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Distribution of Genes Encoding Resistance to Macrolides, Lincosamides, and Streptogramins among Staphylococci

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The relative frequency of 10 determinants of resistance to macrolides, lincosamides, and streptogramins was investigated by PCR in a series of 294 macrolide-, lincosamide-, and/or streptogramin-resistant clinical isolates of *Staphylococcus aureus* and coagulase-negative staphylococci isolated in 1995 from 32 French hospitals. Resistance was mainly due to the presence of *ermA* or *ermC* genes, which were detected in 259 strains (88%), in particular those resistant to methicillin (78% of the strains). Macrolide resistance due to *msrA* was more prevalent in coagulase-negative staphylococci (14.6%) than in *S. aureus* (2.1%). Genes related to *linA*/*linA′* and conferring resistance to lincomycin were detected in one strain of *S. aureus* and seven strains of coagulase-negative staphylococci. Resistance to pristinamycin and quinupristin-dalfopristin was phenotypically detected in 10 strains of *S. aureus* and in three strains of coagulase-negative staphylococci; it was always associated with resistance to type A streptogramins encoded by *vat* or *vatB* genes and occurred in association with *erm* genes. The *vga* gene conferring decreased susceptibility to type A streptogramins was present alone in three strains of coagulase-negative staphylococci and in combination with *erm* genes in 10 strains of coagulase-negative staphylococci. A combination of *vga-vgb-vat* and *ermA* genes was found in a single strain of *S. epidermidis*.

Macrolide, lincosamide, and streptogramin (MLS) antibiotics are widely used in the treatment of staphylococcal infections. Resistance to macrolides (such as erythromycin) and lincosamides (such as lincomycin and clindamycin) is prevalent among staphylococci (9, 13, 28, 29). Resistance against streptogramins, which consist of two components, streptogramin types A and B (e.g., pristinamycin IIA and IA, dalfopristin and quinupristin) with synergistic activity, remains infrequent (23). A number of genes conferring resistance to this group of antibiotics via a variety of mechanisms have been identified in staphylococci. Three related determinants, *ermA*, *ermB*, and *ermC*, have been identified which confer resistance to MLS type B (MLS_B) by target site alteration of the ribosome (11, 21, 29). This resistance is either inducible (strains are resistant to 14- and 15-membered ring macrolides and susceptible to 16-membered ring MLS_B) or constitutive (resistance includes 16-membered ring MLS_B). The *msrA* gene, first identified in *Staphylococcus epidermidis*, confers the so-called MS phenotype (inducible resistance to 14- and 15-membered ring macrolides and resistance to streptogramin type B after induction with erythromycin) by efflux (27); an *msrA*-related gene, *msrB*, has been described in *S. xylosus* (25). The *linA* gene in *S. haemolyticus* and *linA′* in *S. aureus*, which have a high degree of homology, confer resistance to lincosamides only (8). Resistance to type A streptogramin antibiotics in staphylococci can be due to two mechanisms: (i) the *vga* and *vgaB* genes encode related ATP-binding proteins probably involved in active efflux of the A compounds (2, 4) and (ii) the *vat* and *vatB* genes encode related acetyltransferases (1). The *vgb* gene encoding a lactonase inactivates the type B streptogramin antibiotics (5). Genes related to *vat* and *vgb* have been described in *S. cohnii* subsp. *cohnii* and were named *vatC* and *vgbB*, respectively (3).

The present investigation was undertaken to study the relative frequency of each MLS resistance determinant, by PCR, in a series of 294 macrolide, lincosamide, and/or streptogramin-resistant clinical isolates of *S. aureus* and coagulase-negative staphylococci obtained from 32 French hospitals.

MATERIALS AND METHODS

Bacterial strains. A series of 2,091 staphylococcus isolates were collected in 1995 in France during a 3-week period. Isolates were from various clinical specimens and were sent by 32 clinical microbiology laboratories located throughout France. Initial identification as *S. aureus* or coagulase-negative staphylococci was based on colony and microscopic morphology, coagulase testing with rabbit plasma (bioMérieux, Marcy l'Etoile, France), and agglutination tests with the Staphyslide test (bioMérieux). Coagulase-negative isolates were identified to the species level by using the ID 32 Staph gallery (bioMérieux). Strains were stored at −70°C in brain heart broth plus 30% glycerol.

