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MINIREVIEW

Nomenclature for Macrolide and Macrolide-Lincosamide-Streptogramin B Resistance Determinants

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Macrolides are composed of 14 (erythromycin and clarithromycin)-, 15 (azithromycin)-, or 16 (josamycin, spiramycin, and tylosin)-membered lactones to which are attached amino and/or neutral sugars via glycosidic bonds. Erythromycin was introduced in 1952 as the first macrolide antibiotic. Unfortunately, within a year, erythromycin-resistant (Em^r) staphylococci from the United States, Europe, and Japan were described (101). Erythromycin is produced by *Saccharopolyspora erythraea*, while the newer macrolides are semisynthetic molecules with substitutions on the lactone. The newer derivatives, such as clarithromycin and azithromycin, have improved intracellular and tissue penetration, are more stable, are better absorbed, have a lower incidence of gastrointestinal side effects, and are less likely to interact with other drugs. They are useable against a wider range of infectious bacteria, such as *Legionella*, *Chlamydia*, *Haemophilus*, and some *Mycobacterium* species (not *M. tuberculosis*), and their pharmacokinetics provide for less frequent dosing than erythromycin (21, 47, 96, 97). As a result, the usage of the newer macrolides has increased dramatically over the last few years, which has led to increased exposure of bacterial populations to macrolides (101–103, 107).

Macrolides inhibit protein synthesis by stimulating dissociation of the peptidyl-tRNA molecule from the ribosomes during elongation (101, 103). This results in chain termination and a reversible stoppage of protein synthesis. The first mechanism of macrolide resistance described was due to posttranscriptional modification of the 23S rRNA by the adenine-N^6 methyltransferase (101–103). These enzymes add one or two methyl groups to a single adenine (A2058 in *Escherichia coli*) in the 23S rRNA moiety. Over the last 30 years, a number of adenine-N^6-methyltransferases from different species, genera, and isolates have been described. In general, genes encoding these methylases have been designated *erm* (erythromycin ribosome methylation), although there are exceptions, especially in the antibiotic-producing organisms (see Tables 1 and 3) (103). As the number of *erm* genes described has grown, the nomenclature for these genes has varied and has been inconsistent (Table 1). In some cases, unrelated genes have been given the same letter designation, while in other cases, highly related genes (>90% identity) have been given different names.

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The binding site in the 50S ribosomal subunit for erythromycin overlaps the binding site of the newer macrolides, as well as the structurally unrelated lincosamides and streptogramin B antibiotics. The modification by methylase(s) reduces the binding of all three classes of antibiotics, which results in resistance against macrolides, lincosamides, and streptogramin B antibiotics (MLS_B). The rRNA methylases are the best studied among macrolide resistance mechanisms (47, 101–103). However, a variety of other mechanisms have been described which also confer resistance (Table 2). Many of these alternative mechanisms of resistance confer resistance to only one or two of the antibiotic classes of the MLS_B complex.

In this review, we suggest a new nomenclature for naming MLS genes and propose to use the rules developed for identifying and naming new tetracycline resistance genes (51, 52). This system, with a few recent modifications, was originally designed because of the ability of two genes to be distinguished uniquely by DNA-DNA probe methodology (51). It was generally found that two genes with <80% amino acid sequence identity provided enough variability in nucleotide sequence to permit distinct probes to be designed. Although many investigators are likely to sequence new genes, the use of probe technology allows rapid identification of isolates containing potentially new genes, as well as a reliable way to screen populations and determine the frequency of any one resistant determinant. Therefore, we continued this paradigm by assigning two genes of ≥80% amino acid identity to the same class and same letter designation, while two genes that show ≤79% amino acid identity are given a different letter designation. Table 1 shows the results of the classification, with some classes having members with little variability, while others, like classes A and O, show a greater range of homology at both the DNA and amino acid levels. As new gene sequences emerge, ideally they will need to be compared by oligonucleotide probe hybridization and/or sequence analysis against the bank of known genes before a new designation is assigned. If multiple genes are available in any one class, especially when there is a range as in class A, then all representative members of the class should be examined, not just one. To confirm that the proposed name or number for the newly discovered resistance determinant has not been used by another investigator, please contact M. C. Roberts for this information. A similar request has been made for new *tet* genes (52).

