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Mechanisms of Resistance to Macrolides and Lincosamides – A review

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ABSTRACT
Macrolides are a wide class of protein synthesis inhibitors that are of major therapeutic relevance due to their use in human medicine. Macrolides are made up of one or more deoxysugar or amino sugar residues connected to a macrocyclic lactone of various ring diameters. By binding to the bacterial 50S ribosomal subunit and interfering with protein synthesis, macrolides operate as antibiotics. The great affinity of macrolides for bacterial ribosomes, together with the relatively conserved structure of ribosomes across almost all bacterial species, explains their broad spectrum action. Many derivatives of the progenitor macrolide, erythromycin, have been synthesised since its discovery in 1950, resulting in molecules with increased bioavailability, acid stability, and pharmacokinetics. These efforts resulted in the development of the second generation of macrolides, which includes well-known antibiotics like azithromycin and clarithromycin. In order to combat rising antibiotic resistance, a third generation of macrolides was created, which showed enhanced efficacy against numerous macrolide resistant bacteria. These advancements, however, were accompanied with substantial side effects, generating dismay and prompting many researchers to abandon work on macrolide derivatives, believing that the technique had reached its conclusion. A recent development, on the other hand, presented a novel chemical platform for the synthesis and discovery of a wide spectrum of macrolide antibiotics. This chemical synthesis revolution, along with a decrease in side effects, known as 'Ketek effects,' has ushered in a macrolide renaissance, raising hopes for new and safe therapeutic agents to address major human infectious illnesses.

Abbreviations

CAP	community acquired pneumonia
MIC	minimum inhibitory concentration
MLS_B	macrolide–lincosamide–streptogramin B
NPET	nascent peptide exit tunnel
PTC	peptidyl transferase centre

Isolation of natural macrolides and their chemical structure

In 1950, a Streptomyces strain produced the first macrolide antibiotic, which was given the name pikromycin because of its bitter taste. The presence of a macrocyclic lactone ring, from which the name "macrolide" derives, is the primary chemical characteristic of pikromycin that is shared by all subsequently isolated macrolides (see Omura, 2002). This property was first proposed by Woodward in 1950. According to the number of members in the macrocyclic lactone ring, macrolide antibiotics are categorized as having 12, 14, 15, or 16 members. Most macrolides have neutral or amino sugar molecules attached to the lactone ring through a glycosylic link.

Antimicrobial activity and chemical derivatization

According to Nakayama (1984), macrolide antibiotics generally have low activity against Gram-negative bacteria and are most effective against Gram-positive bacteria. In addition to being extremely effective against Gram-positive bacteria including Staphylococcus, Streptococcus, and Diplococcus, macrolides are also effective against Gram-negative bacteria such Neisseria gonorrhoea, Haemophilus influenzae, Bordetella pertussis, and Neisseria meningitis. Although there are significant susceptibility

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variations between 14 and 16-membered macrolides, they are also quite effective against a variety of Mycoplasmas (Bébéar et al., 1997; Doucet-Populaire et al., 1998; Morozumi et al., 2008). Due to their weak binding affinity for eukaryotic ribosomes, they exhibit very little anti-eukaryotic activity (Corcoran, 1984; Böttger et al., 2001). However, this difference is not the sole factor causing the difference in macrolide susceptibility between yeast and prokaryotes (Bommakanti et al., 2008). Additionally, eukaryote rRNAs carry a guanosine at the analogous position A2058 of prokaryotes (Böttger et al., 2001). Although macrolides have remarkable antibacterial action, early attempts for novel derivatives with better characteristics were sparked by their typically poor bioavailability, variable pharmacokinetics, and limited stability in the acidic pH of the stomach. The second generation of macrolides, which were semi-synthetic derivatives of the first generation of natural products, were produced as a result. Clarithromycin, dirithromycin, roxithromycin, flurithromycin, and azithromycin were the five erythromycin derivatives that were created and marketed (Omura et al., 1992; Counter et al., 1991; Chantot et al., 1986; Gialdroni-Grassi et al., 1986; Retsema et al., 1987; . Only two 16-membered second-generation drugs, miokamycin (Omoto et al., 1976; Borzani et al., 1989) and rokitamycin (Sakakibara et al., 1981), were created for human use . A semi-synthetic tylosin derivative called tilmicosin (Debono et al., 1989) was created specifically for veterinary usage . While dirithromycin (Brogden and Peters, 1994; Kirst, 1995), flurithromycin (Benazzo et al., 1998), and roxithromycin (Jain and Danziger, 2004) have had far less widespread distribution, clarithromycin and azithromycin are widely marketed globally. In a quick, four- to six-step chemical transformation process, clarithromycin and azithromycin were created from erythromycin A (Morimoto et al., 1984; Bright et al., 1988). The second-generation erythromycin derivatives are immune to acid-catalyzed inactivation because they don't form the 9,12- and/or 6,9-hemiketal forms, which degrade to spiroketal inactive derivatives and exhibit resistance to inactivation. This is because they contain all modifications at the C6 or C9 positions of the lactone ring. Although at slower rates than erythromycin A, clarithromycin is nevertheless broken down in the presence of acid to produce these compounds (Nakagawa et al., 1992; Mordi et al., 2000).