Antibiotic susceptibility. A representative sampling of 602 isolates consisting of 307 *S. aureus* and 295 coagulase-negative staphylococci was selected from the total collection by choosing a similar proportion of isolates (≈30%) in each hospital. The MICs were determined by a standardized agar dilution technique (26). Isolates were characterized by their response to oxacillin and to the MLS resistance phenotype by determining the MICs of the following antibiotics: oxacillin, erythromycin, dalfopristin (a streptogramin A), lincomycin, pristinamycin, quinupristin (a streptogramin B), and the streptogramin composed of the two components dalfopristin and quinupristin. Oxacillin, erythromycin, and lincomycin were provided by Sigma (St. Louis, Mo.); dalfopristin, quinupristin, pristinamycin, and quinupristin-dalfopristin were provided by Rhone-Poulenc Rorer (Vitry sur Seine, France). MIC breakpoints were those of the CA-SFM (10), namely, >2 μg/ml for oxacillin, >4 μg/ml for erythromycin, >8 μg/ml for lincomycin, and >2 μg/ml for pristinamycin. Since no breakpoints have been defined for quinupristin, dalfopristin, and quinupristin-dalfopristin by national committees, the MIC breakpoints for resistance were considered to be ≥16 μg/ml for quinupristin and dalfopristin and ≥4 μg/ml for quinupristin-dalfopristin as recommended by Barry et al. (6) and as recently approved by the National Committee for Clinical Laboratory Standards (25a).

PCR amplification of MLS resistance genes. Genomic DNA was extracted from staphylococcal cultures (12) and used as a template for amplification. Primers specific for *vga* and *vat* genes were used (23). The other primers were designed from published GenBank sequences to provide specific PCR products (Table 1). The *linA′* gene displays 93% homology with *linA* (8), and the primers defined in this study could not differentiate the two genes, which were referred to as *linA*/*linA′*. These oligonucleotides were synthesized by Eurogentec (Sera-

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TABLE 1. Sequences, primers, and PCR conditions used to detect MLS resistance determinants

Target gene	GenBank accession no.	Primer sequences	PCR fragment size (nt)[a]	No. of PCR cycles (conditions)	Control strain(s) and reference(s)
ermA[b]	K02987	5′-GTTCAAGAAC AATCAATACA GAG-3′ 5′-GGATCAGGAA AAGGACATTT TAC-3′	421	30 (30 s at 94°C; 30 s at 52°C; 1 min at 72°C)	*S. aureus* HM1055 (19)
ermB	U35228	5′-CCGTTTACGA AATTGGAACA GGTAAAGGGC-3′ 5′-GAATCGAGAC TTGAGTGTGC-3′	359	30 (30 s at 94°C; 30 s at 55°C; 1 min at 72°C)	*S. aureus* CR5 80 (Tn*1545*) (31)
ermC[b]	X54338	5′-GCTAATATTG TTTAAATCGT CAATTCC-3′ 5′-GGATCAGGAA AAGGACATTT TAC-3′	572	Same as for *ermA*	*S. aureus* HM290-1 (19)
msrA	X52085	5′-GGCACAATAA GAGTGTTTAA AGG-3′ 5′-AAGTTATATC ATGAATAGAT TGTCCTGTT-3′	940	25 (1 min at 94°C; 1 min at 50°C; 90 s at 72°C)	*S. aureus* RN4220(pUL5054) (27)
msrB	M91802	5′-TATGATATCC ATAATAATTA TCCAATC-3′ 5′-AAGTTATATC ATGAATAGAT TGTCCTGTT-3′	595	Same as for *msrA*	*S. aureus* RN4220(pUL5054) (27)
linA/*linA*′	M14039	5′-GGTGGCTGGG GGGTAGATGT ATTAACTGG-3′ 5′-GCTTCTTTTG AAATACATGG TATTTTTCGA TC-3′	323	30 (30 s at 94°C; 30 s at 57°C; 1 min at 72°C)	*S. haemolyticus* BM4610 (7); *S. aureus* BM4611 (8)
vga	M90056	5′-CCAGAACTGC TATTAGCAGA TGAA-3′ 5′-AAGTTCGTTT CTCTTTTCGA CG-3′	470	30 (30 s at 94°C; 30 s at 54°C; 1 min at 72°C)	*S. aureus* BM3002 (4, 23)
vgb	U19459	5′-ACTAACCAAG ATACAGGACC-3′ 5′-TTATTGCTTG TCAGCCTTCC-3′	734	30 (1 min at 94°C; 1 min at 53°C; 2 min at 72°C)	*S. aureus* BM3002 (4, 23)
vat	L07778	5′-CAATGACCAT GGACCTGATC-3′ 5′-CTTCAGCATT TCGATATCTC C-3′	619	Same as for *ermA*	*S. aureus* BM3002 (4, 23)
vatB	M20129	5′-CCCTGATCCA AATAGCATAT ATCC-3′ (vatB-1) 5′-CTAAATCAGA GCTACAAAGT G-3′ (vatB-2)	602	Same as for *ermA*	*E. coli* LUG369(pLUG247); this study
gyrA		5′-AGTACATCGT CGTATACTAT ATGG-3′ 5′-ATCACGTAAC AGTTCAAGTGTG-3′	280	30 (30 s at 94°C; 30 s at 55°C; 1 min at 72°C)	17
16S-23S spacer region		5′-TTGTACACAC CGCCCGTCA-3′ 5′-GGTACCTTAG ATGTTTCAGTTC-3′	492	Same as for *gyrA*	18

