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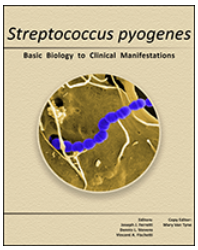

Mechanisms of Antibiotic Resistance

Vincent Cattoir, PharmD, PhD[1]

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Introduction

Streptococcus pyogenes, or group A streptococcus, is a major human pathogen that causes over 600 million infections annually (Lynskey, Lawrenson, & Sriskandan, 2011). This species is able to colonize the upper respiratory tract and skin of asymptomatic people, but is also responsible for a wide range of diseases, including suppurative infections and non-suppurative complications, which may occur either endemically or as outbreaks (Cunningham, 2000; Efstratiou, 2000). The types of infections can be divided into three groups: superficial infections (such as pharyngotonsillitis, impetigo, erysipelas, vaginitis, or post-partum infections), deep infections (such as bacteremia, cellulitis, myositis, necrotizing fasciitis, puerperal sepsis, pericarditis, meningitis, pneumonia, or septic arthritis), and toxin-mediated diseases (such as scarlet fever or streptococcal toxic shock syndrome [STSS]) (Efstratiou, 2000). These infections also play a significant role in the development of post-infection immune sequelae, including rheumatic fever, acute glomerulonephritis, and reactive arthritis (Cunningham, 2000). Clinical isolates of *S. pyogenes* were classically differentiated into M serotypes, based on structural differences of the M protein (encoded by the *emm* gene), which is a fibrillar cell-wall protein involved in adherence to human cells and prevention of opsonophagocytosis (Lynskey, Lawrenson, & Sriskandan, 2011; Cunningham, 2000). This method was replaced in the late 1990s by the typing system based on sequencing of the 5' end of the *emm* gene, and is referred to as *emm* typing (Facklam, et al., 1999). Even though there were significant differences in the *emm*-type distribution that depended on geographical area or clinical disease state, the most common *emm* types found in a large systematic review were *emm*1 (18.3%), *emm*12 (11.1%), *emm*28 (8.5%), *emm*3 (6.9%), and *emm*4 (6.9%) (Steer, Law, Matatolu, Beall, & Carapetis, 2009). As far as antimicrobial resistance, *S. pyogenes* has remained highly susceptible to almost all classes of antibiotics [Table 1] (Bourbeau & Campos, 1982; Kayser, 1994; Chin, Gu, Yu, Zhang, & Neu, 1991; Cohen, et al., 1991; Bouanchaud, 1997; Blondeau, Church, Yaschuk, & Bjarnason, 1999). Among *S. pyogenes* clinical isolates in some geographic regions, only resistance to macrolides (and related compounds) and tetracyclines are commonly found.

Table 1. In vitro activity of 31 antimicrobial agents against wild-type isolates of *S. pyogenes* (Bourbeau & Campos, 1982; Kayser, 1994; Chin, Gu, Yu, Zhang, & Neu, 1991; Cohen, Huband, Mailloux, Yoder, Roland, & Heifetz, 1991; Bouanchaud, 1997; Blondeau, Church, Yaschuk, & Bjarnason, 1999; Amábile-Cuevas, Hermida-Escobedo, & Vivar, 2001; King & Phillips, 2001; Gemmell, 2001; Cantón, Loza,

Author Affiliation: 1 Department of Clinical Microbiology, Caen University Hospital; National Reference Center for Antimicrobial Resistance (Lab Enterococci); Research Unit EA4655 (Team 'Antibioresistance'), University of Caen Basse-Normandie; Avenue de la Côte de Nacre, 14033 Caen Cedex 9, France; Email: cattoir-v@chu-caen.fr.

[1] Corresponding author.

Morosini, & Baquero, 2002; Blondeau & Sanche, 2002; Noviello, Ianniello, Leone, & Esposito, 2003; Carpenter & Chambers, 2004; Keating & Scott, 2004; Brown & Rybak, 2004; Brauers, Kresken, Hafner, & Shah, 2005; Bradford, Weaver-Sands, & Petersen, 2005; Pankey, 2005; Rubinstein & Vaughan, 2005; Al-Lahham, De Souza, Patel, & Reinert, 2005; Lynch, File, & Zhanel, 2006; Ziglam, 2007; Hair & Keam, 2007; Zhanel, et al., 2007; Mazzariol, Koncan, Vitali, & Cornaglia, 2007; Morrissey, Ge, & Janes, 2009; Pfaller, Castanheira, Sader, & Jones, 2010; Biek, Critchley, Riccobene, & Thye, 2010; Jones, Mendes, Sader, & Castanheira, 2011; Karlowsky, Adam, Poutanen, Hoban, Zhanel, & Canadian Antimicrobial Resistance Alliance, 2011; Pérez-Trallero, Tamayo, Montes, Garcia-Arenzana, & Iriarte, 2011; Jones, Sader, & Flamm, 2013).

Antibiotic	MIC values (µg/ml)		EUCAST breakpoints[a] (µg/ml)	
	Range of MIC_{50}	Range of MIC_{90}	S ≤	R >
β-lactams				
Penicillin G	≤0.01	≤0.01-0.03	0.25	0.25
Ampicillin/Amoxicillin	≤0.01	≤0.01-0.03	-	-
Cefaclor	0.06-0.5	0.12-0.5	-	-
Cefuroxime	≤0.01	≤0.01-0.03	-	-
Cefixime	0.12-0.25	0.12-0.25	-	-
Cefpodoxime	0.01	0.01	-	-
Ceftriaxone/Cefotaxime	≤0.01-0.03	≤0.01-0.06	-	-
Cefepime	≤0.01	0.03	-	-
Ceftaroline	≤0.01	≤0.01	-	-
Imipenem	≤0.01	≤0.01	-	-
Aminoglycosides				
Gentamicin	4	4	-	-
Macrolides and related compounds				
Erythromycin	≤0.01-0.06	0.03-0.12	0.25	0.5
Clarithromycin	0.03	0.03-0.06	0.25	0.5
Spiramycin	0.25	0.5	-	-
Clindamycin	≤0.06-0.12	≤0.06-0.12	0.5	0.5
Quinupristin-dalfopristin	≤0.12-0.5	≤0.12-0.5	-	-
Telithromycin	0.01	0.01-0.03	0.25	0.5
Fluoroquinolones				
Ciprofloxacin	≤0.25-0.5	0.5-2	-	-
Levofloxacin	0.25-0.5	0.5-1	1	2
Moxifloxacin	0.06-0.12	0.12-0.25	0.5	1
Tetracyclines				
Tetracycline	≤0.25-0.5	0.25-1	1	2
Doxycycline	0.12	0.5	1	2
Tigecycline	0.01-0.12	0.03-0.25	0.25	0.5
Glycopeptides				
Vancomycin	0.25-0.5	0.25-1	2	2
Teicoplanin	0.06-0.5	0.12-1	2	2
Others				

Table 1. continued from previous page.

Antibiotic	MIC values (µg/ml)		EUCAST breakpoints[a] (µg/ml)	
	Range of MIC_{50}	Range of MIC_{90}	S ≤	R >
Daptomycin	≤0.03-0.06	0.06-0.25	1	1
Linezolid	0.5-1	1-2	2	4
Cotrimoxazole	0.06-0.25	0.25-0.5	1	2
Rifampin	0.12	0.12	0.06	0.5
Bacitracin	1	1-2	-	-
Chloramphenicol	2	4	8	8
Fusidic acid	4	4-8	-	-

[a] Available at http://www.eucast.org/clinical_breakpoints/.

Beta-Lactams

Even though *S. pyogenes* has remained universally susceptible to β-lactams [Table 1] since the 1940s, a significant number of treatment failures have been reported (Gillespie, 1998). For instance, a meta-analysis of therapeutic studies showed that the bacteriological treatment failure rate in streptococcal pharyngotonsillitis was around 12% from 1953 to 1993 (Markowitz, Gerber, & Kaplan, 1993). In the past 15 years, the rate of penicillin failure has dramatically increased to almost 40% in some regions of the world (Brook, 2013). The main explanations for penicillin failure include: (i) intracellular persistence of *S. pyogenes*, due to the poor penetration of penicillin into tonsillar tissues, including tonsillar epithelial cells; (ii) protection of *S. pyogenes* by β-lactamase-producing bacteria (namely *Staphylococcus aureus*, *Haemophilus* spp., *Moraxella catarrhalis*, and anaerobes) that are commonly part of the oral microbiota; (iii) coaggregation between *M. catarrhalis* and *S. pyogenes*, which may enhance *S. pyogenes* colonization through the facilitation of its adherence to human epithelial cells; and (iv) alteration of the commensal bacterial microbiota, which can compete for nutrients (Brook, 2013; Kaplan, Chhatwal, & Rohde, 2006; Pichichero & Casey, 2007; Schaar, Uddbäck, Nordström, & Riesbeck, 2014).

Although penicillin is generally the agent of choice for the treatment of tonsillopharyngitis caused by *S. pyogenes*, a meta-analysis demonstrated that oral cephalosporins (such as cefadroxil and cefpodoxime proxetil) seemed to be more efficient than oral penicillin, with two times fewer bacteriological and clinical failures (Casey & Pichichero, 2004). Also, failure with penicillin is highest in retreatment cases where cephalosporins are more effective (Casey & Pichichero, 2004). The superior activity of cephalosporins, which is likely related to a more important ability for *S. pyogenes* eradication, may be due to their higher efficacy in killing ingested bacterial cells (Kaplan, Chhatwal, & Rohde, 2006).

Mechanistically, β-lactam antibiotics inhibit the last steps of peptidoglycan synthesis by binding to high-molecular-weight penicillin-binding proteins (PBPs) (Rice, 2012). In *Streptococcus pneumoniae* and viridans group streptococci, resistance to β-lactams is mediated by alterations in the PBP binding site by the generation of low-affinity enzymes. By contrast, such a mechanism of β-lactam resistance has not yet been reported in β-hemolytic streptococci, despite the extensive use of penicillins for the treatment of *S. pyogenes* infections (Horn, et al., 1998). One possible explanation for this difference is the limited ability of *S. pyogenes* to exchange genetic material and acquire new resistance determinants. Unlike pneumococci, *S. pyogenes* is not intrinsically competent and does not readily acquire exogenous DNA—although it does produce numerous types of extracellular DNases (Horn, et al., 1998). In addition, gene transfer by conjugation in *S. pyogenes* seems to be very unusual, since clinical isolates rarely contain plasmids (Horn, et al., 1998). Finally, penicillin-resistant and penicillin-tolerant laboratory mutants of *S. pyogenes* were isolated in vitro after treatment by ethyl methane sulfonate (Gutmann & Tomasz, 1982). These strains, which express low-affinity PBPs, exhibited a 32-fold

increase in penicillin G MICs (from 0.006 to 0.2 µg/ml), but showed severe physiological defects with extremely poor growth rates and gross morphological abnormalities (Gutmann & Tomasz, 1982). This finding suggests that these strains have a low probability to develop as clinical isolates, while it seems that tolerance observed in such mutants does not have clinical relevance. In contrast to *Enterococcus faecalis* strains (Murray, 1992), no β-lactamase genes have been identified among any strains of *S. pyogenes*.

Aminoglycosides

Aminoglycosides are bactericidal antimicrobial agents that primarily inhibit bacterial protein biosynthesis by binding to the 16S rRNA of the 30S small ribosomal subunit (Becker & Cooper, 2013). Other metabolic perturbations caused by these molecules include interference with the respiratory chain electron transport system, induction of ionic disorders, disruption of bacterial cell membrane integrity, and disturbances of DNA/RNA synthesis (Kotra, Haddad, & Mobashery, 2000). Aminoglycosides are active against a large spectrum of aerobic Gram-negative bacilli and Gram-positive cocci, while anaerobes are highly resistant. Like enterococci, streptococci are intrinsically resistant to low antibiotic concentrations (MICs ranging from 4 to 64 µg/ml), which is due to their limited drug uptake [Table 1]. However, the combination of aminoglycosides with cell-wall-active agents (such as penicillins and glycopeptides) results in a significant bactericidal synergy. Indeed, the inhibition of peptidoglycan synthesis mediated by such molecules would increase the uptake of aminoglycosides and induce the formation of reactive oxygen species (Zembower, Noskin, Postelnick, Nguyen, & Peterson, 1998; Barnes, Herrero, & Albesa, 2005). High-level resistance to aminoglycosides (MICs >2,000 µg/ml) that entirely abolishes synergistic bactericidal activity is often due to the enzymatic inactivation mediated by aminoglycoside-modifying enzymes (AMEs), while a less common mechanism corresponds to ribosomal alterations (Jana & Deb, 2006). Note that the genes that encode for AMEs are often located on plasmids. There are three different classes of AMEs, which depend on the reaction catalyzed: aminoglycoside acetyltransferases (AACs), aminoglycoside phosphotransferases (APHs), and aminoglycoside nucleotidyltransferases (ANTs) (Chow, 2000). In enterococci (which are closely related to streptococci), the major AME enzymes are: APH(3')-IIIa, which mediates high-level resistance to kanamycin; ANT(4')-Ia, which confers resistance to kanamycin, amikacin, and tobramycin; and AAC(6')-Ie-APH(2")-Ia, a bifunctonial enzyme that mediates resistance to virtually all the clinically available aminoglycosides, including kanamycin, amikacin, tobramycin, gentamicin, and netilmicin, but except streptomycin (Chow, 2000). In *S. pyogenes*, high-level resistance to aminoglycosides appears to be rare, and only a few strains resistant to both kanamycin and streptomycin have been reported (Horodniceanu, Buu-Hoï, Delbos, & Bieth, 1982; Lakshmi & Kim, 1989). This resistance was due to the production of both APH(3')-IIIa and ANT(6)-Ia enzymes, and has been demonstrated to be transferable by conjugation (Lakshmi & Kim, 1989; van Asselt, Vliegenthart, Petit, van de Klundert, & Mouton, 1992). No gentamicin-resistant clinical isolates have been described to date.