TABLE 1. rRNA methylase genes involved in MLS_B resistance

Class	Protein	Gene name	Gene(s) included	% Homology		Plasmid transposon[c]	GenBank no. or reference[e]
				DNA	Amino acid		
A	Erm(A)	*erm*(A)	*erm*(A)	83	81	Tn*554*	X03216
			erm(TR)				AF002716
B	Erm(B)	*erm*(B)	*erm*(AM)	98–100	98–100	Tn*1545*	X52632
			erm(AM)			pAMβ-1	Y00116
			erm(AM)			pAM77	K00551
			erm(B)			Tn*917*	M36722
			erm(B)			pAD2	M11180
			erm(B)			pIP501	X72021
			erm(AMR)				U86375
			erm(BC)			pIP1527	M19270
			erm(P), *erm*(BP)[a]			pIP402	U18931
			erm(IP)			pIP501	U00453
			erm(Z), *erm*(BZ1), *erm*(BZ2)[a]			Tn*5398*	AF109075
			erm			pLEM3	U48430, X82819
			erm(2)			pBT233, pMD101	X64695, X66468
C	Erm(C)	*erm*(C)	*erm*(C)	99–100	98–100	pE194	J01755, V01278
			erm(C)			pT48	M19652
			erm(C)			pE5	M17990
			erm(C)			pJR5	L04687
			erm(C)			pA22	X54338
			erm(C)			pSES6	X82668
			erm(C)			pSES5	Y09001
			erm(C)			pSES4a	Y09002
			erm(C)			pSES21	Y09003
			erm(C)			J3356::pOX7	U36911
			erm(IM)			pIM13	M13761
			erm(M)			pNE131	M12730
			erm(M)			pPV141	U82607
			erm(M)			pPV142	AF019140
D[d]	Erm(D)	*erm*(D)	*erm*(D)	97–99	97–99	pBD90	M29832
			erm(J)			pBA423	L08389
			erm(K)				M77505
E	Erm(E)	*erm*(E)	*erm*(E)	99	96	pUC31, pIJ43	X51891
			erm(E2)				M11200
F	Erm(F)	*erm*(F)	*erm*(F)	98–100	97–100	pBF4	M14730
			erm(F)			Tn*4351*	M17124
			erm(FS)			pBI106, Tn*4551*	M17808
			erm(FU)			Chromosomal	M62487
G	Erm(G)	*erm*(G)	*erm*(G)	99	99	pBD370	M15332
			erm(G)			Tn*7853*	L42817
H[b]	Erm(H)	*erm*(H)	*car*(B)			pOJ159	P13079, M16503
I[b]	Erm(I)	*erm*(I)	*mdm*(A)				34
N[b]	Erm(N)	*erm*(N)	*tlr*(D)				X97721
O[b]	Erm(O)	*erm*(O)	*lrm*	84	84	pLST391	M74717
			srm(A)				AJ223970
Q	Erm(Q)	*erm*(Q)	*erm*(Q)			Chromosomal	L22689
R	Erm(R)	*erm*(R)	*erm*(R)				M11276
S[b]	Erm(S)	*erm*(S)	*erm*(SF)	100	100	pET23	M19269
			tlr(A)				P45439
T[b]	Erm(T)	*erm*(T)	*erm*(GT)			pGT633	M64090
U[b]	Erm(U)	*erm*(U)	*lmr*(B)			pPZ303	X62867
V[b]	Erm(V)	*erm*(V)	*erm*(SV)				U59450
W[b]	Erm(W)	*erm*(W)	*myr*(B)				M77505, P43433
X[b]	Erm(X)	*erm*(X)	*erm*(CD), *erm*(A)[b]	99–100	99–100	pNG2	M36726, X51472
			erm(CX)			Tn*5432*	U21300
Y[b]	Erm(Y)	*erm*(Y)	*erm*(GM)			pMS97	57
Z[b]	Erm(2)	*erm*(2)	*srm*(D)				69
Unclassified			*clr*			pJI702	18

[a] When two or three gene names are listed under "Genes included," it means that the same gene was designated by two or three different names in the literature; for *erm*(B), *erm*(C), and *erm*(M), multiple related genes have been sequenced, and a selection of these are listed, although they are not complete lists, since some of them have not been completely sequenced.

[b] Newly designated classes, proteins, and genes given a single-letter designation rather than the two-letter or different three-letter designations currently used in the literature.

[c] The list of plasmids includes both recombinant and natural plasmids.

[d] Class D includes genes labeled in the literature as *erm*(D), *erm*(J), and *erm*(K); because they share between 97 and 99% DNA and amino acid homology, they have been grouped under class D and *erm*(D).