[a] nt, nucleotide.
[b] Genes detected by duplex PCR with a common primer oligonucleotide.

ing, Belgium). PCR was carried out on the 294 staphylococcal strains displaying resistance to at least one of the MLS antibiotics, as well as on control strains for each resistance determinant (Table 1), the reference *S. aureus* strains ATCC 25923 and ATCC 29213, and 20 strains susceptible to MLS (10 strains of *S. aureus* and 10 coagulase-negative staphylococcus strains) randomly selected from the bacterial collection described above. In the absence of the reference strain harboring the *vatB* gene, which is protected by a patent, a surrogate template for *vatB* amplification was designed on a pCRII vector (Invitrogene, Leek, The Netherlands) in *Escherichia coli*. This plasmid (pLUG247) consists of the sequence of the upstream and downstream primers separated by the tetracycline resistance determinant *tet*(*M*). The PCR assays run on a GeneAmp PCR System 9600 (Perkin-Elmer, Saint-Quentin en Yvelines, France) were initialized by a denaturation step (10 min at 94°C) and finished with a final extension step (10 min at 72°C). Cycles were run as described in Table 1. DNA amplification of *gyrA* for *S. aureus* (17) or the 16S-23S spacer region of the rDNA operon for other species (18) was used to test the quality of the DNA extraction and for the absence of PCR inhibitors. PCR products were analyzed by electrophoresis through 1% agarose gels (Sigma, Saint Quentin Fallavier, France).

RESULTS

MLS resistance phenotypes. A total of 294 strains including 144 *S. aureus* and 150 coagulase-negative staphylococci exhibited resistance to at least one of the MLS antibiotics. Resistance to oxacillin was detected in 103 of the 144 *S. aureus* strains and in 100 of the 143 coagulase-negative staphylococcus strains. For MLS_B-resistant staphylococci, a single MLS-inducible phenotype was demonstrated in 46 *S. aureus* strains and 43 coagulase-negative staphylococcus strains, and constitutive MLS_B resistance was found in 82 *S. aureus* strains and 56 coagulase-negative staphylococcus strains (Table 2). The inducible phenotype was predominant in methicillin-susceptible *S. aureus* (MSSA, 82%), and the constitutive phenotype was predominant in methicillin-resistant *S. aureus* (MRSA, 83%). Resistance to MLS antibiotics, including pristinamycin and quinupristin-dalfopristin, was detected in 10 *S. aureus* strains and 3 coagulase-negative staphylococcus strains; these 13 strains were also resistant to methicillin. Resistance to erythromycin but not to other MLS antibiotics was observed in 3 strains of *S. aureus* and 17 strains of coagulase-negative staphylococci. Other resistance phenotypes were found in 3 strains of *S. aureus* and 31 strains of coagulase-negative staphylococci and are detailed in Table 3.