Macrolides-Lincosamides-Streptogramins-Ketolides

Macrolides, lincosamides, and streptogramins (MLS) are recommended as alternate antibiotics for the treatment of *S. pyogenes* infections in patients who are allergic to β-lactams or in cases of penicillin failure (Bisno, Gerber, Gwaltney, Jr., Kaplan, & Schwartz, 2002). Although MLS compounds are chemically distinct, they are considered to be a unique group, since they share a similar mode of action through binding to (or in the vicinity of) the ribosomal peptidyl transferase center (PTC) (Schlünzen, et al., 2001). Also, they present an overlapping spectrum of activity within the same MIC ranges [Table 1]. Practically, macrolides are classified according to the number of atoms that form the lactone ring, and there are 14- (e.g. erythromycin or clarithromycin), 15- (e.g. azithromycin), or 16-membered macrolides (e.g. spiramycin or josamycin). Notably, a new class of molecules has been recently developed that have evolved from macrolides, and these are known as ketolides (e.g. telithromycin). Lincosamides comprise only two members: lincomycin and its semisynthetic derivative, clindamycin. Streptogramins are actually composed of a mixture of two compounds that act synergistically:

streptogramin A (e.g. dalfopristin) and streptogramin B (e.g. quinupristin) (Dang, Nanda, Cooper, Greenfield, & Bronze, 2007).

The first macrolide-resistant *S. pyogenes* isolate was reported in the USA in 1968 (Sanders, Foster, & Scott, 1968). In the late 1990s and early 2000s, the incidence of macrolide resistance dramatically increased in several European countries, such as Finland, France, Greece, Italy, Portugal, and Spain, with erythromycin resistance rates usually exceeding 20% (Seppälä, et al., 1997; Granizo, Aguilar, Casal, Dal-Ré, & Baguero, 2000; Bingen, et al., 2004; Silva-Costa, Ramirez, & Melo-Cristino, 2005; Creti, et al., 2007; Richter, et al., 2008). Despite some geographical variations, rates of macrolide resistance in the USA have remained relatively low (around 5%) since the 1990s (Brown & Rybak, 2004; Tanz, et al., 2004; Richter, et al., 2005). More recently, some European studies have described a significant decrease in erythromycin resistance in *S. pyogenes*, such as in France or Spain (d'Humières, et al., 2012; Montes M. , et al., 2014). From an epidemiological point of view, it was frequently demonstrated that the prevalence of erythromycin-resistant *S. pyogenes* correlated well with the total consumption of macrolide antibiotics in particular geographical areas (Seppälä, et al., 1997; Granizo, Aguilar, Casal, Dal-Ré, & Baguero, 2000; Seppälä, Klaukka, Lehtonen, Nenonen, & Huovinen, 1995; Albrich, Monnet, & Harbarth, 2004; Bergman, et al., 2004; Hsueh, Shyr, & Wu, 2005). Besides antibiotic consumption, changes in the clonal composition of the *S. pyogenes* population may also be an important cause for fluctuations in macrolide resistance rates (Montes, Tamayo, Mojica, García-Arenzana, Esnal, & Pérez-Trallero, 2014; Silva-Costa, Friães, Ramirez, & Melo-Cristino, 2012).

Notably, a relationship between virulence and macrolide resistance has emerged. Specifically, erythromycin resistance is associated with the increased cell invasiveness of *S. pyogenes* (Facinelli, Spinaci, Magi, Giovanetti, & Varaldo, 2001). Indeed, this association could be due to the presence of the *prtF1* gene, which is more frequently found among macrolide-resistant strains. The *prtF1* gene encodes the fibronectin-binding protein F1, an adhesion that allows *S. pyogenes* to be efficiently internalized by and survive within human respiratory cells (Facinelli, Spinaci, Magi, Giovanetti, & Varaldo, 2001; Haller, Fluegge, Arri, Adams, & Berner, 2005). By contrast, biofilm formation could be an important factor to explain therapeutic failures and recurrences due to macrolide-susceptible *S. pyogenes* clinical isolates (Baldassarri, et al., 2006). Additionally, erythromycin-susceptible strains form a significantly thicker biofilm than resistant isolates, while those harboring *erm*-class genes have a less organized biofilm than *mef*(A)-positive strains (see below). Finally, the presence of *prtF1* appears to be negatively associated with the ability to form biofilm (Baldassarri, et al., 2006).

MLS resistance may be due to several different mechanisms: (i) post-transcriptional target site modifications caused by rRNA methylases (*erm*-class genes); (ii) target mutations (in 23S rRNA or ribosomal proteins L4 and L22); or (iii) the acquisition of active efflux (*mef* genes) (Leclercq & Courvalin, 1991; Weisblum, 1995a).

All genes of the *erm* family encode methyltransferases that specifically add one or two methyl residues on the N^6 amino group of the highly conserved adenine A2058 in domain V of the 23S rRNA, which corresponds to the ribosomal PTC (Lai & Weisblum, 1971). This ribosomal methylation conveys cross-resistance to macrolides-lincosamides-streptogramins B (MLS_B) that can be constitutively expressed (the so-called $cMLS_B$ phenotype) or inducibly expressed (the so-called $iMLS_B$ phenotype) [Figure 1] (Weisblum, 1995b). In streptococci, resistance is commonly mediated by two classes of methylases encoded by *erm*(B) and *erm*(TR) genes, and both are usually located chromosomally (Leclercq, 2002). The *erm*(B) gene (previously known as *ermAM*) was first identified in *Streptococcus sanguinis* (Horinouchi, Byeon, & Weisblum, 1983). Because *erm*(TR) shows 82.5% nucleotide identity with the original *erm*(A) gene (Seppälä, Skurnik, Soini, Roberts, & Huovinen, 1998), it has been proposed that *erm*(TR) belongs to the *erm*(A) class (Roberts, et al., 1999). However, the *erm*(A) subclass *erm*(TR) will be referred to as *erm*(TR) throughout this work.

Whereas *erm*(B) is primarily associated with a $cMLS_B$ phenotype and rarely with a $iMLS_B$ phenotype, macrolide resistance conferred by *erm*(TR) in streptococci is usually expressed inducibly even if some $cMLS_B$ *erm*(TR)-positive strains have occasionally been reported [Figure 1] (Leclercq, 2002). In *S. pyogenes*, there is a substantial

heterogeneity of susceptibility patterns among inducibly-resistant isolates, which have been subdivided into three distinct subtypes, designated i-MLS_B-A, $iMLS_B$-B, and $iMLS_B$-C [Table 2] (Arpin, Canron, Noury, & Quentin, 1999; Giovanetti, Montanari, Mingoia, & Varaldo, 1999; Giovanetti, Montanari, Marchetti, & Varaldo, 2000; Betriu, et al., 2000; Malbruny, et al., 2002; Bingen, et al., 2002). In contrast to cML_B isolates that are highly resistant to lincosamides, all types of iMLSB are associated with susceptibility to lincosamides [Figure 1 and Table 2]. Phenotypically, $iMLS_B$-A strains are highly resistant to all macrolides; $iMLS_B$-B strains are highly resistant to 14- and 15-membered macrolides, but are susceptible to 16-membered macrolides; and $iMLS_B$-C strains present low-level resistance to 14- and 15-membered macrolides, but remain susceptible to 16-membered macrolides [Table 2]. $cMLS_B$ and $iMLS_B$-A isolates usually harbor the *erm*(B) gene, while $iMLS_B$-B and $iMLS_B$-C isolates possess the *erm*(TR) gene (Giovanetti, Montanari, Mingoia, & Varaldo, 1999). Notably, resistance to ketolides is observed in $cMLS_B$ and $iMLS_B$-A *S. pyogenes* isolates, while resistance is correlated to the degree of dimethylation by Erm(B) of the A2058 of the 23S rRNA (Douthwaite, Jalava, & Jakobsen, 2005). Even though the Erm(TR) methylase in *S. pyogenes* is not inducible with lincosamides, clindamycin resistance (MIC, 64 mg/L) due to constitutive expression can easily be obtained in vitro (at a frequency of ca. 10^{-7}) from inducible *erm*(TR)-harboring strains [Figure 2] (Fines, Gueudin, Ramon, & Leclercq, 2001). This is due to alterations in the structure of regulatory sequences, which are composed of two leader peptides (15 and 19 amino acids) involved in post-transcriptional regulation (the so-called translational attenuation) that controls the expression of the methylase gene, in a manner similar to that found for *erm*(C) in staphylococci (Weisblum, 1995b; Horinouchi & Weisblum, 1980). These modifications in the promoter sequence (including base changes, insertions/duplications, or deletions) have also been described in clinical isolates (Doktor & Shortridge, 2005; Malhotra-Kumar, et al., 2009). Mechanistically, these modifications are responsible for modifications in the mRNA secondary structure that result in changes in accessibility of the ribosome-binding site and the initiation codon of the methylase to the ribosomes, and subsequently for the translation of the *erm*(TR) transcripts [Figure 3] (Fines, Gueudin, Ramon, & Leclercq, 2001; Doktor & Shortridge, 2005; Malhotra-Kumar, et al., 2009).

Originally identified as part of Tn*917* on a non-conjugative plasmid from *E. faecalis* (Tomich, An, & Clewell, 1980), the *erm*(B) gene in *S. pyogenes* is carried by different elements, depending on whether it is expressed constitutively or inducibly (Varaldo, Montanari, & Giovanetti, 2009). When constitutively expressed, this gene is carried by Tn*916* family elements, such as Tn*3872* (ca. 24 kb) or Tn*6002* (ca. 21 kb) [Figure 4] (Varaldo, Montanari, & Giovanetti, 2009; Brenciani, Bacciaglia, Vecchi, Vitali, Varaldo, & Giovanetti, 2007; Brenciani, Tiberi, Morici, Oryasin, Giovanetti, & Varaldo, 2012; Brenciani, Tiberi, Morroni, Mingoia, Varaldo, & Giovanetti, 2014). Tn*3872* results from the insertion of Tn*917* into *orf9* of Tn*916*, with *erm*(B) thus physically linked to *tet*(M), while conjugal transfer has been demonstrated from *S. pyogenes* to *S. pyogenes* [Figure 4] (Brenciani, Bacciaglia, Vecchi, Vitali, Varaldo, & Giovanetti, 2007). Tn*6002* corresponds to the insertion of the *erm*(B) element (ca. 3 kb) between *orf20* and *orf19* of Tn*916*, which also leads to an *erm*(B)/*tet*(M) linkage, and for which intraspecific conjugal transfer has been demonstrated in *S. pyogenes* (Brenciani, Bacciaglia, Vecchi, Vitali, Varaldo, & Giovanetti, 2007). When inducibly expressed, *erm*(B) is carried by an element originally named Tn*1116* (ca. 48 kb), but now renamed ICE*Sp1116*, since it has been demonstrated to belong to the Tn*GBS* family of integrative and conjugative elements (ICEs) (Brenciani, Bacciaglia, Vecchi, Vitali, Varaldo, & Giovanetti, 2007; Brenciani, Tiberi, Morici, Oryasin, Giovanetti, & Varaldo, 2012; Brenciani, Tiberi, Morroni, Mingoia, Varaldo, & Giovanetti, 2014). This element presents a unique mosaic structure related to the Tn*Gallo*1 from *Streptococcus gallolyticus* with two inserted fragments separated by an IS*1216*: the *erm*(B)-containing fragment (derived from the plasmid pSM19035) and the right-hand portion of *Clostridium difficile* Tn*5397* that contains a truncated *tet*(M) gene [Figure 4] (Brenciani, Tiberi, Morici, Oryasin, Giovanetti, & Varaldo, 2012).