[e] Information was provided by GenBank and references 10–12, 18, 25, 29, 31, 32, 34, 35, 37, 38, 42, 46, 55–57, 60–62, 65, 69, 71, 77, 88, 89, 91, 95, and 108–110.

TABLE 2. Efflux and inactivating genes

Resistance profile	Protein name	Gene included	Genes	% Homology		Plasmid[b]	GenBank no. or reference[d]
				DNA	Amino acid		
ATP-binding transporters							
Lincomycin	Car(A)	*car*(A)	*car*(A)			pOJ158	M80346
Erythromycin	Msr(A)	*msr*(A)	*msr*(A)	98	98	pUL5054	X52085
						pSR1	AF167161
Streptogramin B			*msr*(SA)			pEP2104	57
			msr(SA′)			pMS97	AB013298
			msr(B)			pCH200	M81802
Oleandomycin	Ole(B)	*ole*(B)	*ole*(B)			pALOR26E	L36601
Oleandomycin	Ole(C)	*ole*(C)	*ole*(C)				L06249
Spiramycin	Srm(B)	*srm*(B)	*srm*(B)			pKC514	X63451
Tylosin	Tlr(C)	*tlr*(C)	*tlr*(C)				M57437
Streptogramin A	Vga(A)	*vga*(A)	*vga*			pIP524	M90056
Streptogramin A	Vga(B)	*vga*(B)	*vga*(B)			pIP1633	U82085
Major facilitators							
Lincomycin	Lmr(A)	*lmr*(A)	*lmr*(A)			pLST21	X59926
Erythromycin	Mef(A)	*mef*(A)	*mef*(A)	90	91	p53-6	U70055
Erythromycin			*mef*(E)			pAT15-5	U83667
Esterases							
Erythromycin	Ere(A)	*ere*(A)	*ere*(A)			pI1100, pAT63	M11277
Erythromycin	Ere(B)	*ere*(B)	*ere*(B)	99	99	pIP1527	A15097
			ere(B)			pAT72	X03988
Hydrolases							
Streptogramin B	Vgb(A)	*vgb*(A)	*vgb*			pIP524	M20129
Streptogramin B	Vgb(B)	*vgb*(B)	*vgb*(B)			pIP1714	AF015628
Transferases							
Lincomycin	Lnu(A)[a]	*lnu*(A)[c]	*lin*(A′)			pIP856	J03947
Lincomycin			*lin*(A)			pIP855	M14039
Lincomycin	Lnu(B)[a]	*lnu*(B)[c]	*lin*(B)			pVMM25	AJ238249
Streptogramin A	Vat(A)	*vat*(A)	*vat*			pIP680	L07778
Streptogramin A	Vat(B)	*vat*(B)	*vat*(B)			pIP524	L38809
Streptogramin A	Vat(C)	*vat*(C)	*vat*(C)			pIP1714	AF015628
Streptogramin A	Vat(D)[a]	*vat*(D)	*sat*(A)			pAT15, pAT421	L12033
Streptogramin A	Vat(E)[a]	*vat*(E)	*sat*(G)				AF139725
Phosphorylases							
Macrolides	Mph(A)	*mph*(A)	*mph*(A)	99	93–99	pTZ3519	D16251
Macrolides			*mph*(K)			pGE64	U36578
Macrolides	Mph(B)	*mph*(B)	*mph*(B)			pTZ3721, pTZ3723	D85892
Macrolides	Mph(C)	*mph*(C)	*mph*(BM)	100	100	pMS97	Q9ZNK8
Macrolides			*mph*(C)			pSR1	AF167161

[a] These are newly designated classes, proteins, and genes.
[b] The list of plasmids includes both recombinant and natural plasmids.
[c] New gene designation because the *lin* designation has been used for other genes. No genes use the *lnu* designation.
[d] Information provide by GenBank and references 1–8, 14, 16, 17, 19, 23, 28, 30, 33, 34, 37–40, 42, 45, 47–50, 54, 55, 60, 63, 64, 66, 67, 69, 70, 72, 73, 83, 85, 87, 90, 93, 94, 99, 105, 110.