Prevalence of *erm* genes. A total of 294 strains were tested for the presence of MLS resistance genes, and 259 (88%) contained one or more of the *erm* genes consistent with an erythromycin resistance phenotype, mainly in strains resistant to methicillin (78% of the strains). The most prevalent *erm* gene in *S. aureus* strains was *ermA*, which was detected alone in 63.2%, mainly in MRSA expressing an MLS_B constitutive phenotype, whereas *ermC* was found as a single MLS resistance gene in 25% of the *S. aureus* strains, essentially in MSSA with an MLS_B inducible phenotype (Table 2). For the coagulase-negative staphylococci, the most prevalent gene was *ermC*; it was detected alone in 44% of the strains with an MLS_B inducible or constitutive phenotype, one which was either susceptible or resistant to methicillin. *ermA* genes were detected in 18% of the coagulase-negative staphylococcus strains, essentially those resistant to methicillin. The *ermB* gene was seldom detected in staphylococci (one strain of *S. aureus* and one coagulase-negative *Staphylococcus* strain). Combination of various *erm* genes was detected in six strains of coagulase-negative staphylococci only (Tables 2 and 3).

Prevalence of other resistance genes. Other determinants encoding resistance to MLS antibiotics were more frequently detected in coagulase-negative staphylococci (51 strains, 34%) than in *S. aureus* (16 strains, 11.1%) (Table 3). The *msrA* gene was detected alone in 3 *S. aureus* strains and 17 strains of coagulase-negative staphylococci, conferring resistance to erythromycin but apparently not to streptogramin type B. This gene was detected in combination with a methylase gene in five other coagulase-negative staphylococcus strains and with the *linA*/*linA*′ genes in two isolates, in each case conferring a resistance phenotype which was the combination of the individual phenotypes (Table 3). The *linA*/*linA*′ genes were never detected alone in *S. aureus* but rather in combination with *ermC* in one strain, giving a resistance phenotype which was the addition of an MLS_B-inducible resistance due to the *erm* gene

TABLE 2. Distribution of *erm* genes among MLS_B-resistant staphylococcal isolates

Strain[a] (no.)	No. (%) of strains with:						
	ermA	*ermB*	*ermC*	*ermA* + *ermB*	*ermA* + *ermC*	*ermB* + *ermC*	Other genotype[b]
S. aureus (144)	91 (63.2)	1 (0.7)	36 (25.0)				16 (11.1)
MLS_B inducible	14 (9.8)	0	32 (22.2)				
MSSA	5 (3.5)	0	26 (18.2)				
MRSA	9 (6.3)	0	6 (4.2)				
MLS_B constitutive	77 (53.5)	1	4 (2.8)				
MSSA	3 (2.1)	1	3 (2.1)				
MRSA	74 (51.4)	0	1 (0.7)				
Total							
MSSA	8 (5.6)	1 (0.7)	29 (20.1)				
MRSA	83 (57.6)	0	7 (4.9)				
Coagulase-negative staphylococci (150)	27 (18.0)	1 (0.7)	66 (44.0)	1 (0.7)	3 (2.0)	1 (0.7)	51 (34.0)
MLS_B inducible	10 (6.6)	0	31 (20.7)	0	1 (0.7)	1 (0.7)	
MSCNS	1 (0.7)	0	14 (9.3)	0	1 (0.7)	1 (0.7)	
MRCNS	9 (6.0)	0	17 (11.3)	0	0	0	
MLS_B constitutive	17 (11.3)	1	35 (23.3)	1 (0.7)	2 (1.3)	0	
MSCNS	1 (0.7)	1	7 (4.7)	0	0	0	
MRCNS	16 (10.7)	0	28 (18.7)	1 (0.7)	2 (1.3)	0	
Total							
MSCNS	2 (1.3)	1 (0.7)	21 (14.0)	0	1 (0.7)	1 (0.7)	
MRCNS	25 (16.7)	0	45 (30.0)	1 (0.7)	2 (1.3)		

