considered as a first choice in pregnant woman, but recent studies suggest that azithromycin is also safe and effective (2, 289, 455). *Chlamydia* infection in children, including ophthalmia neonatorum, is treated by erythromycin 50 mg/kg/day for 14 days divided in 4 administrations; azithromycin 1 g single dose can be considered in children over the age of 8 years or weighting more than 45 kg (68). Most often, azithromycin is thus preferred in these indications because its peculiar pharmacokinetic profile allows for a single administration (minute treatment), insuring optimal compliance, even in developing countries where these diseases are endemic but where follow-up is difficult. Thus, clinical studies in resource-poor environments showed that a single dose of 1 g azithromycin is efficient in the prevention and the treatment of chancroid lesions caused by *Haemophilus ducreyi* (23, 430) or *Treponema pallidum* (2 g of azithromycin as a single dose or as two doses 1 week apart for treatment) (194, 195). Moreover, azithromycin seems protective at long term, since in a 3-4 year follow-up study none of the azithromycin-treated patients developed any signs of visceral syphilis or neurosyphilis (269). The interest of azithromycin in the treatment of *Chlamydia trachomatis* infections was also demonstrated in developing countries (364).

Skin and Soft Tissue Infections

Skin and soft tissue infections are most often caused by *Staphylococcus aureus* or β-hemolytic streptococci in outpatients, but more frequently by *S. aureus* (including methicillin-resistant strains), enterococci, *E. coli*, and *P. aeruginosa* in hospitalized patients (216). In this context, macrolides have long appeared as potentially useful in the community (whereas β-lactams [with an inhibitor of β-lactamases], fluoroquinolones, carbapenems, glycopeptides, streptogramins, or oxazolidinones were recommended for the treatment of severe infections in the hospital (139).

In an environment of low resistance, macrolides were found as effective as other antibiotics in the management of mild infection of the skin and soft tissues (roxithromycin [150 mg twice daily for up to 14 days] versus doxycycline [200 mg once daily] or penicillin [2.5 MU 8 times daily IV then 6 MU daily orally] in adults (5, 32) or clarithromycin [7.5 mg/kg twice daily for 10 days] versus cefadroxil [15 mg/kg twice daily for 10 days in children] (182)). Dirithromycin [500 mg once daily for 5-7 days] and erythromycin [250 mg qid for 7 days]) showed equivalent bacteriological and clinical successes in subcutaneous abscess, pyoderma and impetigo (105). More specific indications have also been proposed. Thus, azithromycin, because of its favorable pharmacokinetic profile, is the most suitable macrolide for the treatment of acne (131, 324). Clarithromycin, because of its higher intrinsic activity, represents a true advance in the management of patients with leprosy and other skin infections with atypical mycobacteria, most often in combination with other anti-mycobacterial drugs (146, 256, 299, 323, 369). Macrolides also proved useful for the treatment of rare infections like reticular bacillary angiomatosis in patients with acquired immunodeficiency syndrome (17, 352), or erythrasma due to *Corynebacterium minitissimum* (224, 459).

The increasing problem of resistance to macrolides in streptococci and staphylococci isolated from skin and soft tissues specimens compromises their usefulness as empirical therapy in community-acquired infections (323). Indeed, a recent worldwide survey indicates that erythromycin resistance in methicillin-sensitive *S. aureus* isolated both from in- and outpatients ranges from 12% (in Spain) to 26% (in USA), and reaches 80% in methicillin-resistant organisms. Likewise, resistance accounts for 10-26% of *S. agalactiae* or *S. pyogenes* isolates (216). Resistance rates are usually higher in younger (< 14 years) and older (> 65 years) patients (86), discouraging the use of macrolides in these populations.

Prevention of Bacterial Endocarditis

Updated prophylactic regimens for dental, oral, respiratory tract, or oesophageal procedures recommended by the American Heart Association for prevention of bacterial endocarditis in individuals at risk has included oral clarithromycin for children (15 mg/kg) and oral azithromycin for adults (500 mg) administered 1 hour before procedure. Macrolide use, should, however be restricted to penicillin-allergic patients (58, 92).