Macrolides, Lincosamides, and Their Spectrum of Activity

The antibiotics macrolide and lincosamide are chemically separate yet have a similar method of action. They have a restricted spectrum of action that includes gram-positive cocci and bacilli, gram-negative cocci, and intracellular bacteria (Chlamydia and Rickettsia species). Except for Bordetella pertussis, Campylobacter, Chlamydia, Helicobacter, and Legionella species, Gram-negative bacilli are often resistant. Macrolides are made up of two amino or neutral sugars joined by a lactone ring of varying size. The lactone ring of commercially available macrolides is 14-membered (clarithromycin, dirithromycin, erythromycin, and roxithromycin) or 15-membered (azithromycin). Certain nations or veterinary practise (tylosin) have sixteen-membered ring macrolides (josamycin, midecamycin, miocamycin, rokitamyin, and spiramycin). Lincosamides (clindamycin and lincomycin) are lactone-free.

Mechanisms of Acquisition of Resistance to Macrolides and Lincosamides

Bacteria resist macrolide and lincosamide antibiotics in three ways: (1) target-site alteration by methylation or mutation, which inhibits the antibiotic from binding to its ribosomal target, (2) antibiotic efflux, and (3) drug inactivation. These processes have been discovered in macrolide and lincosamide manufacturers, who frequently combine several ways to defend themselves from the antimicrobials they make. The impact of the three processes on pathogenic bacteria is uneven in terms of incidence and clinical consequences. The ribosomal target modification imparts broad-spectrum resistance to macrolides and lincosamides, whereas efflux and inactivation impact just a subset of these compounds.

Ribosomal Methylation

Resistance in staphylococci occurred shortly after the introduction of erythromycin into treatment in 1956 [2]. Biochemical investigations revealed that resistance is induced by methylation of the antibiotics' ribosomal target, which results in cross-resistance to macrolides, lincosamides, and streptogramins B, known as the MLSB phenotype [2]. Following that, the MLSB phenotype was found in a wide range of microorganisms expressed by a variety of erm (erythromycin ribosome methylase) genes [3]. The first erythromycin-resistant streptococci strains were identified in the

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UK in 1959 and in North America in 1967 [4, 5]. So far, ribosomal methylation has been identified as the most common mechanism of resistance to macrolides and lincosamides. Erm proteins in pathogenic bacteria dimethylate a single adenine in nascent 23S rRNA, which is a component of the big (50S) ribosomal subunit [2]. The A2058 residue is found in a conserved area of domain V of 23S ribosomal RNA, which is important for MLSB antibiotic binding. Erythromycin's binding to its target is weakened as a result of methylation. The overlapping binding sites of macrolides, lincosamides, and streptogramins B in 23S rRNA are responsible for drug resistance to all three classes. Erm methylases are expressed by a broad variety of bacteria that are targets for macrolides and lincosamides, including gram-positive species, spirochetes, and anaerobes.

