

## Antimicrobial Susceptibility Patterns of Enterococci Causing Infections in Europe

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**In vitro susceptibilities of 4,208 enterococci (83% *Enterococcus faecalis* isolates, 13.6% *Enterococcus faecium* isolates, and 3.4% isolates of other species) from patients in 27 European countries towards 16 antibiotics were determined. High-level resistance to gentamicin varied by country (range, 1 to 49%; mean, 22.6% ± 12.3%) and per species (19.7% *E. faecalis* isolates, 13.6% *E. faecium* isolates, 3.4% by other species). Vancomycin resistance was detected in 0.06% *E. faecalis*, 3.8% *E. faecium*, and 19.1% isolates of other species. All enterococci were susceptible to LY 333328 and everninomicin, and 25% of *E. faecalis* isolates and 85% of other enterococci were susceptible to quinupristin-dalfopristin. The MIC of moxifloxacin and trovafloxacin for ciprofloxacin-susceptible *E. faecalis* at which 90% of the isolates were inhibited was 0.25 to 0.5 µg/ml.**

Development of new glycopeptides, streptogramins, everninomicin, and fluoroquinolones with enhanced activity against gram-positive bacteria is of special interest because of their potential use in the treatment of infections caused by resistant enterococci (13, 15, 17). We determined the in vitro susceptibilities of 4,208 strains to 16 antibiotics.

**Isolates.** The strains were isolated from clinical material in 49 European hospitals in 27 countries, collected from 1 January until 1 April 1997 on behalf of a study on the prevalence of vancomycin-resistant enterococci (VRE) in Europe (14). The number of isolates per hospital was limited to 100 consecutive, unique isolates; an average of 155.9 isolates per country were included. Most hospitals were teaching hospitals. The isolates came from blood and cerebrospinal fluid ( $n = 191$ ) respiratory tract (212), abdomen (554), wounds (604), urine (2,270), and other clinical materials (377). Strains were identified by biochemical tests using Facklam and Collins' recommendations (7) and by testing for methyl- $\alpha$ -D-glucopyranoside (4). The identification of VRE was confirmed by the

API 20 STREP system (BioMerieux, Marcy l'Etoile, France). PCR analyses (5) showed that 18 isolates contained the *vanA* gene, 5 contained the *vanB* gene, and 28 contained the *vanC* gene.

**Susceptibility testing.** MICs were determined by broth microdilution (2) with Mueller-Hinton broth. The antimicrobial agents tested were gentamicin, vancomycin, teicoplanin, LY 333328, everninomicin, quinupristin-dalfopristin, erythromycin, ciprofloxacin, sparflaxacin, trovafloxacin, moxifloxacin, chloramphenicol, amoxicillin, cefpirome, imipenem, and meropenem. Drugs were reconstituted according to the manufacturers' directions. The final inoculum size was  $3 \times 10^5$  to  $5 \times 10^5$  CFU/ml. Plates were incubated at 35°C for 20 h. High-level resistance (HLR) to gentamicin was defined as an MIC of  $\geq 512$  µg/ml, vancomycin resistance (VRE) was defined as an MIC of  $\geq 8$  µg/ml. VRE were also tested with the E-test (AB Biodisk, Solna, Sweden) according to the directions of the manufacturer. Interpretive criteria were published by the National Committee for Clinical Laboratory Standards

TABLE 1. HLR to gentamicin and vancomycin among 4,208 clinical isolates of enterococci by species

Antibiotic	No (%) of resistant strains						
	<i>E. faecalis</i> ( $n = 3,493$ )	<i>E. faecium</i> ( $n = 574$ )	<i>E. durans</i> ( $n = 30$ )	<i>E. gallinarum</i> ( $n = 50$ )	<i>E. casseliflavus</i> ( $n = 21$ )	<i>E. avium</i> ( $n = 19$ )	Other species <sup>a</sup> ( $n = 21$ )
Gentamicin	688 (19.7)	129 (22.5)	2 (6.7)	9 (18)	4 (18.2)	2 (10.5)	4 (21.1)
Vancomycin	1 (0.03)	17 (2.9)		24 (48)	1 (4.8)		
Both gentamicin and vancomycin	1 (0.03)	5 (0.9)		2 (4)			

<sup>a</sup> *E. faecalis* biochemical variant ( $n = 10$ ), *E. hirae* ( $n = 5$ ), *E. pseudovium* ( $n = 3$ ), *E. mundtii* ( $n = 2$ ), and *E. raffinosum* ( $n = 1$ ) isolates are included in this category.