Mycobacterium avium Complex (MAC) Disease

Mycobacterium avium complex (MAC) is an important pathogen that can cause chronic lung disease in immunocompetent patients and disseminated disease, and has become widely known because of its isolation in increasing frequency in patients with the acquired immunodeficiency syndrome (AIDS), observed since the early and mid 80's (31, 180). Mycobacteria in general show a high degree of intrinsic resistance to most common antibiotics, which may be due to the presence of the mycobacterial cell wall with its specific composition and structure. Yet, rifabutin on the one hand, and clarithromycin and azithromycin on the other hand, were shown very effective *in vitro* as well as in animal models (129, 205, 335, 466). Both clarithromycin and azithromycin greatly improved the outcome of treatment regimens for MAC in patients (96, 97, 471). The United States Public Health Service

recommends that every regimen should contain either clarithromycin (500-1000 mg twice daily) or azithromycin (500 mg daily) and preferably ethambutol as a second drug with or without rifabutin (273). MAC prophylaxis is indicated in individuals with CD4+ cell counts < 50 cells/mm^3 with clarithromycin 500 mg twice daily or azithromycin 1200 mg weekly. Rifabutin plus azithromycin was even more effective but not well tolerated (179).

Shortly after the introduction of these drugs, resistant strains appeared due mainly to mutations at the level of the ribosome. Thus, resistance to clarithromycin both in the laboratory and in patients was already described as early as the early 90's (101, 214, 363), and these bacteria are also resistant to azithromycin (184). This resistance is often of high level and related to mutations of the rRNA (283, 429). Not surprising, it is most often selected in patients receiving macrolides as monotherapy (283) and with very low CD4+ counts (84). It is therefore proposed to administer macrolides as monotherapy in patients with cell counts ≥ 50/µl but in combination when cell counts are lower (161). This suggestion is rationalized by *in vitro* studies finding fewer resistant bacilli upon exposure to clarithromycin and ethambutol (303). Of concern, is the prolonged use of macrolides for MAC prophylaxis which is frequently selected for resistance in the respiratory flora of HIV-patients, discouraging the use of such a prophylaxis in patients who respond to antiretroviral therapy and therefore present a lower risk of developing MAC infection (1).

Helicobacter pylori Infections

Recognized as a potential cause of gastric and gastroduodenal ulcer in the late 80's (117, 263, 434), infection by *Helicobacter pylori* is now considered as the major cause of both the uncomplicated and complicated forms of this disease when discounting those caused by the inappropriate administration of non-steroidal anti-inflammatory agents (148). Macrolides were quickly recognized as being active *in vitro* against *H. pylori*, together with tetracyclines, ampicillin or amoxicillin, metronidazole, and fluoroquinolones and several other antibiotics (155). Accordingly, several trials demonstrated that, for patients with peptic ulceration and colonized with *H. pylori*, eradication of the bacteria is associated with substantially lower ulcer recurrence rates than are short-course therapies directed exclusively against gastric acidity (157, 187). Eradication of *H. pylori* is also considered as one most cost-effective approach in this set up for most patients (218). However, clinical trials have also illustrated several basic principles of chemotherapy. First, and as in most chronic infections, all treatments must use combination therapy partly for synergy (326) but also for prevention of resistance (see below). Second, *in vitro* activity is not necessarily predictive of *in vivo* efficacy, and erythromycin is a good example of this phenomenon, most likely in account of its acid instability (281). Third, acquired resistance frequently develops, ruling out certain antibiotics such fluoroquinolones, and largely jeopardizing others like metronidazole (259). Within this context, clarithromycin (250 mg for 14 days), combined with omeprazole (a proton pump inhibitor) and/or the anti-anaerobe metronidazole was shown quite effective in eradicating *Helicobacter pylori* (83 %) with frequent but mild side effects. In a later study, clarithromycin 500 mg thrice daily and omeprazole 40 mg daily for two weeks showed an eradication rate of 78% and was suggested as an as alternative to standard triple therapy (260). This lead was, however, not followed and, in a meta-analysis of 666 studies that included 53,228 patients, combinations of a proton-pump inhibitor, clarithromycin, and a nitroimidazole; or a proton-pump inhibitor, clarithromycin, and amoxicillin; or a proton-pump inhibitor, amoxicillin, and a nitroimidazole were judged to be necessary and offering similar, adequate cures of 78.9 to 82.8% according to intention-to-treat analyses (240). The same meta analysis showed (i) that increasing the dose of clarithromycin to 1.5 g per day improved rates of cure, but increasing the doses of the other antibiotics did not, and, quite interestingly, (ii) that the countries in which the studies were performed had a significant impact on eradication rates, and (iii) that treatment duration did not influence the outcome. In a pharmacoeconomic analysis, the highest eradication rate (in excess of 90%) was achieved using 1-week regimen including omeprazole in combination with either clarithromycin or amoxicillin and a nitroimidazole, and was considered the most cost effective in comparison to episodic therapy with omeprazole or maintenance therapy with ranitidine (217).