Diversity in MLS_B Resistance Expression

Resistance to MLSB might be constitutive or inducible. Inducible resistance occurs when bacteria create dormant mRNA that is incapable of encoding methylase. Only in the presence of a macrolide inducer can the mRNA become active. Active methylase mRNA is generated in the absence of an inducer in constitutive expression. The presence of an attenuator upstream from the structural erm gene for the methylase is associated with induction. According to the translation attenuation hypothesis, induction occurs posttranscriptionally in the case of the erm(C) (a staphylococcal determinant) and, most likely, in the case of the erm(A) and erm(B) determinants [6]. The presence of an inducer causes mRNA rearrangements, allowing ribosomes to translate the methylase coding sequence. The pattern of macrolide inducers is determined by the erm gene or, more specifically, by the structure of the attenuator that controls gene expression. Different patterns of MLSB-inducible resistance are reported because the structure of the attenuator vary in each class or subclass of erm gene. The genetic background or bacterial host also influences induction specificity, presumably due to changes in ribosomal structure or methylase expression. However, due to the preferential distribution of erm genes in particular bacterial species, we only address a few significant phenotypes of inducible MLSB resistance identified in staphylococci and streptococci/enterococci.

Targeted Mutations

In vitro selection of Escherichia coli mutants that are highly resistant to erythromycin has been of considerable value for characterization of the binding site of this antibiotic to the ribosome. The clinical importance of this mechanism was only recently recognized with identification of mutations at either A2058 or A2059 in domain V of rRNA; A2058 and A2059 confer MLS_B and ML resistance, respectively [16]. Depending on the species, bacteria possess from 1 to several rrn operons encoding 23S rRNA. In general, the mutations are observed in pathogens with 1 or 2 rrn copies, often with each copy carrying the mutation. This mechanism is responsible for clarithromycin resistance in the vast majority of, if not all, strains of Mycobacterium avium and Helicobacter pylori [16]. Similar mutations have also been reported in Treponema pallidum and Propionibacterium species. Clinical strains and laboratory mutants have recently been identified in S. pneumoniae, which harbors 4 rrn copies [17].

Mutations in ribosomal proteins L4 and L22 that confer erythromycin resistance have been documented in laboratory and clinical isolates of S. pneumoniae [17]. The changes are clustered in a highly conserved sequence of L4 and confer resistance to macrolides but not to clindamycin. Although these types of resistance are considered, by definition, to be nontransferable, the ability displayed by pneumococci to acquire extrinsic genes easily by transformation followed by homologous recombination might then lead to spread.

The prevalence and clinical importance of the pneumococcal mutants are not known. In particular, the in vivo conditions that lead to selection of mutant strains have not been studied. Because attention has been brought on these new types of resistance only recently, however, we believe that, so far, their importance has been underestimated.

Antibiotic Efflux

In gram-negative bacteria, chromosomally encoded pumps contribute to intrinsic resistance to hydrophobic compounds, such as macrolides. The pumps often belong to the resistance/nodulation/division family composed of proteins with 12 membrane-spanning regions. In gram-positive organisms, acquisition of macrolide resistance by active efflux is caused by 2 classes of pumps, members of the ATP-binding-cassette

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(ABC) transporter superfamily and of the major facilitator superfamily (MFS).

To date, the only efflux proteins conferring acquired macrolide resistance characterized in Staphylococccus species are ABC transporters encoded by plasmidborne msr(A) genes [18]. The msr(A) resistance determinant was originally detected in Staphylococcus epidermidis, and, since then, it has been found in a variety of staphylococcal species, including S. aureus. ABC transporters require ATP to function and are usually formed by a channel composed of 2 membrane-spanning domains and 2 ATP-binding domains located at the cytosolic surface of the membrane.

The msr(A) gene encodes a protein with 2 ATP-binding domains characteristic of ABC transporters. The nature of the transmembrane component of the MsrA pump remains unknown. The efflux system appears to be multicomponent in nature, involving msr(A) and chromosomal genes to constitute a fully operational efflux pump that has specificity for 14- and 15-membered macrolides and type B streptogramins (the MS_B phenotype) [18]. The resistance is inducibly expressed. Erythromycin and other 14- and the 15-membered macrolides are inducers, whereas streptogramins B are not. Therefore, the strains are resistant to streptogramins B only after induction with erythromycin. Clindamycin is neither an inducer nor a substrate for the pump, and thus the strains are fully susceptible to this antimicrobial (table 1).

As expected, constitutive mutants are resistant to both erythromycin and streptogramins B but remain fully susceptible to clindamycin. This phenotype can be easily distinguished from the MLS_B-inducible phenotype by use of the double-disk diffusion test, which shows a lack of interaction between erythromycin and clindamycin. This determinant is common in coagulase-negative staphylococci and increasingly is found in methicillin-susceptible strains of S. aureus, with a reported incidence of 13% in a recent European study [19]. Another gene, msrB from Staphylococcus xylosus, which is nearly identical to the 3′ end of msr(A), has been reclassified as msr(A) [3]. It contains a single ATP-binding domain but also confers an MS_B phenotype.