[a] MSCNS, methicillin-susceptible coagulase-negative staphylococci; MRCNS, methicillin-resistant coagulase-negative staphylococci.
[b] See Table 3 for more details.

plus a constitutive resistance to lincomycin due to *linA*/*linA′*. In two strains of *S. epidermidis*, *linA*/*linA′* was the single resistance gene present and was associated with a methylase gene in three strains.

Resistance to dalfopristin was associated with the presence of the *vga* gene alone in three coagulase-negative staphylococcus strains, one of which was also resistant to lincomycin (Table 3). The presence of *vga* alone was not associated with

TABLE 3. Distribution of *msrA*, *linA*/*linA′*, *vga*, *vgb*, *vat*, and *vatB* resistance genes among staphylococcal isolates[a]

Gene	*S. aureus* (n = 144)		Coagulase-negative staphylococci (n = 150)		
	No. (%)	Resistance phenotype	No. (%)	Resistance phenotype	Species (no.)
msrA	3 (2.1)	MSSA or MRSA, M	17 (11.3)	MSCNS, M	*S. epidermidis* (2)
				MRCNS, M	*S. epidermidis* (1)
				MRCNS, M	*S. haemolyticus* (10)
				MSCNS, M	*S. saprophyticus* (2)
				MSCNS, M	*S. hominis* (2)
msrA + *ermA*			3 (2.0)	MSCNS, MLS inducible	*S. hominis* (1)
				MRCNS, MLS inducible	*S. haemolyticus* (2)
msrA + *ermC*			2 (1.3)	MRCNS, MLS constitutive	*S. haemolyticus* (1)
				MSCNS, MLS inducible	*S. hominis* (1)
linA/*linA′*			2 (1.3)	MRCNS, L	*S. epidermidis* (2)
linA/*linA′* + *msrA*			2 (1.3)	MRCNS, M, L	*S. epidermidis* (1)
				MRCNS, M, L	*S. haemolyticus* (1)
linA/*linA′* + *ermA*			1 (0.7)	MSCNS, L	*S. hominis* (1)
linA/*linA′* + *ermC*	1 (0.7)	MSSA, MS inducible, L constitutive	1 (0.7)	MRCNS, MS inducible, L constitutive	*S. epidermidis* (1)
linA/*linA′* + *ermB* + *ermC*			1 (0.7)	MRCNS, MS inducible, L constitutive	*S. haemolyticus* (1)
vga			3 (2.0)	MRCNS, SgA	*S. epidermidis* (2)
				MRCNS, SgA, L	*S. haemolyticus* (1)
vga + *ermA*			8 (5.3)	MRCNS, MLS constitutive, SgA	*S. epidermidis* (6)
				MRCNS, MLS constitutive, SgA	*S. haemolyticus* (1)
				MSCNS, MLS inducible	*S. epidermidis* (1)
vga + *ermA* + *ermC*			1 (0.7)	MRCNS, MLS constitutive, SgA	*S. epidermidis* (1)
vga + *vgb* + *vat* + *ermA*			1 (0.7)	MRCNS, MLS constitutive, SgA, Pr, QD	*S. epidermidis* (1)
vatB + *ermA*	10 (7.6)	MRSA, MLS constitutive, SgA, Pr, QD			
	1 (0.7)	MRSA, MLS constitutive			
vatB + *ermC*			2 (1.3)	MRCNS, MLS constitutive, SgA, Pr, QD	*S. epidermidis* (2)
No resistance gene	1 (0.7)	MRSA, L, SgA	4 (2.7)	MSCNS, L, SgA	*S. sciuri* (3)
				MRCNS, L, SgA	*S. sciuri* (1)
			1 (0.7)	MSCNS, M	*S. saprophyticus* (1)
			1 (0.7)	MRCNS, SgA	*S. warneri* (1)
			1 (0.7)	MSCNS, MLS constitutive	*S. warneri* (1)