rRNA METHYLASES

Over the last 30 years, a large number of different rRNA methylase genes (*erm*) have been isolated from a variety of bacteria that range from *E. coli* to *Haemophilus influenzae* in gram-negative species and from *Streptococcus pneumoniae* to *Corynebacterium* spp. in gram-positive species (Table 3). In addition, a variety of gram-positive and gram-negative anaerobes, and even spirochetes such as *Borrelia burgdorferi* and *Treponema denticola*, have all been shown to carry *erm* genes (Table 3) (36, 77, 78). All *erm* enzymes methylate the same adenine residue, resulting in an MLS_B phenotype (9, 100–103). This adenine (A2058) or one of the adjacent residues in the

TABLE 3. Location of antibiotic resistance genes[a]

Gene	Genus or genera
Methylases	
erm(A)	*Actinobacillus*, *Staphylococcus*, *Streptococcus*
erm(B)	*Actinobacillus*, *Clostridium*, *Escherichia Enterococcus*, *Klebsiella*, *Neisseria*, *Pediococcus*, *Staphylococcus*, *Streptococcus*, *Wolinella*
erm(C)	*Actinobacillus*, *Bacillus*, *Eubacterium*, *Lactobacillus*, *Neisseria*, *Staphylococcus*, *Streptococcus*, *Wolinella*
erm(D)	*Bacillus*
erm(E)	*Streptomyces*
erm(F)	*Actinobacillus*, *Actinomyces*, *Bacteroides*, *Clostridium*, *Eubacterium*, *Fusobacterium*, *Gardnerella*, *Haemolphilus*, *Neisseria*, *Porphyromonas*, *Prevotella*, *Peptosteptococcus*, *Selenomonas*, *Streptococcus*, *Treponema*, *Veillonella*, *Wolinella*
erm(G)	*Bacillus*, *Bacteroides*
erm(H)	*Streptomyces*
erm(I)	*Streptomyces*
erm(N)	*Strepomyces*
erm(O)	*Streptomyces*
erm(Q)	*Actinobacilus*, *Clostridium*, *Streptococcus*, *Wolinella*
erm(R)	*Aeromicrobium*
erm(S)	*Streptomyces*
erm(T)	*Lactobacillus*
erm(U)	*Streptomyces*
erm(V)	*Streptomyces*
erm(W)	*Micromonospora*
erm(X)	*Corynebacterium*
erm(Y)	*Staphylococcus*
clr	*Streptomyces*
ATP-binding transporters	
car(A)	*Strepomyces*
msr(A)	*Staphylococcus*
ole(B)	*Streptomyces*
ole(C)	*Streptomyces*
srm(B)	*Streptomyces*
tlr(C)	*Streptomyces*
vga(A)	*Staphylococcus*
vga(B)	*Staphylococcus*
Major facilitators	
lmr(A)	*Streptomyces*
mef(A)	*Corynebacterium*, *Enterococcus*, *Micrococcus Staphylococcus*, *Streptococcus*
Esterases	
ere(A)	*Enterobacter*, *Escherichia*, *Klebsiella*, *Citrobacter*
ere(B)	*Escherichia*, *Klebsiella*, *Proteus*
Hydrolases	
vgb(A)	*Enterococcus*, *Staphylococcus*
vgb(B)	*Staphylococcus*
Transferases	
lnu(A)	*Staphylococcus*
lnu(B)	*Enterococcus*
vat(A)	*Staphylococcus*
vat(B)	*Staphylococcus*
vat(C)	*Staphylococcus*
vat(D)	*Enterococcus*
vat(E)	*Enterococcus*
Phosphorylases	
mph(A)	*Escherichia*
mph(B)	*Escherichia*
mph(C)	*Staphylococcus*

[a] Data were taken from references 1, 2, 6, 8, 9, 14, 16, 19, 22, 27, 33, 34, 37–41, 43, 44, 47, 48, 53–57, 59–67, 69–85, 88, 90, 93, 94, 98, 100, 105, and 108–110.

peptidyltransferase region (A2057 or A2059) is changed to another nucleotide by mutation in macrolide-resistant *Mycobacterium intracellulare*, *Mycobacterium avium*, *Propionibacterium* spp., and *Helicobacter pylori* (58, 84, 100–103).