The usefulness of other acid-stable macrolides has been assessed, but these remain less popular than clarithromycin. Initial studies with roxithromycin alone or in combination with metronidazole were encouraging (69, 408). In triple therapy studies, roxithromycin was shown less effective than clarithromycin in one study (412), but another study did not find such differences (342). In a quadruple therapy consisting of omeprazole, amoxicillin, metronidazole, and roxithromycin, cure rates as high as 95% were recorded (315). No reinfection after apparent successful eradication of *H. pylori* with 20 mg of omeprazole once per day, 500 mg of amoxicillin three times per day, 250 mg of metronidazole three times per day, and 150 mg of roxithromycin twice per day for 1 week was seen (387).

Results have also been variable for azithromycin. Initial studies with 30 patients concluded that 750 mg or more of azithromycin might eventually be able to replace metronidazole or clarithromycin in standard triple therapy, but that additional studies were necessary to identify a regime that is both effective and tolerable (7). In a further study two-week triple therapy with omeprazole, amoxicillin, and (for the first 3 days) 500 mg azithromycin was said to be highly effective (91.6% in 48 patients) in eradicating *H. pylori* (33), but considerably lower values (70%)

were obtained with azithromycin (500 mg) for the first 3 days combined with bismuth subcitrate (120 mg q.i.d) or omeprazole (40 mg) for 14 days plus metronidazole (250 mg q.i.d) for the first 7 days (107). A lower efficacy of azithromycin was reported in a similar study (54), and in a subsequent study using azithromycin 500 mg daily for 7 days combined with an extended-release formulation of metronidazole and with omeprazole (242). Conversely, azithromycin 500 mg once a day for 3 days combined with metronidazole 250 mg twice a day for the same 3 days and lansoprazole 30 mg once a day for 1 week was highly effective (91.2% in 57 patients) (66). In a congress report written in 1997, the current data were taken as confirming the equivalence of azithromycin to clarithromycin (330), but the optimal dose of azithromycin was later found to be at least 1 g daily (76).

Resistance of *H. pylori* to clarithromycin is increasing, possibly as a consequence of increased usage of roxithromycin and clarithromycin, suggesting that more patients are likely to fail to respond to empirical therapy and will need microbiological investigation (162). Failure in *H. pylori* eradication concerns as much as 10-30% of the patient population. The most frequent factors associated with these failures are the poor compliance, the younger age, smoking, and the weak gastric inflammatory activity, but resistance is certainly an important determinant (50). Whereas resistance to tetracycline or amoxicillin remains quite infrequent so far (2 and 6 % of isolates, respectively), it is frighteningly high for metronidazole (30 % in France to 66 % in some countries such as Alaska), and clarithromycin (from 15 to 30% in the same countries) (50, 280, 282). Macrolide resistance is still increasing, probably in relation to the substantial use of macrolides in the community for other indications (162). The risk for clarithromycin resistance was increased (relative odd factor: 1.6) among patients who were given macrolide prescriptions in the past 10 years (280). In this context, the first line treatment should follow the official recommendations, which are the combination of an inhibitor of proton pump, amoxicillin, and clarithromycin, and to avoid associating clarithromycin and metronidazole. In case of failure, the dose of the inhibitor of proton pump should be doubled and the antibiotic not used during the first line treatment introduced (metronidazole if clarithromycin was initially used or clarithromycin if metronidazole was used initially). Culture with measurement of the strain sensitivity is required in case of further failure (50).