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TABLE 2. MIC<sub>50</sub>s, MIC<sub>90</sub>s, MIC ranges, and percentages of susceptibility for beta-lactams, carbapenems, quinolones, and chloramphenicol for 4,208 enterococci of which 846 were HLR

Bacterial species (n) and drug	MIC (μg/ml)			% Susceptible <sup>a</sup>
	Range	50%	90%	
<i>E. faecalis</i> (2,804)				
Amoxicillin	0.03–≥32	0.5	0.5	99 (≤8)
Cefpirome	0.03–≥256	8	16	70 (≤8)
Imipenem	0.03–256	1	2	99
Meropenem	0.03–256	4	8	97 (≤8)
Chloramphenicol	0.25–64	4	32	75
Ciprofloxacin	0.12–64	0.5	1	94
Sparfloxacin	0.03–64	0.25	0.5	94 (≤2)
Trovaflaxacin	0.03–16	0.12	0.25	94 (≤2)
Moxifloxacin	0.03–16	0.12	0.25	94 (≤2)
<i>E. faecalis</i> with HLR to gentamicin (689)				
Amoxicillin	0.03–≥32	0.5	1	99
Cefpirome	0.12–≥256	32	≥256	17
Imipenem	0.03–128	2	4	99
Meropenem	0.03–256	8	16	63
Chloramphenicol	1–64	8	32	43
Ciprofloxacin	0.12–64	16	64	21
Sparfloxacin	0.03–64	16	32	23
Trovaflaxacin	0.03–16	4	8	31
Moxifloxacin	0.03–32	4	8	28
<i>E. faecium</i> (440)				
Amoxicillin	0.03–64	4	32	60
Cefpirome	0.12–≥256	≥256	≥256	16
Imipenem	0.03–≥256	16	128	41
Meropenem	0.12–≥256	64	≥256	24
Chloramphenicol	0.5–64	4	8	74
Ciprofloxacin	0.12–64	2	64	67
Sparfloxacin	0.03–64	0.5	16	78
Trovaflaxacin	0.03–16	1	8	83
Moxifloxacin	0.03–64	1	8	84
<i>E. faecium</i> with HLR to gentamicin (134)				
Amoxicillin	0.03–256	32	64	15
Cefpirome	0.03–≥256	≥256	≥256	1
Imipenem	0.03–≥256	128	≥256	6
Meropenem	0.03–≥256	≥256	≥256	3
Chloramphenicol	0.12–32	4	16	56
Ciprofloxacin	0.25–≥64	4	≥64	48
Sparfloxacin	0.12–≥64	1	32	55
Trovaflaxacin	0.12–16	2	8	57
Moxifloxacin	0.25–32	2	8	58
Other species (118)				
Amoxicillin	0.03–64	0.25	2	92
Cefpirome	0.03–≥256	32	≥256	37
Imipenem	0.03–256	1	16	89
Meropenem	0.03–256	4	32	73
Chloramphenicol	1–64	4	8	88
Ciprofloxacin	0.03–≥64	0.5	4	89
Sparfloxacin	0.03–32	0.5	2	92
Trovaflaxacin	0.03–8	0.12	2	94
Moxifloxacin	0.03–16	0.12	2	91
Other species with HLR to gentamicin (23)				
Amoxicillin	0.25–64	32	64	35
Cefpirome	2–≥256	≥256	≥256	7
Imipenem	0.5–≥256	128	≥256	26
Meropenem	2–≥256	≥256	≥256	17
Chloramphenicol	2–32	16	32	26
Ciprofloxacin	0.5–32	1	16	83
Sparfloxacin	0.12–32	0.5	8	87
Trovaflaxacin	0.03–8	0.5	4	87
Moxifloxacin	0.12–8	1	4	87

<sup>a</sup> Criteria are those published by the NCCLS. The MIC breakpoints chosen if no criteria were given by the NCCLS were those of the class representatives (ampicillin for amoxicillin and cefpirome, imipenem for meropenem, and ciprofloxacin for sparfloxacin, trovaflaxacin, and moxifloxacin) and are given in parentheses.