The msr(A) gene has not been found in streptococci. In the genus Streptococcus, mef(A) genes encode an efflux pump, which can be found in clinical isolates of S. pneumoniae and S. pyogenes, in other species of streptococci (oral streptococci, group C and G streptococci, and Streptococcus agalactiae), and in enterococci. The original mef(A) gene was reported in S. pyogenes [20]. A similar gene, once called mef(E), but now reclassified as mef(A), was reported later in S. pneumoniae [21]. The Mef(A) protein belongs to the MFS family and spans the membrane 12 times. The efflux is driven by the proton motive force and affects only 14- and 15-membered ring macrolides (M phenotype). There is no resistance to 16-membered ring macrolides, clindamycin, or streptogramin B, even after induction with erythromycin (table 1). Resistance is inducible by 14- and 15-membered macrolides but not by the other macrolides and clindamycin. S. pneumoniae, S. pyogenes, or S. agalactiae strains that harbor mef(A) are resistant to low or moderate levels of macrolides, with MICs of clarithromycin, azithromycin, and erythromycin generally comprising between 4 and 32 µg/mL, but sometimes less (0.12–2 µg/mL).

The mef(A) genes can be transferred by conjugation in S. pyogenes and S. pneumoniae and are borne by large transposons in S. pneumoniae [22]. Combinations of erm(B) and mef(A) genes can be found in S. pneumoniae, S. pyogenes, or S. agalactiae strains [23, 24]. These strains have an MLS_B phenotype.

Drug Modification

Inherent to this mechanism of resistance, and unlike target modification, inactivation of antibiotics confers resistance to structurally related antibiotics only. Esterases and phosphotransferases reported in enterobacteria confer resistance to erythromycin and other 14- and 15-membered macrolides but not to lincosamides. So far, these resistances have not been considered of major clinical importance, because enterobacteria are not targets for macrolides, apart from the particular use of oral erythromycin for selective decontamination of the digestive tract. More worrisome is the finding of clinical isolates of S. aureus producing phosphotransferases encoded by mph(C) genes, although only a few strains have been reported to date [25]. Lincosamide nucleotidyltransferases encoded by lnu(A) (formerly linA) and lnu(B) (formerly linB) genes in staphylococci (S. aureus and coagulase-negative staphylococci) and Enterococcus faecium, respectively, inactivate lincosamides only [3]. Both genes confer frank resistance to lincomycin, but clindamycin remains active, with MICs that are increased by only 1 or 2

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dilutions [26, 27]. However, the bactericidal activity of clindamycin, which is already weak against susceptible strains, is totally abolished [26]. Because of dissociated resistance among lincosamides, detection of this phenotype is possible only if lincomycin, instead of clindamycin, is tested. The impact of the in vitro alteration of clindamycin activity on the therapeutic efficacy of the drug is unknown. In addition, this resistance is rare in S. aureus (having been found in <1% of the strains) but is more frequent in coagulase-negative staphylococci (estimated frequency 1%–7% of strains), depending on the staphylococcal species [26]. The lnu(B) gene was detected in 10% of E. faecium strains in 1 study, but its expression was masked by the coexistence of erm in all strains [27].

On the whole, although a panel of genes is able to inactivate macrolides and lincosamides, their presence in gram-positive cocci has not turned out to be a success story for bacteria. This could be the result of (1) a weak clinical impact caused by the low-level of resistance conferred to erythromycin, by mph(C) when present alone and to clindamycin, by the lnu genes, or (2) of a failure of detection.