Differences between the various *erm* genes are seen in the regulation of expression of the phenotype. Some of the enzymes are inducibly regulated by translational attenuation of a mRNA leader sequence; in the absence of erythromycin, the mRNA is in an inactive conformation due to a sequestered Shine-Dalgarno sequence, preventing efficient initiation of translation of the *erm* transcripts. Mutational analyses of the *erm*(C) leader peptide suggested that the peptide, (FS)IFVI, is critical for induction (103). However, when the *erm* peptides from the *erm* genes are compared, little sequence similarity is apparent (103). Recently, a second mechanism of regulation has been described in which the lack of erythromycin prevents the complete synthesis of the mRNA due to rho factor-independent termination. This type of regulation has been described for the *erm*(K) system (20), and by homology, we hypothesize that it may also exist for *erm*(D), as well as *erm*(J), because they are highly related and have been grouped together under class D (Table 1). In either system, inducible isolates, when tested, may appear to be susceptible or intermediately resistant to macrolides and susceptible to lincosamides. Erythromycin is generally a good inducer in most species; in animal or human streptococcal isolates, lincosamides and/or streptogramin B may be good inducers (47, 76). Good overviews of regulation of the *erm* genes can be found in recent reviews by Weisblum (100–103).

Inducible strains predominated in the 1960s to 1970s. However, today it is more common in many geographical areas to find isolates that constitutively produce the rRNA methylase without preexposure to antibiotics. Constitutive *erm* gene expression is usually associated with structural alterations in the *erm* translational attenuator, including deletions, duplications, and point mutations in *erm*(C) (104). They can be distinguished from inducible isolates by the stable MICs for them regardless of whether they are pregrown with or without an inducer (76, 102).

Many of the *erm* genes are associated with conjugative or nonconjugative transposons which tend to reside on the chromosomes, although some have been found in plasmids. They are often associated with other antibiotic resistance genes, especially tetracycline resistance genes. The *erm*(F) gene is often linked with the *tet*(Q) gene, while the *erm*(B) gene is often linked with the *tet*(M) gene (24, 86, 95). These conjugative transposons can have a wide host range, which may explain why clinical isolates of many different bacterial species have been found to carry these *erm* genes (Table 3). The *erm* genes in general have low G+C contents (31 to 34%), while the overall chromosomal G+C contents found in gram-negative species are ≥50% and ~35% in gram-positive species.

It has been common practice for investigators to give their *erm* gene a new name regardless of the DNA and predicted amino acid sequence similarity to previously characterized *erm* genes and without regard to whether the gene resides in a different isolate, species, or genus. The result has been that, over the years, the names of these *erm* genes have become confusing, and often a complex table is required to remember which genes are closely related (Table 1). In the worst cases, genes for unrelated enzymes have been given the same name (*erm*(A), causing confusion in the literature and GenBank listings (Table 1). The opposite also has occurred where very closely related or virtually identical enzymes have been given a variety of different names. For example, *erm*(F) (GenBank no. M14730) is found on the *Bacteroides* transposons Tn*4351* and Tn*4000* (71), *erm*(FS) (no. M17808) is on *Bacteroides* transposon Tn*4551* (91), and *erm*(FU) (no. M62487) (32) is also from *Bacteriodes*. All three enzymes share ≥97% DNA and amino acid identity (Table 1). Since there are no phenotypic differences between the three *erm*(F) genes and distinguishing them

by any method other than sequencing is problematic, we propose that all three should be known as class F: the Erm(F) protein and the *erm*(F) gene (Table 1).

The situation is even worse with class B, which is composed of a larger number of genes, including *erm*(AM), *erm*(B), *erm*(BC), *erm*(BP), and *erm*(Z), whose sequences share ≥98% homology (Table 1). Because the normal gene designation is to use a single letter (26) and the possibility of confusion between *erm*(A) and *erm*(AM), we propose that this group be known as class B: the *erm*(B) genes and the Erm(B) protein (Table 1). Recent dendrograms of many of the *erm* genes can be found in articles by Seppälä et al. (88) and Matsuoka et al. (56) and support this grouping of all of these genes within the class B designation.

To help those in the field, GenBank numbers or references for sequences that have not been deposited are listed in Table 1. If a new gene sequence shows ≥80% amino acid homology to any member of a gene class and confers a similar phenotype to the host, we propose that the new gene be placed in the existing group and not be given a new letter or number designation. Thus, with classes that show a wide range of homologies, like class A (81% amino acid homology) or class O (84% amino acid homology), multiple members must be compared to the new gene. Note that the class designation is based on the amino acid sequence of the structural gene only and does not include the various regulatory sequences that can occur upstream of the gene. These guidelines are intended to apply to all of the *N*-methyltransferases, regardless of whether the gene was originally identified in pathogenic, opportunistic, normal flora bacteria or an antibiotic-producing species. Once all of the single capital letters have been used to identify new *erm* genes, we recommend naming genes as follows: *erm*(30), *erm*(31), etc. This system has been proposed for naming of new *tet* genes [*tet*(30), etc.] (52). Furthermore, a similar set of guidelines should be adopted for the genes that encode other mechanisms of resistance to any of the MLS antibiotics (Table 1). Class Y for gene *erm*(GM), class S for gene *erm*(SF), class T for gene *erm*(GT), class V for gene *erm*(SV), class X for genes *erm*(CD), *erm*(CX), and *erm*(A), and class 2 for gene *srm*(D) are new class designations that conform to the single-letter designation (Table 1).