Different *erm*(TR)-carrying ICE elements have been described in *S. pyogenes*: ICE 10750-RD.2 (ca. 49 kb) and ICE*Sp1108* (ca. 45 kb) in tetracycline-susceptible strains, and ICE*Sp2905* (ca. 66 kb) in tetracycline-resistant strains, due to the presence of the *tet*(O) gene [Figure 5] (Varaldo, Montanari, & Giovanetti, 2009; Brenciani, Tiberi, Bacciaglia, Petrelli, Varaldo, & Giovanetti, 2011; Giovanetti, Brenciani, Tiberi, Bacciaglia, & Varaldo, 2012). While the element ICE 10750-RD.2 is integrated into an *hsdM* chromosomal gene-encoding host DNA

restriction/modification methyltransferase, both ICE*Sp1108* and ICE*Sp2905* are integrated in the chromosome at the 3' end of the conserved RNA uracil methyltransferase (*rum*) gene (Varaldo, Montanari, & Giovanetti, 2009; Brenciani, Tiberi, Bacciaglia, Petrelli, Varaldo, & Giovanetti, 2011). The ICE*Sp2905* results from one ICE (ICE*Sp2907*) being integrated into another (ICE*Sp2906*), with the former containing *erm*(TR) and the latter containing *tet*(O), and the whole inserted into a scaffold of clostridial origin [Figure 5] (Giovanetti, Brenciani, Tiberi, Bacciaglia, & Varaldo, 2012). Notably, all these structures share an almost identical conserved core sequence (ca. 2 kb) that includes *erm*(TR) and two adjacent antibiotic resistance (tetronasin and spectinomycin) genes [Figure 5] (Brenciani, Tiberi, Bacciaglia, Petrelli, Varaldo, & Giovanetti, 2011). Note that *erm*(TR) can be transferred by conjugation to susceptible recipients of *S. pyogenes* and other Gram-positive bacteria (Giovanetti, et al., 2002). In addition, it has been shown that *Peptostreptococcus* spp. may serve as an important reservoir for *erm*(TR)-mediated macrolide resistance (Reig, Galan, Baquero, & Perez-Diaz, 2001).

Another methylase gene, *erm*(T) (previously named *ermGT*), has also been identified in *S. pyogenes* that expresses an $iMLS_B$ resistance phenotype (Woodbury, et al., 2008). Originally described in *Lactobacillus reuteri* in a chromosomal location (Tannock, et al., 1994), this gene is borne on a small mobilizable plasmid (ca. 5 kb) in *S. pyogenes* (Woodbury, et al., 2008; DiPersio, DiPersio, Beach, Loudon, & Fuchs, 2011).

Macrolide resistance can also be due to ribosomal mutations, either in the domain V of 23S rRNA (*rrn*) operons or in the ribosomal proteins L4 and L22 (*rplD* and *rplV* genes, respectively) (Leclercq, 2002). In *S. pyogenes*, two clinical isolates with such target mutations were described for the first time in 2002 (Malbruny, et al., 2002). The former strain exhibited a C2611U mutation in the domain V of all six 23S rRNA copies, and was phenotypically resistant to azithromycin and clindamycin, but remained susceptible to erythromycin and spiramycin [Figures 2 and 6, Table 2] (Malbruny, et al., 2002). The latter strain harbored an insertion of six nucleotides in the *rplD* gene sequence, which resulted in a KG insertion after position 69 in the L4 ribosomal protein, and was phenotypically resistant to azithromycin and spiramycin, but remained susceptible to erythromycin (borderline) and clindamycin [Figures 2 and 6, Table 2] (Malbruny, et al., 2002). Since then, additional ribosomal mutations in the L4 ribosomal protein have been reported in a few clinical isolates [Figure 6]: a two-amino-acid deletion (65RW66), an RA insertion after position 73, and a TG deletion at positions 70 to 71 (Bingen, et al., 2002; Bozdogan, Appelbaum, Ednie, Grivea, & Syrogiannopoulos, 2003). Other mutations in 23S rRNA have also been identified in clinical isolates [Figure 6]: a A2058G mutation (5/6 mutated *rrn* copies) with resistance to all macrolides, ketolides, and lincosamides (Jalava, Vaara, & Huovinen, 2004); A2058G (n=4) and A2059G (n=2) mutations in clinical isolates that present a $cMLS_B$ phenotype (Tanz, et al., 2004; Richter, et al., 2005); dual mutations (A2058G and U2166C) in seven clonally-related strains resistant to macrolides and ketolides (Farrell, Shackcloth, Barbadora, & Green, 2006); and in two isolates with a A2058G substitution with a $cMLS_B$ phenotype (Montes, Tamayo, Mojica, García-Arenzana, Esnal, & Pérez-Trallero, 2014).

Active efflux due to *mef* genes is responsible for resistance only to 14- and 15-membered macrolides (the so-called M phenotype), while there is no resistance to 16-membered macrolides, lincosamides, and streptogramins (Sutcliffe, Tait-Kamradt, & Wondrack, 1996). Mef proteins are proton-dependent efflux pumps that belong to the major facilitator superfamily (MFS) with 12 transmembrane segments (TMS) (Poole, 2005). Several allelic variants or subclasses of the *mef* gene have been described, mainly *mef*(A) originally reported in *S. pyogenes* (Clancy, et al., 1996) and *mef*(E) later identified in *S. pneumoniae* (Tait-Kamradt, et al., 1997). Because these two *mef* genes show 90% nucleotide identity, it has been proposed to consider them as a single class, designated *mef*(A) (Roberts, et al., 1999). However, some authors argued for the need to distinguish these determinants, since there are major differences between them (Klaassen & Mouton, 2005). First, erythromycin MICs associated with the *mef*(A) gene (MIC_{50}, 16 μg/ml) are higher than those associated with *mef*(E) (MIC_{50}, 8 μg/ml) (Amezaga, Carter, Cash, & McKenzie, 2002; Blackman Northwood, et al., 2009). Second, and most importantly, these determinants are carried by completely different genetic elements (Del Grosso, et al., 2002). Note that the *mef*(A) subtype is by far the most prevalent *mef* allele among *S. pyogenes* clinical isolates (Blackman Northwood, et al., 2009; Sangvik, Littauer, Simonsen, Sundsfjord, & Dahl, 2005; Ardanuy, et al., 2005).

In *S. pneumoniae*, the *mef*(A) gene is part of Tn*1207.1* (ca. 7 kb), a 7.2-kb defective transposon integrated into the chromosome, while the *mef*(E) is borne by a transferable macrolide efflux genetic assembly (mega) element (ca. 5 kb) that is integrated into composite transposons Tn*2009* (ca. 23 kb) or Tn*2010* (ca. 26 kb) (Varaldo, Montanari, & Giovanetti, 2009). In *S. pyogenes*, the *mef*(A) gene is carried by larger and mobile composite elements (all chimeric in nature since they result from an insertion of a transposon into a prophage) that are different, depending on whether the isolates are susceptible or resistant to tetracyclines [Figure 7] (Varaldo, Montanari, & Giovanetti, 2009; Giovanetti, Brenciani, Lupidi, Roberts, & Varaldo, 2003; Banks, Porcella, Barbian, Martin, & Musser, 2003; Brenciani, et al., 2004; Giovanetti, Brenciani, Vecchi, Manzin, & Varaldo, 2005; Iannelli, Santagati, Oggioni, Stefani, & Pozzi, 2014). In tetracycline-susceptible isolates, a regular Tn*1207.1* forms the left end of the 52-kb Φ1207.3 (formerly Tn*1207.3*) (Iannelli, Santagati, Oggioni, Stefani, & Pozzi, 2014; Santagati, et al., 2003), or is part of Φ10394.4 (ca. 59 kb) [Figure 7] (Banks, Porcella, Barbian, Martin, & Musser, 2003; Banks, et al., 2004), with both integrated into the same chromosomal gene (*comEC*) and inserted into the same prophage (Varaldo, Montanari, & Giovanetti, 2009; Brenciani, et al., 2004). It appears that Φ1207.3 is more common than Φ10394.4 in *mef*(A)-positive, tetracycline-susceptible *S. pyogenes* isolates, and it has been shown that it was transferable both intra- and interspecifically (Varaldo, Montanari, & Giovanetti, 2009; Santagati, et al., 2003). In tetracycline-resistant isolates, evidence has emerged of a genetic linkage between *mef*(A) and *tet*(O) in a mobile phage-like element (Giovanetti, Brenciani, Lupidi, Roberts, & Varaldo, 2003; Giovanetti, Brenciani, Vecchi, Manzin, & Varaldo, 2005). Actually, this linkage corresponds to a variety of related *tet*(O)-*mef*(A) elements in which *mef*(A) is contained in a range of changeable and defective variants of Tn*1207.1* (Brenciani, et al., 2004; Giovanetti, Brenciani, Vecchi, Manzin, & Varaldo, 2005). The most common representative is the transferable Φm46.1 element (ca. 60 kb) that is integrated into the chromosome within the 23S rRNA uracil methyltransferase gene (Giovanetti, Brenciani, Lupidi, Roberts, & Varaldo, 2003; Giovanetti, et al., 2014; Brenciani, Bacciaglia, Vignaroli, Pugnaloni, Varaldo, & Giovanetti, 2010). As described in *S. pneumoniae*, *mef*(E) is part of a typical mega element and is sometimes physically associated with *tet*(M) in the composite transposon Tn*2009* [Figure 8] (Del Grosso, et al., 2011). Note that both *mef*(A) and *mef*(E) alleles are always adjacent to the *msr*(D) gene originally named *mel* (Varaldo, Montanari, & Giovanetti, 2009; Ambrose, Nisbet, & Stephens, 2005). Similar to *msr*(A) in staphylococci, this gene also codes for an ABC family protein that contains the two prototypical ATP-binding domains, but lacks any obvious TMS. Consequently, it has not been clearly proven if this class 2 ABC protein functions as a drug exporter (Davidson, Dassa, Orelle, & Chen, 2008). Nonetheless, *msr*(D) alone is sufficient to confer a 64-, 128-, and 16-fold increase in MICs of erythromycin, clarithromycin, and telithromycin, respectively, but not to streptogramins, which distinguishes it from Msr(A) (Daly, Doktor, Flamm, & Shortridge, 2004).

Additional *mef* alleles have been detected in *S. pyogenes*, such as *mef*(I) and *mef*(O), as well as diverse mosaic variants (Sangvik, Littauer, Simonsen, Sundsfjord, & Dahl, 2005; Mingoia, et al., 2007). The subclass *mef*(I), 91% and 94% identical to *mef*(A) and *mef*(E), respectively, was first identified in *S. pneumoniae* and then among *S. pyogenes* clinical isolates (Blackman Northwood, et al., 2009; Mingoia, et al., 2007). In *S. pneumoniae*, *mef*(I) is embedded in a genetic element that also contains *tet*(M) and *catQ*. This element, designated 5216IQ complex (ca. 30 kb), consists of two portions, one derived from Tn*5252* and Tn*916* (which harbors a copy of *tet*(M) not expressed due to the lack of the promoter, the ribosome-binding site, and a part of the leader peptide) and another called IQ module, which encloses *mef*(I) and *catQ*, a gene that encodes a chloramphenicol acetyltransferase found in *Clostridium perfringens* [Figure 8] (Mingoia, et al., 2007). In *S. pyogenes*, *mef*(I) and *catQ* are also linked through a partial fragment of the 5216IQ complex, designated the 5216IQ-like complex, with a defective IQ module and a partial or absent Tn*916* (Del Grosso, et al., 2011). Note that all these IQ elements are ICEs that belong to the Tn*5253* family, and are named ICE*Spy*029IQ (ca. 55 kb) and ICE*Spy*005IQ (ca. 50 kb) in *S. pyogenes* [Figure 8] (Mingoia, et al., 2014; Mingoia, Morici, Brenciani, Giovanetti, & Varaldo, 2014). The *mef*(O) allele was first described in *S. pyogenes*, and exhibits 88% and 89% nucleotide identity with *mef*(A) and *mef*(E), respectively (Sangvik, Littauer, Simonsen, Sundsfjord, & Dahl, 2005).

Even if there are significant differences in the distribution of MLS resistance genes that depend on the country or year of isolation, the most common gene present in an international study appeared to be *mef*(A) (ca. 45%), followed by *erm*(B) (30%), and *erm*(TR) (ca. 25%) (Farrell, Morrissey, Bakker, & Felmingham, 2002).