Impact of Macrolide Resistance on Patient Outcome

There is controversy concerning the clinical relevance of in vitro macrolide resistance, because few patients with clinical failure and resistant strains have been reported [28, 29]. Certain authors have attributed this paradox to the ability of newer macrolides—in particular, azithromycin—to reach high concentrations in the infected tissues [28]. It should be stressed, however, that newer macrolides are, in fact, concentrated in the phagocytic cells rather than in the extracellular fluids [30]. Because S. pneumoniae and S. pyogenes are thought to be primarily extracellular pathogens, extracellular drug concentrations should be considered as being predictive of therapeutic success. Internalization of a few S. pyogenes organisms, however, might contribute to the building of a reservoir of persisting bacteria that escape penicillins that do not enter eukaryotic cells or macrolides when the strains are resistant to these antimicrobials [31]. A recent study has shown that Italian erythromycin-resistant S. pyogenes has a greater ability to be internalized in human cells than does the erythromycin-susceptible strains, possibly leading to difficulties in eradication [28].

In fact, the frequent use of macrolides for nonsevere infections that often have a spontaneous favorable evolution makes it difficult to establish the correlation between the in vitro resistance of microorganisms to macrolides and the clinical outcome of patients treated with these antibiotics. Therefore, to reach firm conclusions, studies based on clinical evaluation should include a large number of patients infected with macrolide-resistant microorganisms and treated with these antibiotics. For these reasons, bacterial eradication is often used as an evaluation criterion. The question of the accuracy and clinical relevance of this criterion has been addressed in few studies and is not completely solved [29]. Clear correlation between eradication of bacteria on days 4–5 and clinical outcome was, however, shown in children with acute otitis media due to S. pneumoniae [29, 32]. The impact of macrolide resistance on bacterial eradication has been evaluated in children with acute otitis media or tonsillitis and in adults with pneumonia. In a study comparing the efficacies of azithromycin and cefaclor in young children with acute otitis media, Dagan et al. [33] found that pneumococcal eradication by azithromycin was achieved at day 4 or 5 in a group of 12 patients infected with strains for which the MIC of the antibiotic was <0.06 µg/mL. By contrast, pneumococcal strains with an MIC of azithromycin ⩾32 µg/mL persisted in all 5 patients initially infected with resistant strains, whereas 1 patient acquired a resistant strain during treatment. Although the genetic content of the strains had not been studied, the high level of resistance to macrolides suggested that resistance was due to erm genes. In another study, the review of the records of 41 patients with pneumococcal bacteremia revealed that 7 had previously received antibiotic therapy [34]. Three of the patients did not appear to have true antibiotic therapy failure, whereas the 4 remaining patients had previously been treated with azithromycin or clarithromycin for 3–5 days. The 4 blood isolates had an M phenotype and a moderate level of resistance to macrolides, with MICs of erythromycin equal to 8 µg/mL or 16 µg/mL.

The data from the studies of acute pharyngitis are even more difficult to analyze, because recolonization or spontaneous clearance of S. pyogenes in the throat appears to occur frequently. Varaldo et al. [35] failed to find a correlation between in vitro resistance to macrolides and noneradication in children with pharyngotonsilitis due to S. pyogenes who were

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receiving macrolide therapy. In another study, the rate of eradication of S. pyogenes in patients who had pharyngitis and who were treated with clarithromycin did not differ significantly from that in patients with erythromycin-resistant strains or those in patients with erythromycin-susceptible strains, despite a trend toward a higher rate of eradication in the latter group [36]. Of note, none of the 6 patients with strains highly resistant to erythromycin were cured. Failure of erythromycin could be demonstrated by Seppälä et al. [37], who found that this antibiotic significantly failed to cure 9 (47%) of 19 patients infected with erythromycin-resistant group A streptococci (including moderately resistant strains), as compared with 1 (4%) of 26 patients with erythromycin-susceptible isolates. Taken together, these studies tend to suggest a correlation between macrolide resistance, at least when expressed at a high level, and clinical failure. Because of differences in pharmacokinetics, all macrolides probably are not equivalent in their ability to eradicate strains with low-level macrolide resistance. Finally, more studies that include homogeneous groups of patients are needed to confirm the in vivo impact of in vitro resistance—in particular, that caused by drug efflux—and to propose breakpoints that are predictive of clinical failure or success.