There are a number of other methylase genes, most often found in methylase-producing organisms which have not been given *erm* designations, such as *tlr*(D), *car*(B), *myr*(B), and *smr* (A). All are from species which confer resistance to a 16-membered ring macrolide (Table 1). We have grouped and renamed them classes H for *car*(B), I for *mdm*(A), N for *tlr*(D), O for genes *lrm* and *srm*(A), U for *lmr*(B), and W for *myr*(B). The *clr* gene could not be classified, because there is no sequence in the database or literature available. Less work has been done to determine if these genes are found outside their respective antibiotic producers (Table 3). *erm* genes are often linked with *tet* genes, and since genes conferring resistance to oxytetracycline, originally found in antibiotic-producing streptomycetes, are now found in some clinical *Mycobacterium* isolates, it is certainly possible that some *erm* genes have also moved into *Mycobacterium* spp. and other genera (68).

To prevent two unrelated genes from being given the same designation, we propose to establish a reference center, as has recently been recommended for tetracycline resistance genes. By using the guideline presented above in governing the identification of new *erm* genes, surveys can be conducted in bacterial populations to examine the spread of particular MLS_B-resistant determinants. A single internal DNA fragment or oligonucleotide probe or a PCR assay that detects all members of a gene class can be established to screen large numbers of isolates. Not only will the adoption of a uniform naming system reduce the number of new *erm* gene names, but it will hopefully prevent confusion over unrelated genes being given the same designation and also prevent highly related genes from having different gene designations.

EFFLUX SYSTEMS

A number of different antibiotic resistance genes code for transport (efflux) proteins. These do not modify either the antibiotic or the antibiotic target, but instead pump the antibiotic out of the cell or the cellular membrane, keeping intracellular concentrations low and ribosomes free from antibiotic. Many of these proteins [*mef*(A), *mef*(E), and *lmr*(A)] have homology to the major facilitator superfamily (MFS) of efflux proteins. Others [*car*(A), *msr*(A), *msr*(B), *ole*(B), *ole*(C) *srm*(B), *tlr*(C), *vga*, and *vga*(B)] are putative members of the ABC transporter superfamily (70). In early years, most macrolide resistance was mediated by the presence of *erm* genes. However, more recently, other mechanisms of macrolide resistance have been found in increasing frequency in certain gram-positive populations (23, 27, 41, 43, 44, 92, 93, 106). Three different efflux systems which confer resistance have been described for gram-positive cocci [*msr*(A) (macrolide and streptogramin B resistant), *mef*(A) (macrolide efflux), and *vga* and *vga*(B) (virginiamycin factor A)] (4) (Table 2). Besides the academic interest in these genes, their presence in an erythromycin-resistant bacterial pathogen of interest may also have implications in terms of therapeutic choices. If an isolate carries a *mef* gene, clindamycin can be considered, whereas the presence of an *erm*(B) gene would preclude consideration of a lincosamide. Recently, we and others have identified *Streptococcus pneumoniae* strains which carry both *mef* and *erm*(B) genes and, as expected, have the MLS_B phenotype (41, 53).

The *mef* genes have been found in a variety of gram-positive genera, including corynebacteria, enterococci, micrococci, and a variety of streptococcal species (30, 43, 53, 90) (Table 3), suggesting a much wider distribution of this group of genes than originally imagined. Many of these genes are associated with conjugative elements located in the chromosome and are readily transferred conjugally across species and genus barriers (43, 53).

Two *mef* genes have been characterized in the literature: *mef* (A) (23) and *mef*(E) (94). The *mef*(A) gene was described in *Streptococcus pyogenes*, while the *mef*(E) gene was found in *S. pneumoniae*. Since the two genes share 90% DNA and 91% amino acid homology (Table 2), we recommended that these two genes be considered a single class, A: *mef*(A) gene and Mef(A) protein (Table 2).