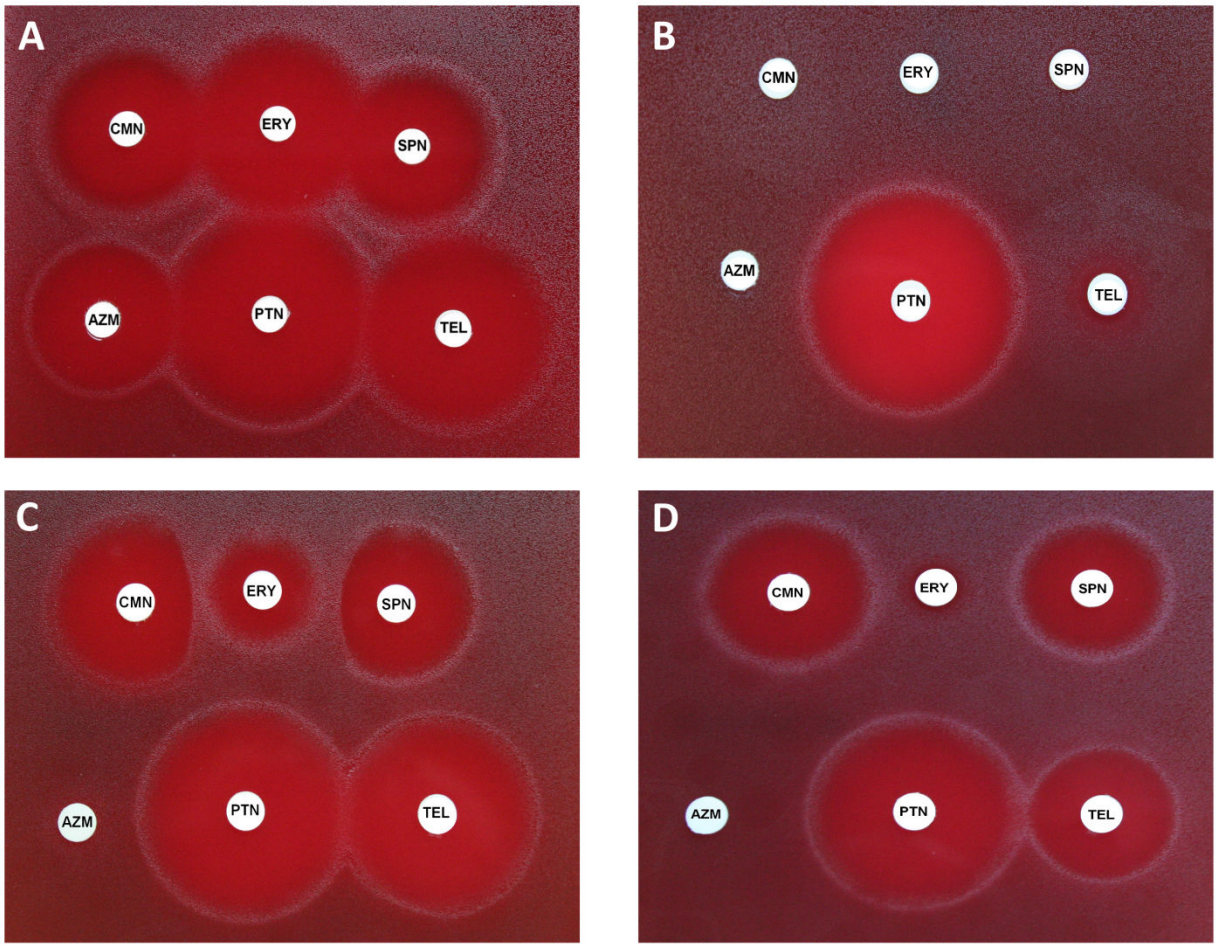

Figure 1. Common phenotypes of MLS resistance in *S. pyogenes*. (A) Wild-type susceptible strain (*S. pyogenes* ATCC 19615); (B) *S. pyogenes* containing an *erm*(B) gene constitutively expressed; (C) *S. pyogenes* containing an *erm*(TR) gene inducibly expressed (a D-shaped zone can be observed between ERY and CMN/SPN); (D) *S. pyogenes* resistant to ERY and AZM by *mef*(A)-mediated efflux (note the absence of the D-shaped zone). AZM, azithromycin; CMN, clindamycin; ERY, erythromycin; PTN, pristinamycin; SPN, spiramycin; TEL, telithromycin. L, lincomycin (Photo credits: Michel Auzou).

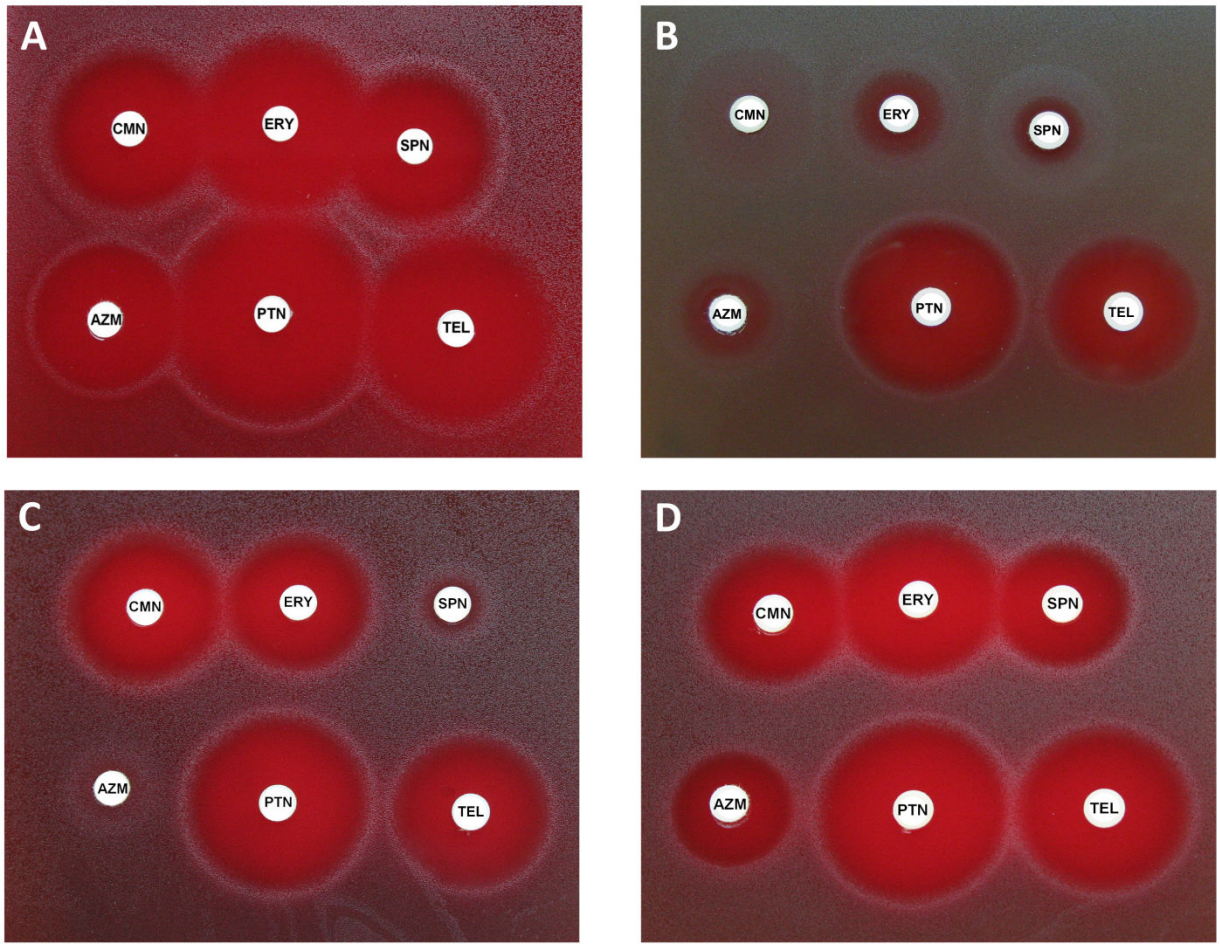

Figure 2. Unusual phenotypes of MLS resistance in *S. pyogenes*. (A) Wild-type susceptible strain (*S. pyogenes* ATCC 19615); (B) *S. pyogenes* containing an *erm*(TR) gene constitutively expressed due to attenuator alterations (Fines, Gueudin, Ramon, & Leclercq, 2001); (C) *S. pyogenes* 237 with L4 ribosomal protein mutation (KG insertion after position 69) (Malbruny, et al., 2002); (D) *S. pyogenes* 544 with 23S rRNA mutation (C2611U) (Malbruny, et al., 2002). AZM, azithromycin; CMN, clindamycin; ERY, erythromycin; PTN, pristinamycin; SPN, spiramycin; TEL, telithromycin. L, lincomycin (Photo credits: Michel Auzou).

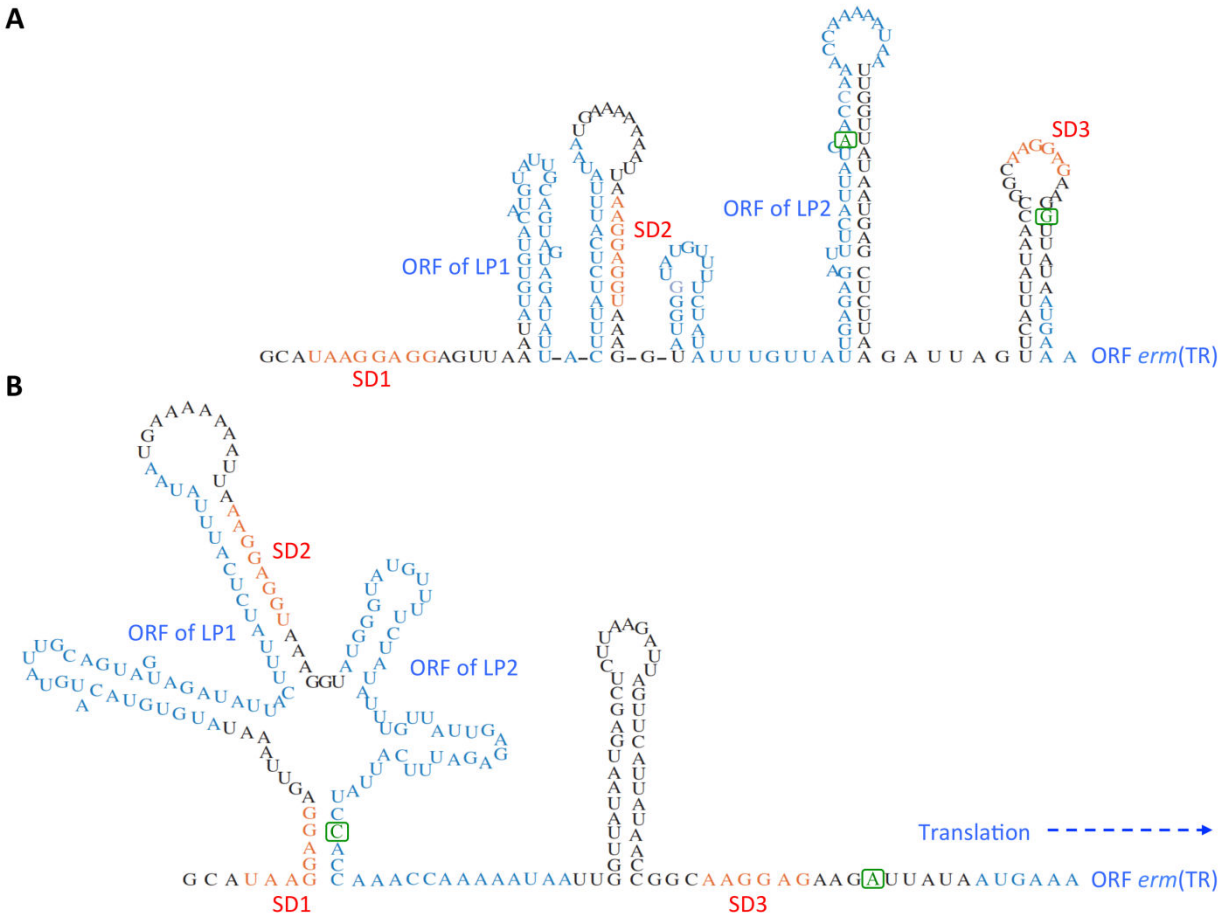

Figure 3. Predicted mRNA secondary structures of the *erm*(TR) regulatory region (called the attenuator). (A) Conformational isomer of the wild-type *erm*(TR) mRNA (Malhotra-Kumar, et al., 2009). Open reading frames (ORFs) are indicated in blue: LP1, leader peptide 1 (15 amino acids); LP2, leader peptide 2 (19 amino acids). Proposed Shine-Dalgarno (SD) sequences are indicated in red: SD1, SD2, and SD3 correspond to ribosome-binding sites for LP1, LP2, and *erm*(TR), respectively. (B) Proposed structure of the *erm*(TR) mRNA in presence of A137C and G205A mutations (boxed and colored in green), responsible for the releasing of the SD3 and the initiation codon of *erm*(TR) and then leading to translation (Malhotra-Kumar, et al., 2009).