[a] Abbreviations: M, macrolides; MSCNS, methicillin-susceptible coagulase-negative staphylococci; MRCNS, methicillin-resistant coagulase-negative staphylococci; L, lincosamides; MS, macrolides-streptogramin B; SgA, streptogramin A; Pr, pristinamycin; and QD, quinupristin-dalfopristin.

resistance to pristinamycin and quinupristin-dalfopristin. The *vga* gene was detected in combination with a methylase gene in 10 strains of coagulase-negative staphylococci but had no phenotypic consequence in one (MIC of dalfopristin, 2 μg/ml). Resistance to pristinamycin and quinupristin-dalfopristin was detected in 10 strains of *S. aureus* and in 3 strains of coagulase-negative staphylococci and was associated with resistance genes such as *ermA* and *vatB* (in the 10 strains of *S. aureus*) or *ermA*, *vat*, *vga*, and *vgb* (in the three coagulase-negative staphylococcus strains). The presence of the *vatB* gene had no phenotypic consequence in one strain of *S. aureus* (MIC of dalfopristin, 0.5 μg/ml; MIC of quinupristin-dalfopristin, 0.25 μg/ml; MIC of pristinamycin, 1 μg/ml). No resistance genes were detected in a strain of *S. aureus*, in four strains of *S. sciuri* which were resistant to lincomycin and streptogramin A, and in two *S. warneri* strains (Table 3). No MLS resistance genes were detected in 20 strains which were susceptible to MLS antibiotics.

DISCUSSION

We have studied the distribution of MLS resistance determinants by PCR in clinical staphylococcal isolates resistant at least to one of the MLS antibiotics with primers specific for 10 resistance genes. PCR was not performed for *vgaB*, *vgbB*, and *vatC* since the sequence of these genes was not available at the time of the study (2, 3). It cannot be ruled out that some of these genes may be present in resistant strains of the present study, notably those with no detectable resistance genes (Table 3). *msrB* from *S. xylosus* (25) was not detected in any of the staphylococcus strains studied. Resistance to MLS was predominantly due to the presence of two evolutionary variants of the *erm* determinant, but with different distributions depending on the type of staphylococci (coagulase positive or negative) and the antibiotic resistance pattern (methicillin resistant or susceptible). When a single resistance determinant was present in *S. aureus*, the *ermA* gene was more common in MRSA (57.6%), mainly in strains with a constitutive expression, than in MSSA (5.6%), whereas *ermC* was predominant in MSSA (20.1%), mainly in strains with an inducible expression, and less so in MRSA (4.9%).

Analysis of strains from Denmark isolated from 1959 to 1988 indicated that the *ermA* and *ermC* genes were responsible for erythromycin resistance in 98% of 428 *S. aureus* isolates (32). *ermA* was part of transposon Tn*554* (30) in the chromosome, whereas *ermC* was found on plasmids (29). In coagulase-negative staphylococci, *ermC* was more common in methicillin-resistant coagulase-negative staphylococci (30%), but the *ermA* gene was detected in a rather high percentage of methicillin-resistant coagulase-negative staphylococci (16.7%); the most common gene in methicillin-susceptible coagulase-negative staphylococci was *ermC* (14.0%). These results confirmed those of Eady et al. (14), who documented the predominance of *ermC* in a large series of clinical and commensal coagulase-negative staphylococci. As previously described (14), *ermB* was present in a minority of strains but was formerly found in only animal strains (14, 29). Association of different *erm* genes was not detected in *S. aureus* and very rarely in coagulase-negative staphylococci (five strains). The *erm* genes were also detected in combination with other resistance genes such as *msrA*, *linA*/*linA′*, *vga*, *vgb*, *vat*, and *vatB* but only in a limited number of strains (12 *S. aureus* strains and 20 coagulase-negative staphylococcus strains).