TABLE 3. MIC<sub>50</sub>s, MIC<sub>90</sub>s, MIC ranges, and percentages of susceptibility for glycopeptides, everninomicin, quinupristin-dalfopristin, and erythromycin for 4,156 vancomycin-susceptible and 52 vancomycin-resistant enterococci (VRE)

Bacterial species (n) and drug	MIC (μg/ml)			% Susceptible <sup>a</sup>
	Range	50%	90%	
<i>E. faecalis</i> (3,491)				
Vancomycin	0.12–4	1	2	100
Teicoplanin	0.03–1	0.12	0.12	100 (≤4)
LY 333328	0.03–16	1	2	99 (≤4)
Everninomicin	0.015–2	0.25	1	100 (≤4)
Quinupristin-dalfopristin	0.03–64	4	8	25 (≤2)
Erythromycin	0.03–≥256	2	≥256	53
<i>E. faecalis</i> VRE (2)				
Vancomycin	256			
Teicoplanin	16–128			
LY 333328	2			
Everninomicin	0.5–1			
Quinupristin-dalfopristin	4–8			
Erythromycin	≥256			
<i>E. faecium</i> (552)				
Vancomycin	0.03–4	0.5	2	100
Teicoplanin	0.03–1	0.25	0.25	100
LY 333328	0.03–2	0.5	1	100
Everninomicin	0.015–2	0.5	1	100
Quinupristin-dalfopristin	0.25–32	0.5	2	92
Erythromycin	0.03–≥256	8	≥256	25
<i>E. faecium</i> VRE (22)				
Vancomycin	8–≥256	≥256	≥256	0
Teicoplanin	0.12–256	32	128	27
LY 333328	0.12–2	1	2	100
Everninomicin	0.12–1	0.5	1	100
Quinupristin-dalfopristin	0.25–8	0.5	2	91
Erythromycin	1–≥256	≥256	≥256	5
Other species (114)				
Vancomycin	0.25–4	0.5	4	100
Teicoplanin	0.03–0.5	0.12	0.5	100
LY 333328	0.03–2	0.25	1	100
Everninomicin	0.06–2	0.5	1	100
Quinupristin-dalfopristin	0.06–8	1	4	87
Erythromycin	0.03–≥256	2	≥256	51
Other species VRE (27)				
Vancomycin	8	8	8	0
Teicoplanin	0.25–0.5	0.25	0.5	100
LY 333328	0.25–1	0.5	1	100
Everninomicin	0.12–2	0.5	1	100
Quinupristin-dalfopristin	1–4	2	2	96
Erythromycin	0.03–≥256	1	≥256	81

<sup>a</sup> Criteria are those published by the NCCLS. The MIC breakpoints chosen in case no criteria were given by the NCCLS were those of the class representatives (vancomycin for teicoplanin and LY333328; erythromycin for quinupristin-dalfopristin) or optional (everninomicin) and are given in parentheses.

(NCCLS) (11) except where noted in the tables. *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 2921 were used as reference strains. Statistical analysis was performed by the chi-square test.