Incidence of Macrolide Resistance

Table 2 provides data on the incidence of macrolide resistance in S. pneumoniae published for <2 years. Huge geographic differences, from 3% to 74%, are observed in the resistance frequencies reported for individual countries. In addition, considerable variations can be seen within a country, depending on the source of the strains (teaching/nonteaching hospital, or community), patient age, sample origin, seasonal factors, and pneumococcal serotype [39, 58]. Similar to the case of penicillin resistance, higher prevalence of macrolide resistance is generally seen among children and for pneumococci from middle ear fluids. These differences have obvious impact on the therapeutic efficacy of agents of the MLS class. Although useful for analysis global trends toward resistance, nationwide surveys do not always take into account these parameters, and there is a need for physicians to be aware of local resistance patterns according to patient age and type of infection. In general, the higher the rate of penicillin resistance, the higher the rate of macrolide resistance. In a large study that involved hospitals from 21 countries around the world, macrolide resistance was detected in 12.8% of penicillin-susceptible pneumococci versus 55.7% of penicillin-resistant strains [59]. In another recent study [42], similar variations between penicillin-susceptible and -resistant strains (4% and 61% in the United States, 4% and 27% in Latin America, 10% and 52% in Europe, and 22% and 76% in Asia, respectively), were found. This relationship is especially marked in the United States (table 2) and is also shown for trimethoprim-sulfamethoxazole resistance. There are, however, some exceptions. For instance, in Italy, the low rate of penicillin resistance contrasts with the high rate of erythromycin resistance (table 2).

No substantial difference can be observed between percentages of resistance to azithromycin, clarithromycin, and erythromycin, which confirms cross-resistance between the 3 antimicrobials [42, 44, 52]. By contrast, in several countries, the incidence of clindamycin resistance may be much lower than that of erythromycin resistance. The spread of erythromycin-resistant strains that harbor the mef(A) gene accounts for this difference. This holds true especially in the United States, in contrast to most European countries, where erm(B)-containing strains are widespread. The reasons for these differences are unexplained. Longitudinal studies showed that the incidence of macrolide resistance, which was 10%–16% in 1994, doubled in 1999 in several areas of the United States [41, 58]. This marked increase was, for the most part, related to the emergence of mef(A)-containing strains [41].

Several European countries (i.e., Finland, Italy, and Spain) faced an increase in erythromycin resistance in S. pyogenes at the beginning of the 1990s [37, 60, 61] (table 3). Recent data show that very high frequencies of macrolide resistance are reported in Asia, whereas, to date, resistance does not seem to be a problem in the United States (table 3); however, particular high frequencies can be seen, as exemplified by a 32% rate of erythromycin resistance in S. pyogenes collected from invasive disease-related specimens in San Francisco County [63]. In the vast majority of S. pyogenes strains, erythromycin resistance is caused by the presence of the efflux gene mef(A) or the methylase genes erm(TR) [erm(A)] and erm(B). The mef(A) and erm(TR) genes are frequently predominant [24, 64].

In several studies, investigators have tried to establish connections between consumption of macrolides and widespread resistance. Frequent coresistance to several antibiotics in pneumococci

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makes evaluation of the impact of a specific class of antibiotic on resistance problematic. This is not the case for S. pyogenes, which remains susceptible to penicillins. The most convincing data, from Finland, were high rates of macrolide resistance in S. pyogenes, along with an increase in macrolide consumption and a subsequent decrease after significant reduction in the use of macrolides in outpatients [67]. Similarly, an increase in macrolide resistance in Spain since 1995 was related to the increase in consumption of macrolides, especially those that are taken once or twice daily [61]. This relationship was not found in a Canadian study [64], however, and temporal relations do not prove causality. To explain differences between countries with regard to sudden emergences of resistance, Granizo et al. [61] have hypothesized that spread of resistance occurs when macrolide consumption exceeds a critical threshold of selective pressure. It is remarkable that, in intracellular pathogens, such as Legionella, Chlamydia, and Mycoplasma species, findings of resistance remain anecdotal.

CONCLUSIONS

The multiplicity of mechanisms that confer resistance to macrolides is reflected by the complexity of the resistance phenotypes; however, the most clinically important and widespread determinants in gram-positive organisms are the methylase and efflux genes. Identification of the resistance mechanisms is important with regard to the use of clindamycin and 16-membered ring macrolides. The double-disk diffusion technique with erythromycin and lincomycin (or clindamycin) is useful to guide interpretation of the susceptibility test [72]). The incidence of resistance is highly variable with regard to the country and, most importantly, the patterns of infections observed among patients. For this reason, local statistics are of crucial value for empiric therapy. Surveillance of both the incidence of macrolide resistance and the respective prevalence of the various resistance mechanisms is justified by the rapid variations in macrolide resistance observed in several countries.

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