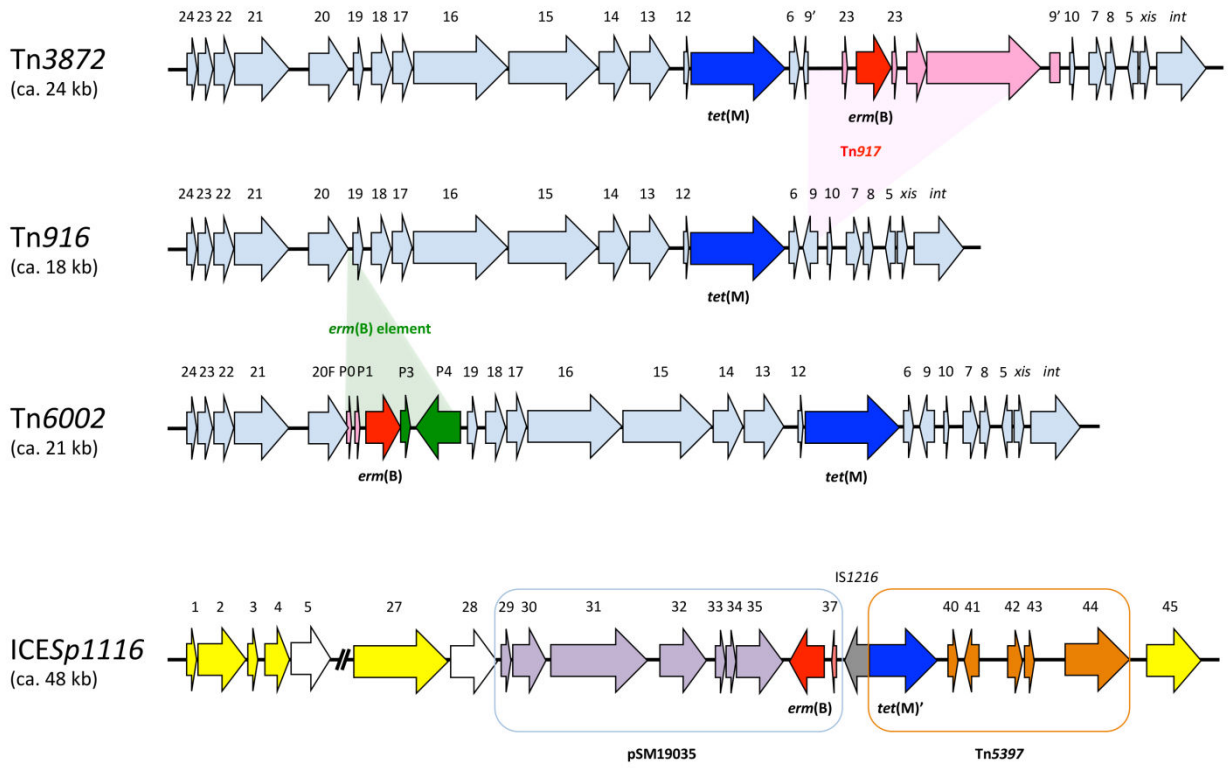

Figure 4. *erm*(B)-carrying genetic elements (Varaldo, Montanari, & Giovanetti, 2009; Brenciani A. , et al., 2007; Brenciani A. , et al., 2012; Brenciani A. , et al., 2014). Open reading frames (ORFs) are indicated by horizontal arrows; *erm*(B) and *tet*(M) genes are indicated in red and blue, respectively. Light blue arrows indicate Tn*916* and Tn*916*-related ORFs other than *tet*(M). Pink, green, yellow, light purple, and orange arrows indicate ORFs from Tn*917*, the *erm*(B) element, Tn*Gallo*1, pSM19035, and Tn*5397* elements, respectively.

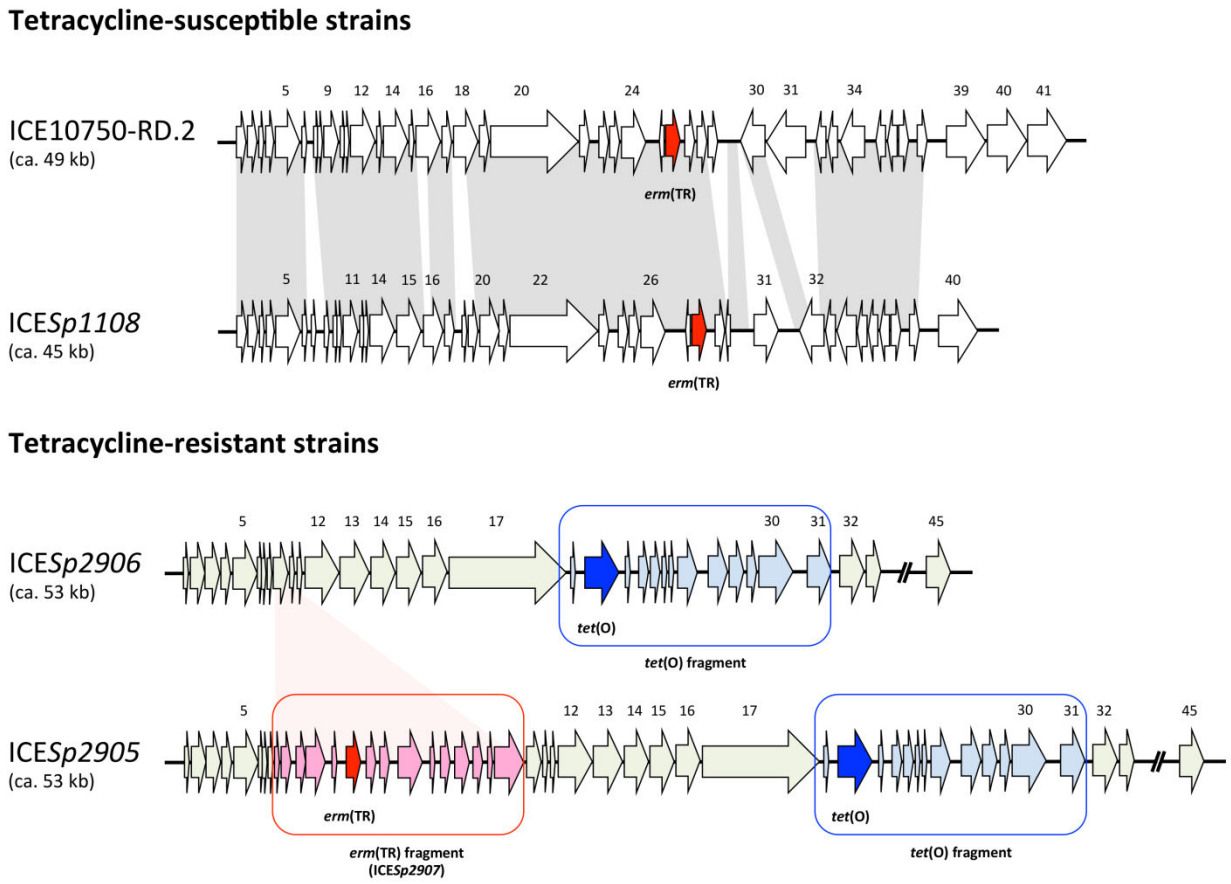

Figure 5. *erm*(TR)-carrying genetic elements that depend on tetracycline susceptibility/resistance (Varaldo, Montanari, & Giovanetti, 2009; Brenciani A. , et al., 2011; Giovanetti E. , Brenciani, Tiberi, Bacciaglia, & Varaldo, 2012). Open reading frames (ORFs) are indicated by horizontal arrows. *erm*(TR) and *tet*(O) genes are indicated in red and blue, respectively. Gray areas between ORF maps indicate areas with >90% homology. Light blue and pink arrows indicate ORFs from *tet*(O) and *erm*(TR) fragments (both boxed), respectively.

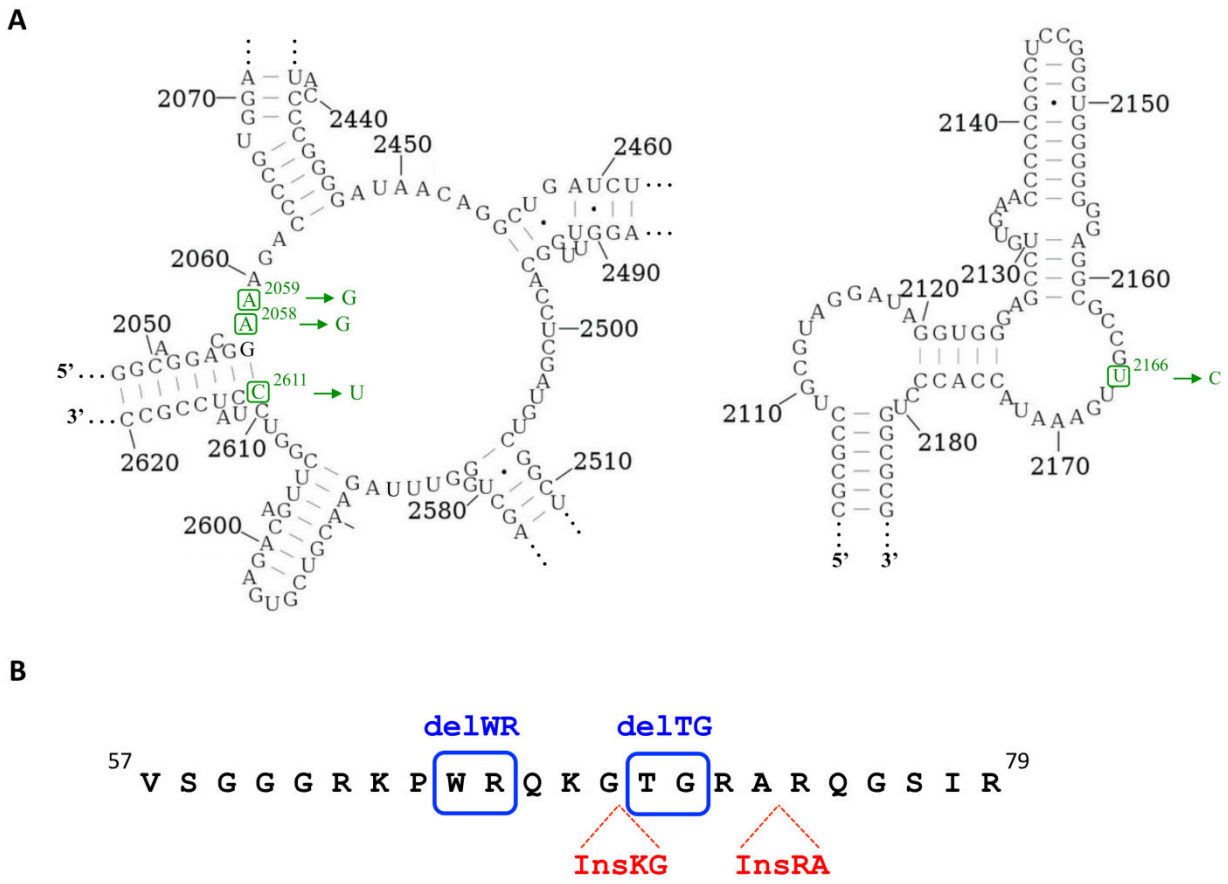

Figure 6. Ribosomal mutations responsible for MLS resistance in *S. pyogenes*. (A) Secondary structure of the domain V of 23S rRNA. Positions (according to *E. coli* numbering) and mutations described in *S. pyogenes* are indicated in green (Tanz, et al., 2004; Richter, et al., 2005; Montes M. , et al., 2014; Malbruny, et al., 2002; Jalava, Vaara, & Huovinen, 2004; Farrell, Shackcloth, Barbadora, & Green, 2006). (B) Partial amino acid sequence (from position 57 to 79, *S. pyogenes* numbering) of the L4 ribosomal protein (*rplD* gene). Deletions and insertions reported in *S. pyogenes* are indicated in blue and red, respectively (Malbruny, et al., 2002; Bingen, et al., 2002; Bozdogan, Appelbaum, Ednie, Grivea, & Syrogiannopoulos, 2003).