The *msr*(A), *msr*(SA), *msr*(SA)′, and *msr*(B) group differs from the *mef* genes because they confer resistance to both macrolide and streptogramin B antibiotics (MS) (13, 55–57). The *msr*(B) gene is roughly half the size of *msr*(A), but very homologous to it. Though this gene is significantly shorter than the *msr*(A) gene sequence, we placed it with the other *msr* genes (Table 2).

In antibiotic producers, there are efflux pumps specific for MLS_B antibiotics that generally belong to the ABC transporter superfamily (87). They include *car*(A) from *Streptomyces thermotolerans* (87), *ole*(B) from *Streptomyces antibioticus* (7, 80), *srm*(B) from *Streptomyces ambofaciens* (73), *lmr*(C) from *Streptomyces lincolnensis* (70), and *tlr*(C) from *Streptomyces fradiae* (87). In addition to the *msr*(A) efflux pumps, there are two efflux systems identified in staphylococci that confer resistance to streptogramin A antibiotics, *vga* and *vga*(B) (4). Besides *mef*(A), other efflux proteins that appear to be fueled by the

proton motive force have been described for MLS_B antibiotics. A lincomycin-specific efflux pump encoded by *lmr*(A) has been described in *S. lincolnensis* (110).

OTHER MECHANISMS

A variety of other mechanisms which usually confer resistance to only one of the three classes (M, L, or S) or one component such as streptogramin A, but not streptogramin B, have been described (103) (Table 2). These proteins modify the antibiotic rather than the rRNA target or serve as pumps that shuttle the antibiotic out of the bacterial cell. Enzymes which hydrolyze streptogramin B [*vgb* (virginiamycin factor B hydrolase), *vgb*(B) genes] or modify the antibiotic by adding an acetyl group (acetyltransferases) to streptogramin A [*vat* (virginiamycin, factor A acetylation), *vat*(B), *vat*(C), *sat*(A), and *sat*(G) genes] have been described (1–6) (Table 2). Many of these genes are plasmid borne, and often these *vat*-related genes [*vat*, *vat*(B), and *vat*(C) genes] are downstream of other genes encoding resistance to streptogramins [*vgb*, *vga*(B), and *vgb*(B) genes, respectively] in staphylococci (2), but not in enterococci (72). The acetyltransferase genes are related, in the active site region, to a novel chloramphenicol acetyltransferase family of enzymes. We have renamed *sat*(A) as *vat*(D) and *sat*(G) as *vat*(E) to simplify the nomenclature (Table 2).

Unlike most of the other genes described in this review, both the *ere* (erythromycin esterification) and *mph* (macrolide phosphotransferase) genes (Table 2) were first described in *E. coli* rather than gram-positive cocci (8, 63, 64, 66, 67). According to our guidelines, *mph*(K) has been reassigned to *mph*(A), because there are only 10 amino acid (1%) differences between the two proteins. *mph*(BM) and *mph*(C) (66a) are grouped under Mph(C), because these genes are nearly identical to each other and distinct from *mph*(A) and *mph*(B) (Table 2). Several lincomycin nucleotidyltransferases have been identified: *lin*(A) in *Staphylococcus haemolyticus* (16), *lin*(A′ in *Staphylococcus aureus* (17), and *lin*(B) in *Enterococcus faecium* (14). We propose changing *lin*(A) and *lin*(B) to *lnu*(A) and *lnu*(B) (for lincomycin nucleotidyltransferase), because the former letters have already been used for gamma BHC dehydrochlorinase and cyclohexadiene hydrolase genes. It is suggested that prior to naming a new gene class, it is necessary to determine if the proposed three-letter designation has been used for other previously characterized genes.

CONCLUSIONS

With the introduction of the newer, more stable macrolides with enhanced properties, there has been a significant increase in macrolide usage. Macrolides like azithromycin and clarithromycin are recommended for prophylactic use to prevent *Mycobacterium avium* complex disease in human immunodeficiency virus patients. As macrolide use increases, so does its exposure to bacterial populations, increasing the opportunity for bacteria to acquire macrolide or MLS resistance. Given that intragenic transfer of macrolide-resistant determinants is possible (15), it is likely that all of the genes described in this review will spread into new species and that new genes will be identified. Therefore, it is important to clarify the nomenclature of these resistance genes for their expanding audience.

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