Toxoplasmosis

Infection by *Toxoplasma gondii* is the most common parasitic infection worldwide, with severe manifestations in immunosuppressed patients and foetuses (71). In immunosuppressed patients, the most effective therapy is a combination of pyrimethamine and sulfadiazine, but adverse effects limit its use. Based on pilot studies, acceptable alternatives include pyrimethamine plus clindamycin or azithromycin (500 mg daily for 4 weeks) or clarithromycin (2 g daily during 6 weeks) (71, 103, 130, 365). Further studies with azithromycin suggest that higher doses (900-1200 mg daily) provide reasonable success (67%) in the induction phase of the treatment but that relapses are more frequent in the maintenance phase if compared with the conventional therapy, suggesting that azithromycin should be reserved for patients intolerant to other drugs (211). Spiramycin does not kill the parasite efficiently, and cannot be recommended for eradicating the most severe forms of toxoplasmosis (72). Since pyrimethamine cannot be administered to pregnant women because of its teratogenic potential, spiramycin (2-3 g/day) has been proposed for prophylaxis (72). It is unclear whether this may really prevent congenital transmission of the parasite (450). Variability in maternal serum and in amniotic fluid may partly explain the failures observed (158).

Trachoma

Trachoma remains a serious public-health problem, and a major cause of blindness in many developing countries (305, 414). The World Health Organization has, therefore, initiated a program aiming at eliminating blinding trachoma by the year 2020, based on a combination of surgery (for trichiasis), appropriate antibiotic treatment and distribution, efforts to promote facial cleanliness, and overall environmental improvement [SAFE programme; (305)]. Azithromycin was selected as the antibiotic since it reaches a therapeutic concentration in the infected eye (222) with a simple administration scheme, and because *Chlamydia* is an intracellular pathogen (414) that may respond to the large intracellular concentrations of the drug. In clinical trials, a single dose of azithromycin (20 mg/kg) was found more efficient than local tetracyclines administered for up to 6 weeks (22, 138, 373, 415). A pilot study also showed that trachoma can be eradicated in a community by administering an annual unique dose of drug (144). This systematic use of azithromycin raises the question of its impact on the selection of resistance in other pathogens such as *S. pneumoniae*. The first data suggest that this risk will be low in regions where azithromycin use for other indications is rare and/or where resistance to macrolides is still low (27, 375). In a context of a rational antibiotic use, it must be reminded that chemotherapy cannot replace general measures aimed at preventing transmission or improving hygiene conditions (77, 98).

Mediterranean Spotted Fever

The classical treatment of infections by *Rickettsia* spp. has long been the administration of tetracyclines. However, these antibiotics are contraindicated in pregnant women and in children. *In vitro* and preliminary *in vivo* data support the place of macrolides in this indication (353). A first trial showed a 5-day course of josamycin was as effective as 1-day of doxycycline (29). More recent

studies have evaluated azithromycin in children, because of its more convenient scheme of administration (10 mg/kg/day for 10 days), and found it as active as comparators (doxycycline or clarithromycin) (65, 285).

Lyme Disease

Macrolides are so far the most active antibiotics against *Borrelia burgdorferi in vitro* (see MIC values in Table 2). These are also characterized by an adequate penetration in the skin and soft tissues and they also reach therapeutic concentration in joints and bone. This could have made them good candidates for the treatment of erythema migrans and the early articular forms of the disease. Clinical experience with macrolides has been quite disappointing. An early study comparing erythromycin to penicillin and tetracycline showed that the development of late stage complications was more frequent in patients treated with by the macrolide (4/29) than with penicillin (3/40) or tetracycline (0/88) (400). Roxithromycin (150 mg bid for 10 days) proved no more effective since the only study designed with this drug was stopped earlier than anticipated because of an exceedingly high proportion of failures (5/9 patients) (174). A reasonable rate of success was observed with clarithromycin (500 mg bid for 21 days), which was effective in 91% of the patients, but this was an open–labeled study with only 33 evaluable patients (95). In parallel, small-scale studies with azithromycin (250 or 500 mg for 4 to 10 days) was found as effective (success rate > 75%) or even to cure faster than comparators (amoxicillin, penicillin V, or doxycycline) (270, 409, 454). These optimistic data with azithromycin were quickly counterbalanced by the negative results of a large study enrolling 246 patients and comparing azithromycin (500 mg for 7 days) to amoxicillin (500 mg tid for 20 days), in which azithromycin inferiority with respect to clinical response (76 versus 88 %) and late stage complications (16 versus 4 %) became evident (262). Macrolides should therefore be considered as second line antibiotics only in the treatment of the early manifestations of Lyme disease, when β-lactams and tetracyclines are not an option (258). Since macrolides do not penetrate well in the central nervous system, their usefulness for treating the CNS manifestations of Lyme disease have never been seriously considered.