Macrolide resistance due to *msrA* was more prevalent in coagulase-negative staphylococci (total of 14.6%) than in *S. aureus* (2.1%). Eady et al. (14) considered that their reported proportion of one-third of 221 coagulase-negative staphylococcus strains harboring *msrA* was biased since they selected for their study a greater proportion of strains with a macrolide-resistant phenotype. It also appeared in this study (14) that *msrA* was most commonly encountered in *S. hominis* and *S. cohnii*, whereas in our study it was detected more frequently in *S. haemolyticus* (Table 3). This difference could simply reflect the different distribution of the coagulase-negative staphylococcal species in the two studies. Coagulase-negative staphylococci harboring both *erm* and *msrA* accounted for 3.3% of our strains, and a similar proportion (3.6%) was reported by Eady et al. (14). We detected no *S. aureus* with such combinations of resistance mechanisms. Three *S. aureus* strains harboring determinants encoding different mechanisms, an esterase activity hydrolyzing macrolides, and a macrolide efflux system were reported (24, 33).

The incidence of staphylococci with lincomycin resistance but without resistance to macrolides and streptogramins is usually low. Leclercq et al. (20) reported an incidence of 0.2% in *S. aureus* (2,100 strains screened), 4.6% in *S. epidermidis* (240 strains screened), and 8% in *S. cohnii* (50 strains screened). In our study, we detected a single strain of *S. aureus* and seven strains of coagulase-negative staphylococci with *linA*/*linA′*, most frequently in association with an *erm* gene (Table 3). Such a combination has not been reported before.

Resistance to pristinamycin and quinupristin-dalfopristin was phenotypically detected in 10 *S. aureus* strains (seven isolates from the same hospital and possibly of the same clone) and 3 coagulase-negative staphylococcus isolates. The prevalence of pristinamycin-resistant staphylococci can be higher in hospitals where pristinamycin is used extensively, as reported previously for an Algerian hospital (22). The prevalence of pristinamycin resistance remains usually low in most French hospitals (<5%) (16, 23), as is probably the case for quinupristin-dalfopristin resistance since we found a complete concordance between pristinamycin and quinupristin-dalfopristin resistance. Resistance to pristinamycin and quinupristin-dalfopristin in staphylococci is usually associated with an accumulation of various genes such as *vga*, *vat*, and *vgb* on different plasmids in association with methylase genes (22). The *vat* gene initially cloned from plasmid pIP680 was shown to be contiguous to a *vgb* gene (5); both genes were also simultaneously detected on different plasmids harbored by independent *S. aureus* and *S. simulans* isolates (15), which in several cases also harbored the *vga* determinant (1). Such a combination of *vga-vgb-vat* genes previously described in *S. aureus* and in coagulase-negative staphylococci (1, 22) was found in our series in an *S. epidermidis* strain and was associated with an *erm* gene (Table 3). Allignet et al. (1) reported also the association of pristinamycin resistance with the presence of the *vatB* gene mostly in *S. aureus*; in our series, it was found in 10 *S. aureus* strains resistant to pristinamycin and quinupristin-dalfopristin and was always associated with the *ermA* gene.

Given the distribution and prevalence of the various MLS resistance genes in this collection of clinical isolates of staphylococci, it appears that resistance stricto sensu to pristinamycin and quinupristin-dalfopristin remains low due to the low incidence of resistance to streptogramin type A (*vat* or *vatB* genes), a necessary but not necessarily sufficient condition for resistance to quinupristin-dalfopristin or pristinamycin. In every other combination of resistance genes, pristinamycin and quinupristin-dalfopristin are either not affected (i.e., presence of *erm*-inducible and/or *linA*/*linA′*) or only partially affected in one component (i.e., presence of *erm*-constitutive, *msrA*, or *vga*). In cases where the activity of the B compounds is re-

duced, the bactericidal efficacy of pristinamycin and quinupristin-dalfopristin remains to be evaluated as well as its clinical efficacy. However, at present, these promising molecules (pristinamycin for oral use and quinupristin-dalfopristin for intravenous use) are potentially fully active in a large proportion of cases.

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