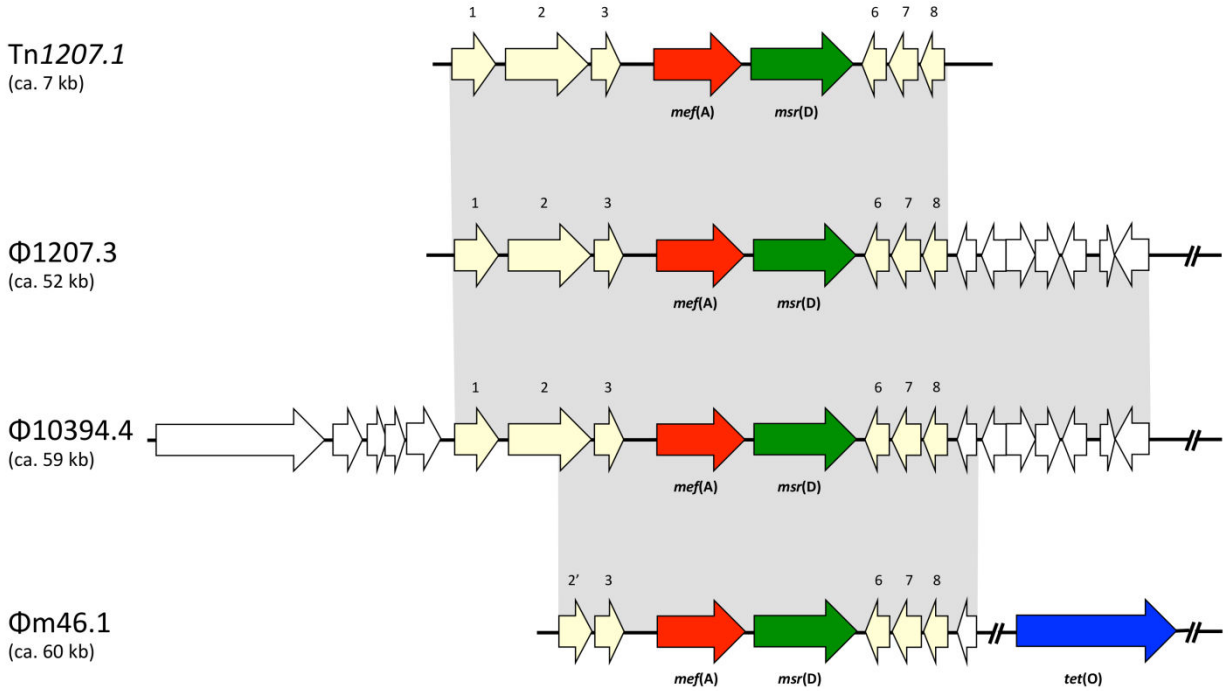

Figure 7. *mef*(A)-carrying genetic elements (Varaldo, Montanari, & Giovanetti, 2009; Giovanetti E. , Brenciani, Lupidi, Roberts, & Varaldo, 2003; Brenciani, et al., 2004; Giovanetti E. , Brenciani, Vecchi, Manzin, & Varaldo, 2005; Iannelli, Santagati, Oggioni, Stefani, & Pozzi, 2014; Iannelli, Santagati, Oggioni, Stefani, & Pozzi, 2014). Open reading frames (ORFs) are indicated by horizontal arrows. *erm*(TR), *msr*(D), and *tet*(O) genes are indicated in red, green, and blue, respectively. Gray areas between ORF maps indicate areas with >90% homology. Light yellow arrows indicate ORFs from Tn*1207.1*.

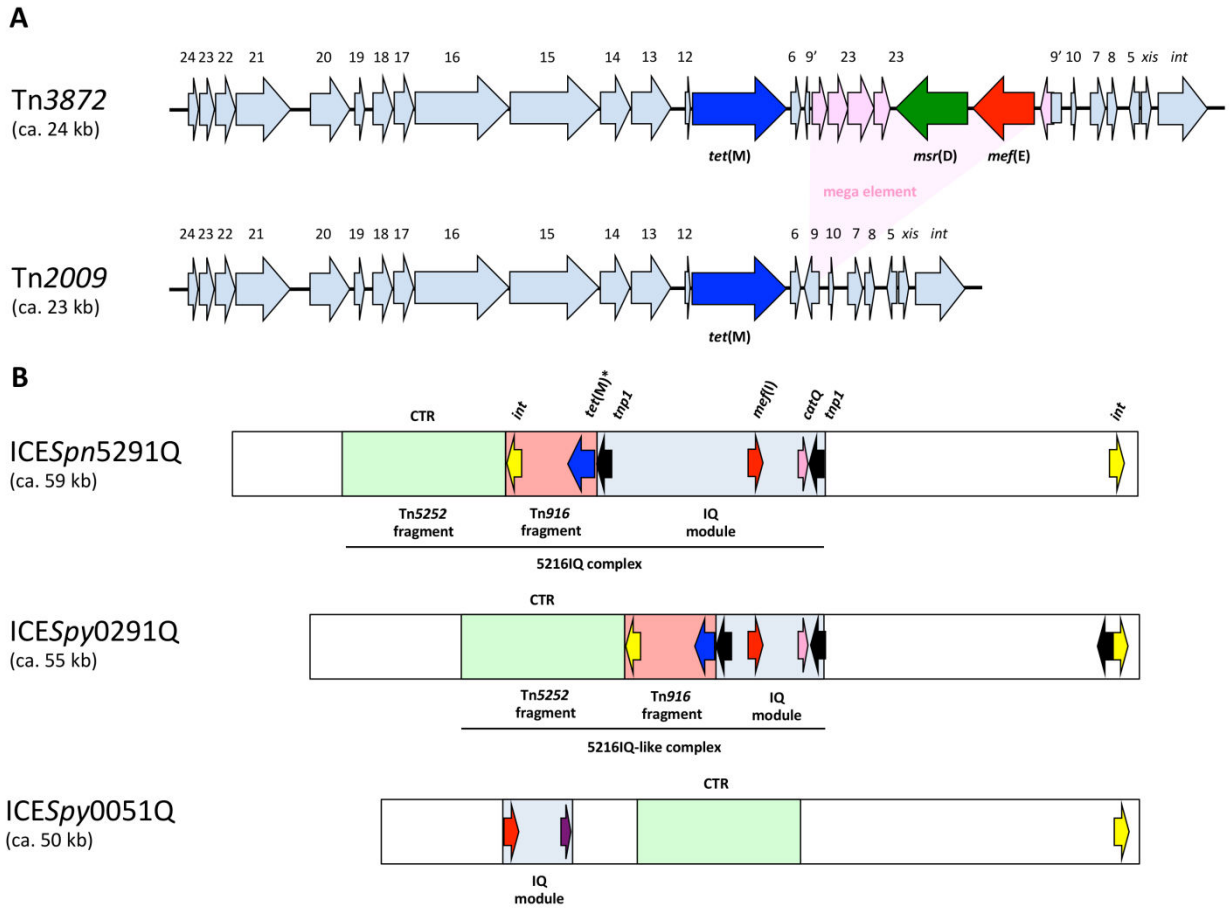

Figure 8. Genetic elements carrying *mef* genes other than *mef*(A) (Varaldo, Montanari, & Giovanetti, 2009; Del Grosso, et al., 2011; Mingoia M. , et al., 2014; Mingoia M. , Morici, Brenciani, Giovanetti, & Varaldo, 2014). Open reading frames (ORFs) are indicated by horizontal arrows. (A) *mef*(E)-carrying elements. *mef*(E), *msr*(D), and *tet*(M) genes are indicated in red, green, and blue, respectively. Light blue arrows indicate Tn*3872* ORFs other than *tet*(M). Pink arrows indicate ORFs from the mega element (macrolide efflux genetic assembly). (B) *mef*(I)-carrying elements. *mef*(I), *tet*(M)* (silent copy of *tet*(M) due to the lack of the promoter, the ribosome-binding site, and a part of the leader peptide), *catQ* genes are indicated in red, blue, and pink, respectively. The Tn*5252* fragment (which corresponds to the conjugal transfer-related [CTR] functional module), the Tn*916* fragment, and the IQ module are indicated in boxes colored in green, red, and blue, respectively. ORFs coding for transposase (*tnp1*) and integrase (*int*) genes are also indicated in black and yellow, respectively.

Table 2. Profiles of susceptibility to MLS antibiotics in *S. pyogenes* according to phenotypes/ genotypes of resistance (Arpin, Canron, Noury, & Quentin, 1999; Giovanetti, Montanari, Mingoia, & Varaldo, 1999; Giovanetti, Montanari, Marchetti, & Varaldo, 2000; Betriu, et al., 2000; Malbruny, et al., 2002; Bingen, et al., 2002).

Phenotype[a]	MIC (μg/ml)								
	WT	$cMLS_B$	$iMLS_B$-A	$iMLS_B$-B	$iMLS_B$-C	M	Other		
Genotype	-	*erm*(B)	*erm*(B)	*erm*(A)	*erm*(A)	*mef*(A)	23S rRNA (C2611U)	23S rRNA (A2058G)	L4
14-membered macrolides									
Erythromycin	0.03-0.06	≥128	≥128	≥128	2-8	8-16	0.12	≥256	0.5-2
Clarithromycin	≤0.01-0.06	≥128	≥128	≥128	1-2	8	-	-	1

Table 2. continued from previous page.

Phenotype[a]	MIC (µg/ml)								
	WT	$cMLS_B$	$iMLS_B$-A	$iMLS_B$-B	$iMLS_B$-C	M	Other		
15-membered macrolides									
Azithromycin	0.12-0.25	≥128	≥128	≥128	8-16	4-8	2	≥256	1-8
16-membered macrolides									
Spiramycin	0.25-0.5	≥128	≥128	0.25-0.5	0.25-1	0.25-0.5	0.5	64	64
Josamycin	0.25-0.5	≥128	≥128	0.03-0.12	0.03-0.12	0.03-0.12	-	64	1-2
Ketolides									
Telithromycin	≤0.01-0.06	2-8	4-8	≤0.01-0.06	≤0.01	0.12-0.25	0.06	1-16	0.06-0.12
Lincosamides									
Clindamycin	0.03-0.12	≥128	0.12-0.25	0.06-0.12	0.03-0.06	0.03-0.12	2	16	0.06-0.12
Streptogramins									
Quinupristin-dalfopristin	0.12-0.25	0.12-0.5	0.12-0.5	0.12-0.5	0.12-0.5	0.12-0.5	0.25	-	0.25

[a] WT, wild-type; $cMLS_B$, constitutive MLS_B resistance; $iMLS_B$, inducible MLS_B resistance (existence of 3 types: A, B, and C).

Fluoroquinolones

Fluoroquinolones (FQs) are bactericidal agents that are widely used in both human and veterinary medicine. The targets of FQ molecules are the type II topoisomerases (namely, DNA gyrase and DNA topoismerase IV) that are both heterotetramers that consist of two subunits, $GyrA_2B_2$ and $ParC_2E_2$ (Hawkey, 2003). Due to the greater clinical use of FQ, bacterial resistance to these compounds has been increasingly reported during the last three decades. In Gram-positive cocci, FQ resistance results from target alterations due to point mutations that occur primarily in 120-bp conserved fragments, the so-called quinolone resistance-determining regions (QRDRs), of both *parC* and *gyrA* genes (Hooper, 2002). Active efflux of hydrophilic FQ molecules is also possible (Poole, 2005). Note that plasmid-mediated resistance has been recently described in *Enterobacteriaceae*, but has not yet been found in Gram-positive cocci (Cattoir & Nordmann, 2009).

In streptococci, high-level FQ resistance is only mediated by target modifications, whereas active efflux may confer low-level resistance in *S. pneumoniae* and viridans group streptococci (Guerin, Varon, Hoï, Gutmann, & Podglajen, 2000). However, the latter mechanism has not yet been detected in *S. pyogenes* (Malhotra-Kumar, et al., 2005). Importantly, the emergence and spread of FQ resistance may also be due to interspecies recombination within the *parC* QRDR and the acquisition of resistance via horizontal gene transfer from *S. dysgalactiae* subsp. *equisimilis*, which shares a global gene pool with *S. pyogenes* (Pletz, et al., 2006; Duesberg, et al., 2008; Pinho, Melo-Cristino, & Ramirez, 2010). Due to the lack of natural transformability of *S. pyogenes*, the genetic information is likely to be transferred by transduction through bacteriophages (Pinho, Melo-Cristino, & Ramirez, 2010). Different substitutions have been reported in clinical isolates of *S. pyogenes*: Ser81Ala/Tyr/Phe, Glu85Ala and Met99Leu in GyrA; Ser79Ala/Tyr/Phe, Asp83Asn, Asp91Asn, Ala121Val, Gly128Val, and Ser140Pro [Figure 9] (Yan, et al., 2000; Alonso, Galimand, & Courvalin, 2002; Richter, et al., 2003; Reinert, Lütticken, & Al-Lahham, 2004; Albertí, et al., 2005; Orscheln, et al., 2005) Note that highly-resistant strains (levofloxacin MIC ≥16 mg/L) generally possess several mutations in the QRDRs of both *gyrA* and *parC* genes (Yan, Fox, Holland, Stock, Gill, & Fedorko, 2000; Richter, et al., 2003; Reinert, Lütticken, & Al-Lahham, 2004; Rivera, et al., 2005; Alonso, Mateo, Ezpeleta, & Cisterna, 2007; Wajima, et al., 2013), while low-level resistance (levofloxacin MIC, 2-4 mg/L) are commonly due to a single substitution in ParC (Alonso, Galimand, & Courvalin, 2002; Orscheln, et al., 2005; Rivera, et al., 2005; Wajima, et al., 2013; Yan, et al., 2008).