Shigellosis

Antibiotic resistance in enteropathogenic bacteria is increasing in developing countries (see e.g. (192)), in particular with respect to sulfamethoxazole and quinolones. In this context, alternative antibiotic treatments may need to be considered. Macrolides and azithromycin in particular, are active *in vitro* as well as in models of infected cells against *Shigella* spp. (193, 407). Accordingly, the clinical efficacy of azithromycin (500 mg on the first day followed by 250 mg once daily for 4 days) was compared to that of ciprofloxacin (500 mg bid for 5 days) in a double-blind randomized trial including patients with multi-resistant strains (227). Both treatments were found clinically and bacteriologically effective, with however a lower success rate in patients infected with *S. dysenteriae* type 1.

Coronary Artery Disease

Epidemiological and pathology-based studies performed in the early 90's suggested that coronary artery disease could be associated, and potentially linked to *Chlamydia pneumoniae* infection, through the presence of the organism in atheromatous plaques (235, 236, 236, 348, 390). Further animal models and cell biology studies demonstrated that *C. pneumoniae* infection influences key parameters related to atheroma, namely lipid- and inflammatory-related processes, smooth muscle cell proliferation, and release of typical atherogenic cytokines (119, 220, 386), but no aetiological link has been established, perhaps based on the lack of a gold standard for diagnosing chronic vessel infection (244). Since macrolides are active *in vitro* against this bacteria and are accumulating in cells, it has nevertheless been proposed in the late 90's to administer macrolides at low doses for a few months as a prophylactic treatment (383). Azithromycin has been most often selected because of its easy therapeutic scheme for a long course treatment (600 mg once a week during three months after a loading period of three days). Results have so far been disappointing, since azithromcyin caused only a modest reduction of inflammation markers in a pilot study with 302 patients (14), and did not significantly reduce the clinical sequelae of coronary heart disease in a large scale double-blinded, placebo-controlled trial with 7747 adults with previous myocardial infection and an immunological demonstration of the infection by *C. pneumoniae* (311). A similar conclusion was reached in a study using roxithromycin (251). There seems, therefore, that there is no justification for the use of macrolides (or other antibiotics) for treating or preventing cardiovascular disease (244).

CONCLUSIONS

Macrolides have long been a model of useful drugs because of their spectrum that allowed them to come into replacement to β-lactams for patients intolerant to these antibiotics and their activity against intracellular organisms. The main drawbacks of the lead compound, erythromycin (poor and variable bioavailability, drug interactions, short half-life) have been largely corrected with the semi-synthetic derivatives collectively named neomacrolides. These drawbacks were also minimized in the 16-membered macrolides, which, however, were less potent than the 14- or the 15-membered drugs. Macrolides have, therefore, received indications for a number of

community-acquired infections, and also for selected hospital and other severe infections, and have enjoyed a large popularity among prescribers. The mounting resistance of key pathogens such as *S. aureus* and *S. pneumoniae* has made the use of macrolides more and more difficult as empiric therapy in a number of these indications. In areas where resistance of common pathogens has reached a critical threshold, the role of macrolides, today, seems therefore limited to specific indications, such as treatment of atypical pneumonia, eradication of *Chlamydia spp.*, *H. pylori*, or control of *Mycobacterium avium* infection where these drugs show unique properties compared to many other antimicrobials.

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