While high-level resistance remains exceptional among clinical isolates, FQ-non-susceptible strains that exhibit a low-level resistance (usually defined as ciprofloxacin MIC from 2 to 8 mg/L) may be common in some countries, such as Belgium (ca. 5% in 1999–2002, ca. 7% in 2003–2006), the USA (ca. 11% in 2002–2003), Spain (ca. 3% in 1999–2004, ca. 13% in 2005–2007), Portugal (ca. 5% in 1999–2006), Japan (ca. 16% in 2010–2012), and Italy (ca. 9% in 2012) (Malhotra-Kumar, et al., 2009; Malhotra-Kumar, et al., 2005; Orscheln, et al., 2005; Wajima, et al., 2013; Petrelli, et al., 2014). Notably, a vast majority of these isolates belong to *emm*-type 6, while some other genotypes (such as *emm*75 and *emm*89) have also been recorded (Malhotra-Kumar, et al., 2009; Malhotra-Kumar, Lammens, Chapelle, Mallentjer, Weyler, & Goossens, 2005; Montes, Tamayo, Orden, Larruskain, & Perez-Trallero, 2010; Yan, et al., 2008; Petrelli, Di Luca, Prenna, Bernaschi, Repetto, & Vitali, 2014; Alonso R. , Mateo, Galimand, Garaizar, Courvalin, & Cisterna, 2005). Indeed, *emm*-type 6 *S. pyogenes* seems to have an intrinsic reduced susceptibility to FQs, as a result of a polymorphism at position 79 of the *parC* gene (Orscheln, et al., 2005; Montes, Tamayo, Orden, Larruskain, & Perez-Trallero, 2010). However, despite this polymorphism, these strains are not more likely to develop high-level FQ resistance when compared to other *emm* types (Billal, et al., 2007).

Tetracyclines

Tetracyclines are broad-spectrum antibiotics with bacteriostatic activity. They inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit and blocking entry of the amino-acyl tRNA into the A site of the ribosome (Chopra & Roberts, 2001). The prevalence of tetracycline resistance varies greatly (approximately from 10 to 40%), depending on the countries or regions reporting (Brown & Rybak, 2004; Al-Lahham, De Souza, Patel, & Reinert, 2005; Jones, Sader, & Flamm, 2013; Jasir, et al., 2000; Hammerum, Nielsen, Agersø, Ekelund, & Frimodt-Moller, 2004; Ayer, et al., 2007).

Three mechanisms of tetracycline resistance have been described: drug inactivation, active efflux, and ribosomal protection (Chopra & Roberts, 2001). Tetracycline/minocycline resistance is often encoded by the *tet*(M) gene in Gram-positive bacteria, and more rarely by *tet*(O), *tet*(Q), *tet*(S), *tet*(T), and *tet*(W) genes, which all encode ribosomal protection proteins (Chopra & Roberts, 2001). Tetracycline resistance alone is usually due to the efflux genes *tet*(K) and *tet*(L).

In *S. pyogenes*, *tet*(M) is also the major resistance determinant, while *tet*(O), *tet*(S), and *tet*(T) have all been reported (Hammerum, Nielsen, Agersø, Ekelund, & Frimodt-Moller, 2004; Clermont, Chesneau, De Cespédès, & Horaud, 1997; Betriu, et al., 2002; Betriu, Culebras, Rodríguez-Avial, Gómez, Sánchez, & Picazo, 2004; Nielsen, Hammerum, Ekelund, Bang, Pallesen, & Frimodt-Møller, 2004; Dundar, Sayan, & Tamer, 2010). The predominance of *tet*(M) may be explained by the fact that this gene is carried by conjugative transposons (such as Tn*916*) or by composite structures (such as Tn*3701*), which can easily translocate from chromosome to chromosome (Le Bouguénec, de Cespédès, & Horaud, 1988; Burdett, 1990). While a highly significant association between *tet*(M) and *erm*(B) has been shown, there is also evidence of a genetic linkage between *tet*(O) and *erm*(TR)/*mef*(A) [Figures 4, 5, and 7] (Giovanetti, Brenciani, Lupidi, Roberts, & Varaldo, 2003; Brenciani, et al., 2004; Ayer, Tewodros, Manoharan, Skariah, Luo, & Bessen, 2007).

Tigecycline is a novel glycylcycline that has potent activity against a wide spectrum of both Gram-positive and -negative bacteria, including those that are resistant to classical tetracyclines. Indeed, it is not affected by the two major mechanisms of tetracycline resistance, i.e. active efflux and ribosomal protection (Borbone, et al., 2008). For instance, MICs of tetracycline, minocycline, and tigecycline against *tet*(M)- and *tet*(O)-positive *S. pyogenes* strains are 32, 2-4, and 0.03-0.06 µg/ml and 16-32, 2, and 0.03 µg/ml, respectively (Borbone, et al., 2008).

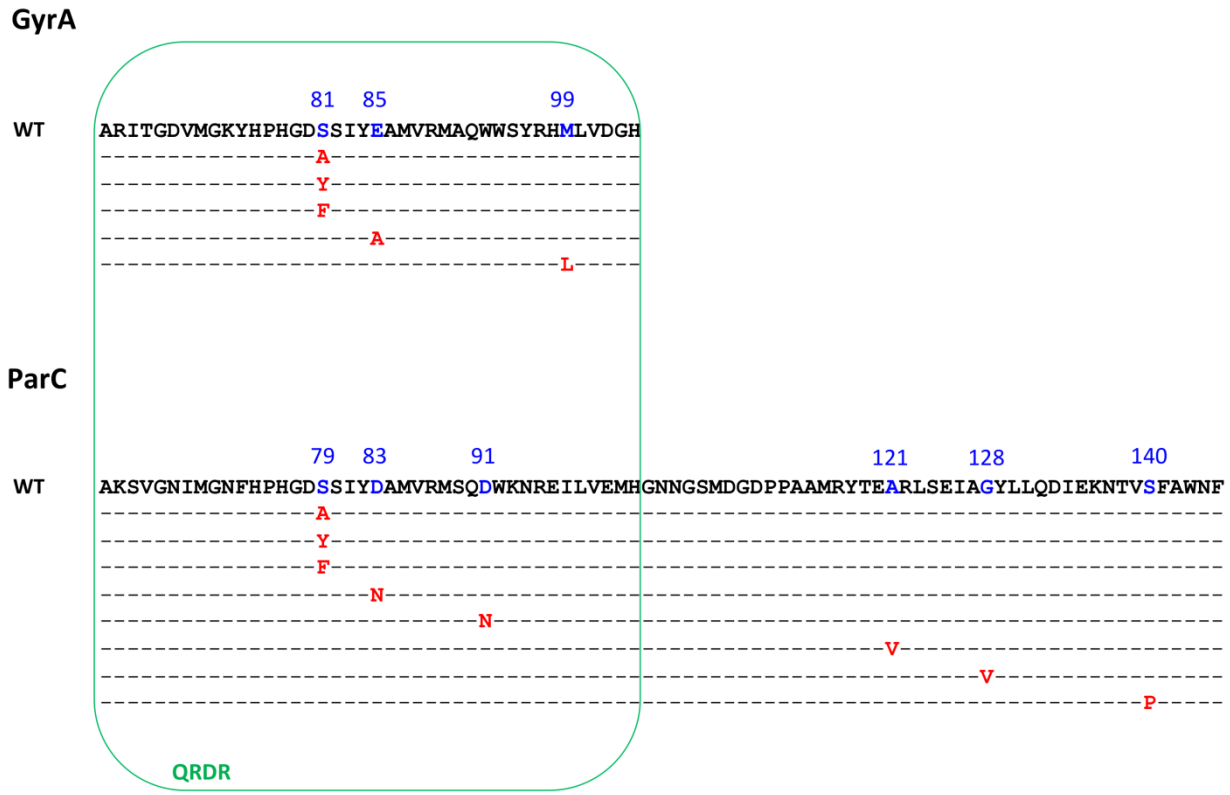

Figure 9. Amino acid sequences in *S. pyogenes* of quinolone resistance-determining regions (QRDRs) of GyrA (amino acids from 65 to 104, which correspond to positions 67-106 in *E. coli* numbering) and ParC (amino acids from 63 to 102, which correspond to positions 64-103 in *E. coli* numbering). Classical QRDRs (40 amino acids) are boxed in green. Mutations described in clinical isolates are indicated in red, as well as their occurring positions (blue) (Yan, Fox, Holland, Stock, Gill, & Fedorko, 2000; Alonso, Galimand, & Courvalin, 2002; Richter, et al., 2003; Reinert, Lütticken, & Al-Lahham, 2004; Albertí, et al., 2005; Orscheln, et al., 2005; Rivera, et al., 2005; Biedenbach, Toleman, Walsh, & Jones, 2006; Alonso, Mateo, Ezpeleta, & Cisterna, 2007; Wajima, Murayama, Sunaoshi, Nakayama, Sunakawa, & Ubukata, 2008; Montes, Tamayo, Orden, Larruskain, & Perez-Trallero, 2010; Pires, et al., 2010; Arai, et al., 2011; Wajima, et al., 2013).

Others

Glycopeptides

Glycopeptides (vancomycin and teicoplanin) are high-molecular weight molecules that interact with the D-Alanine-D-Alanine (D-Ala-D-Ala) termini of pentapeptide peptidoglycan precursors (Gold, 2001). They actually form a stable complex that involves five hydrogen bonds, which prevent the transglycosylation and transpeptidation reactions of the peptidoglycan synthesis.

In enterococci, resistance to glycopeptides is based on the presence of operons encoding enzymes i) that synthesize new precursors with low affinity where the last D-Ala residue is changed by a D-Lactate (D-Lac) or a D-Serine (D-Ser) residue; and ii) that eliminate or prevent the formation of a native precursor with a high affinity. Precursors with the D-Ala-D-Lac terminus have a 1,000-fold lower affinity to vancomycin than those ending in D-Ala-D-Ala, which results in a high-level resistance (MICs >16 µg/ml). On the other hand, the precursors that end in D-Ala-D-Ser have a 7-fold less affinity for vancomycin, which leads to a low-level resistance (MICs from 8 to 16 µg/ml) (Courvalin, 2006). Eight acquired operons (*vanA, vanB, vanD, vanE,*

vanG, vanL, vanM, and *vanN*) and one intrinsic operon (*vanC1-4*) have been characterized to date (Watanabe, et al., 2009; Hegstad, Mikalsen, Coque, Werner, & Sundsfjord, 2010; Cattoir & Leclercq, 2013). The *vanA*, *vanB*, *vanD*, and *vanM* operons confer resistance through the synthesis of peptidoglycan precursors with C-terminal D-Ala-D-Lac residues, whereas isolates that harbor the *vanC*, *vanE*, *vanG*, *vanL*, and *vanN* operons contain precursors that end in D-Ala-D-Ser (Cattoir & Leclercq, 2013). Only *vanA*, *vanB*, and *vanG* have been identified in rare strains of *Streptococcus* spp. but never among *S. pyogenes* clinical isolates (Poyart, et al., 1997; Mevius, et al., 1998; Park, Nichols, & Schrag, 2014). The *vanB* gene cluster (*vanB2* subtype) has only been identified in two *Streptococcus lutetiensis* isolates (MICs of vancomycin and teicoplanin at ≥256 and 3-4 µg/ml, respectively) as well as in two *vanA*-positive *Streptococcus gallolyticus* isolates (MICs of vancomycin and teicoplanin at ≥256 and 32-64 µg/ml, respectively) in France and the Netherlands (Poyart, et al., 1997; Mevius, et al., 1998; Dahl & Sundsfjord, 2003; Bjørkeng, Hjerde, Pedersen, Sundsfjord, & Hegstad, 2013). Two isolates of *Streptococcus agalactiae* and one of *Streptococcus anginosus* have been reported with low-level resistance to vancomycin (MIC of 4 µg/ml) in the US (Park, Nichols, & Schrag, 2014; Srinivasan, et al., 2014). Recently, a third strain of *vanA*-positive *S. gallolyticus* (MICs of vancomycin and teicoplanin both at ≥256 µg/ml) was described in Spain (Romero-Hernández, et al., 2015).

Sulfonamides and trimethoprim

Both sulfonamides and 2,4-diaminopyrimidines are synthetic agents and act as bacteriostatic inhibitors of bacterial biosynthesis of tetrahydrofolic acid, which is an essential cofactor for nucleic acid and protein syntheses (Masters, O'Bryan, Zurlo, Miller, & Joshi, 2003). They are generally given together due to a synergistic effect in vitro, and the most commonly used combination is sulfamethoxazole-trimethoprim, also called cotrimoxazole (or SXT) (Masters, O'Bryan, Zurlo, Miller, & Joshi, 2003). The sulfonamides are structural analogs of para-aminobenzoic acid that interfere with the formation of dihydropteroic acid, which is the first step in dihydrofolic acid synthesis, by blocking the enzymatic activity of the dihydropteroate synthase (DHPS). Trimethoprim inhibits a later step of the metabolic pathway (namely, the formation of tetrahydrofolic acid from dihydrofolic acid) by binding to the dihydrofolate reductase (DHFR) enzyme.

Bacterial resistance to sulfonamides results from chromosomal point mutations in the *dhps* (*fol*P) gene coding for the natural DHPS, or the acquisition of plasmid-borne *sul* genes coding for resistant DHPS enzymes (Huovinen, Sundström, Swedberg, & Sköld, 1995). Resistance to trimethoprim in bacteria may be due to one or more of the following mechanisms: auxotrophy in thymine/thymidine; reduced intracellular antibiotic concentration (impaired permeability, active efflux); production of a naturally-insensitive DHFR; alterations and/or overexpression of the intrinsic DHFR encoded by the *fol*A gene; or the presence of an additional plasmid-mediated *dfr* gene that codes for a resistant DHFR (Huovinen, Sundström, Swedberg, & Sköld, 1995).

Because of early inappropriate antimicrobial susceptibility testing (AST) approaches, *S. pyogenes* has been considered to be universally resistant to SXT for a long time. However, recent studies using standardized conditions (particularly AST media with low thymidine content) have confirmed the in vitro susceptibility of *S. pyogenes* to SXT (Bowen, et al., 2012). When appropriate methods are used, MICs of SXT are typically low [Table 1] and the prevalence of resistance among clinical isolates has ranged from 0% to 3% (Bowen, et al., 2012; Yourassowsky, Vanderlinden, & Schoutens, 1974; Eliopoulos & Wennersten, 1997). High-level sulfonamide resistance (MIC ≥128 µg/ml) in *S. pyogenes* is due to alterations within the chromosomally encoded DHPS (Swedberg, Ringertz, & Sköld, 1998; Jönsson, Ström, & Swedberg, 2003). Acquired resistance to trimethoprim in *S. pyogenes* may be due to the acquisition of transferable *dfrF* or *dfrG* genes (MICs from 32 to >512 µg/ml) or an amino acid substitution (Ile100Leu) in the intrinsic DHFR (MIC from 8 to 16 µg/ml) (Bergmann, Sagar, Nitsche-Schmitz, & Chhatwal, 2012; Bergmann, van der Linden, Chhatwal, & Nitsche-Schmitz, 2014).

Rifampin

Rifampin is a broad-spectrum antibiotic with bactericidal activity and is widely used for the treatment of tuberculosis. Like other members of the rifamycin family, it inhibits bacterial transcription through high-affinity binding to the DNA-dependent RNA polymerase (Lester, 1972). More precisely, rifampin interacts with the RNA polymerase β subunit encoded by the *rpoB* gene.

Rifampin resistance mainly results from chromosomal *rpoB* mutations that are responsible for target alterations, which occur at a frequency of ca. 10^{-6}-10^{-8}. These mutations are generally clustered in an 81-bp conserved fragment (the so-called rifampin resistance-determining region [RRDR]), which corresponds to codons 507-533 (according to *Escherichia coli* numbering) (Herrera, Jiménez, Valverde, García-Aranda, & Sáez-Nieto, 2003).

In *S. pyogenes*, rifampin resistance appears to be rare among clinical isolates (<0.5%) while MICs for wild-type strains are very low [Table 1] (Perez-Trallero, Urbieta, Montes, Ayestaran, & Marimon, 1998; Aubry-Damon, Galimand, Gerbaud, & Courvalin, 2002). High-level resistance to rifampin (>128 µg/ml) is due to RpoB changes at position 522 (Ser522Leu) (Aubry-Damon, Galimand, Gerbaud, & Courvalin, 2002; Herrera, et al., 2002).

Bacitracin

Like β-lactams and glycopeptides, bacitracin disrupts bacterial cell wall synthesis. It actually acts by preventing dephosphorylation and recycling of the lipid carrier (undecaprenol pyrophosphate) that allows the translocation of *N*-acetylmuramyl pentapeptide intermediates onto the surface of the cytoplasmic membrane (Butaye, Devriese, & Haesebrouck, 2003). Bacitracin is a narrow-spectrum antibiotic that is only active against Gram-positive bacteria.

Bacitracin is used in some topical preparations in human and veterinary medicine and has been employed in clinical laboratories as a presumptive marker for *S. pyogenes* identification. Indeed, among β-hemolytic streptococci, only *S. pyogenes* is susceptible to bacitracin. However, some bacitracin-resistant clones (MICs ≥16 µg/ml) have been uncommonly reported (York, Gibbs, Perdreau-Remington, & Brooks, 1999; Malhotra-Kumar, Wang, Lammens, Chapelle, & Goossens, 2003; Perez-Trallero, Garcia, Orden, Marimon, & Montes, 2004; Pires, et al., 2009). Notably, bacitracin resistance is commonly associated with macrolide resistance ($cMLS_B$ phenotype) mediated by the *erm*(B) gene with most of the isolates belonging to the *emm*28 genotype (Malhotra-Kumar, Wang, Lammens, Chapelle, & Goossens, 2003; Perez-Trallero, Garcia, Orden, Marimon, & Montes, 2004; Perez-Trallero, Garcia, Orden, Marimon, & Montes, 2004; Pires, et al., 2009; Mihaila-Amrouche, Bouvet, & Loubinoux, 2004). Even though the molecular mechanism of resistance is not well defined in this species, it might be associated with an overproduction of undecaprenol kinase encoded by the *bacA* gene, as shown in *E. coli* (Cain, Norton, Eubanks, Nick, & Allen, 1993; Chalker, et al., 2000). Notably, an ABC transporter (encoded by the *bcrABD* operon) responsible for bacitracin resistance in *E. faecalis* has not been detected among bacitracin-resistant *S. pyogenes* clinical isolates (Pires, et al., 2009; Manson, Keis, Smith, & Cook, 2004).

Chloramphenicol

The phenicols are inhibitors of bacterial protein synthesis and prevent peptide chain elongation after reversible binding to 23S rRNA (Schlünzen, et al., 2001). Chloramphenicol resistance is primarily due to the acquisition of chloramphenicol *O*-acetyltransferase (CAT) enzymes or to active efflux mediated by specific or multidrug transporters (Schwarz, Kehrenberg, Doublet, & Cloeckaert, 2004). Target modifications are also possible through point mutations or Cfr-mediated methylation in 23S rRNA (Schwarz, Kehrenberg, Doublet, & Cloeckaert, 2004; Kehrenberg, Schwarz, Jacobsen, Hansen, & Vester, 2005). CATs inactivate the antibiotic by acetylation in the three-step reaction, and there are two types of enzymes, according to their structure: type A CATs and type B CATs (also known as xenobiotic acetyltransferases or XATs) (Schwarz, Kehrenberg, Doublet, & Cloeckaert,

2004). Notably, chloramphenicol resistance is inducibly expressed through a translational attenuation regulation (Lovett, 1996).

Chloramphenicol resistance is rarely encountered in clinical isolates of β-hemolytic streptococci (ca. 0.5%), while it appears to be much more common among enterococcal species (ca. 40-50%) (Trieu-Cuot, et al., 1993). In *S. pyogenes*, only a few type-A CATs have been detected, such as *cat(pC221)* (group A-7), *cat(pC194)* (group A-9), *catS* (group A-12), and *catQ* (group A-16) (Del Grosso, et al., 2011; Schwarz, Kehrenberg, Doublet, & Cloeckaert, 2004; Trieu-Cuot, et al., 1993). Notably, *mef*(I) and *catQ* were demonstrated to be co-located in Tn*5253*-like ICEs (see above) [Figure 8] and were cotransferred by transformation (Mingoia, et al., 2014).

Fusidic acid

Fusidic acid is a bacteriostatic antibiotic that inhibits bacterial protein synthesis by interfering with elongation factor G (EF-G) (Collignon & Turnidge, 1999). While it is very active against staphylococci (MIC_{50} and MIC_{90} at 0.12 and 0.25 µg/ml, respectively), β-hemolytic streptococci, including *S. pyogenes*, are less susceptible (MIC_{50} and MIC_{90} both at 4 µg/ml) [Table 1] (Jones, Mendes, Sader, & Castanheira, 2011). Acquired resistance has only been characterized in *S. aureus*, and is caused by mutations in the EF-G that encodes the *fusA* gene, or results from horizontal transfer of a plasmid-mediated determinant (*fusB-E*) (Turnidge & Collignon, 1999; O'Neill, McLaws, Kahlmeter, Henriksen, & Chopra, 2007). No *S. pyogenes* isolate highly resistant to fusidic acid has been reported to date.

Fosfomycin

Fosfomycin interferes with the cell wall synthesis at an early intra-cytoplasmic stage by specifically and irreversibly inhibiting the enzymatic activity of UDP-*N*-acetylglucosamine enolpyruvyltransferase (named MurA) (Falagas, Giannopoulou, Kokolakis, & Rafailidis, 2008). It exerts a slow bactericidal activity against a large panel of both Gram-positive and -negative bacteria, but is mainly used for staphylococcal infections and uncomplicated acute cystitis in young women (Patel, Balfour, & Bryson, 1997). Fosfomycin is moderately active against *S. pyogenes* with MICs from 2 to 64 µg/ml, while no high-level resistance has been reported in this species to date (Falagas, et al., 2010).

New Antibiotics

Linezolid

Linezolid is a member of the family of oxazolidinones and targets the initiation phase of protein synthesis by direct interaction with the PTC in 23S rRNA (Hancock, 2005). It is only active against Gram-positive bacteria, including *S. pyogenes* (MIC_{50} and MIC_{90} at 1 µg/ml) [Table 1] (Gemmell, 2001; Brauers, Kresken, Hafner, & Shah, 2005). In staphylococci and enterococci, linezolid resistance is due to the emergence of ribosomal point mutations (23S rRNA, L4, or L22) or acquisition of the Cfr protein (Cattoir & Giard, 2014), but none of these resistance mechanisms has been identified in *S. pyogenes* to date.

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic that exhibits a potent and rapid bactericidal activity against Gram-positive bacteria (Kanafani & Corey, 2007). Daptomycin irreversibly binds to the bacterial cell membrane in a calcium-dependent manner, which causes depolarization and thus results in cell death (Hancock, 2005). It is highly active against β-hemolytic streptococci with MICs from 0.01 to 0.06 µg/ml [Table 1] (King & Phillips, 2001). No daptomycin-resistant *S. pyogenes* isolate has been reported to date.

Conclusion

Except for MLS and tetracyclines, *S. pyogenes* has remained highly susceptible to antimicrobial agents in vitro since the 1940s, particularly to penicillins, which are usually the first-line treatment. Indeed, even if therapy failures are quite common with β-lactams in clinical practice, no acquired mechanism of resistance has been reported to date. Note that there have not been any minor changes in the MICs of penicillin. In cases of allergy or therapy failure, MLS antibiotics are considered to be alternate options. However, macrolide resistance may become a problem, since it has emerged in numerous countries, and as a result, in vitro antimicrobial susceptibility testing should be performed. Such testing will not only allow researchers to distinguish susceptible phenotypes from resistant phenotypes, but also to differentiate between the different resistant phenotypes (such as $cMLS_B$, $iMLS_B$, and M phenotypes) since they unravel the potential activity of the different MLS members. Besides MLS antibiotics, *S. pyogenes* can also acquire resistance to the tetracycline family. Notably, numerous clinical isolates are co-resistant to MLS and tetracyclines, since both resistance determinants are borne by the same mobile genetic elements. High-level resistance to aminoglycosides or fluoroquinolones remains very uncommon, while there is no (or exceptional) resistance to other antibiotics. More specifically, no resistance has been described to date for newer molecules (such as linezolid, tigecycline, and daptomycin).

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