**Distribution.** Strain distribution was 3,493 (83%) *Enterococcus faecalis*, 574 (13.6%) *E. faecium*, and 141 (3.4%) other *Enterococcus* species, including *Enterococcus gallinarum* (50 strains), *Enterococcus durans* (30 strains), *Enterococcus casseliflavus* (21 strains), *Enterococcus avium* (19 strains), *E. faecalis* biochemical variant (10 strains), *Enterococcus hirae* (5 strains), *Enterococcus pseudavium* (3 strains), *Enterococcus mundtii* (2 strains), and *Enterococcus raffinosum* (1 strain). This distribution resembled that in other parts of the world (6, 9, 16). VRE were found in 0.06% of *E. faecalis* (*vanA*)

strains, 3.8% of *E. faecium* (*vanA* and *vanB*) strains, and 52% of *E. gallinarum* (*vanC*) strains. Susceptibility data are listed in the tables and are discussed by antimicrobial agent or group.

**HLR to gentamicin.** HLR to gentamicin was demonstrated in all countries, with a prevalence ranging from 1 to 48% (mean, 22.6% ± 12.3%). This overall prevalence is lower than that in other parts of the world (6, 9, 16). Countries with high percentages of resistance were scattered over Europe; there were no geographic relationships. There was no indication of clonal spread of a single resistant organism. HLR to gentamicin was combined with vancomycin resistance in one *E. faecalis*, five *E. faecium*, and two *E. gallinarum* isolates (Table 1). HLR to gentamicin was often com-

bined with fluoroquinolone resistance in *E. faecalis* and *E. faecium* (Table 2).

**Amoxicillin.** Amoxicillin resistance was strongly correlated with HLR to gentamicin in *E. faecium*: 85% of *E. faecium* isolates with HLR to gentamicin were amoxicillin resistant in comparison to 40% of *E. faecium* strains with no HLR to gentamicin ( $P < 0.0001$ ); accordingly, 91% of *E. gallinarum* isolates with HLR to gentamicin were amoxicillin resistant in comparison to 33% of *E. gallinarum* isolates with no HLR to gentamicin ( $P < 0.005$ ).

**Carbapenems.** The MICs of imipenem ranged from 0.03 to 256  $\mu\text{g/ml}$ . The MICs of imipenem were consistently twice or four times lower than those of meropenem (Table 2). *E. faecium* strains were more often resistant than *E. faecalis* strains ( $P < 0.0005$ ). HLR was linked with resistance against meropenem for *E. faecalis* ( $P < 0.0005$ ) and against imipenem and meropenem for *E. faecium* and the other species ( $P < 0.0005$ ).

**Cefpirome.** Only *E. faecalis* isolates with no HLR to gentamicin were susceptible to cefpirome, with the MICs for a majority of the isolates equal to 8  $\mu\text{g/ml}$ . Resistance of *E. faecium* was almost complete.

**Chloramphenicol.** The MICs for the majority of *E. faecalis*, *E. faecium*, *E. durans*, *E. avium*, *E. casseliflavus*, and *E. gallinarum* isolates were at the breakpoint of 8  $\mu\text{g/ml}$ ; strains with HLR to gentamicin were more likely to be resistant to chloramphenicol. Chloramphenicol resistance was not linked to vancomycin resistance. This may suggest a possible role of chloramphenicol in VRE infections (10).

**Fluoroquinolones.** The MICs of sparfloxacin, trovafloxacin, and moxifloxacin for the majority of *E. faecalis* strains were 0.12 to 0.25  $\mu\text{g/ml}$ , which is two to four times lower than those of ciprofloxacin. Over 90% of *E. faecalis* isolates were susceptible at the breakpoint. The activities of sparfloxacin, trovafloxacin, and moxifloxacin towards *E. faecium* were much lower, with susceptibilities of 78, 83, and 84%, respectively. The susceptibility of the other species resembled that of *E. faecalis*. The MICs of sparfloxacin, trovafloxacin, and moxifloxacin for ciprofloxacin-resistant strains were higher than those for ciprofloxacin-susceptible isolates, thus reflecting fluoroquinolone cross-resistance (13, 16). Decreased fluoroquinolone susceptibility was not linked to vancomycin resistance. Fluoroquinolone resistance was linked with HLR to gentamicin: 79% of *E. faecalis* isolates with HLR to gentamicin were resistant to ciprofloxacin in comparison with 6% of strains with no HLR to gentamicin ( $P < 0.0005$ ); accordingly, 52% of *E. faecium* isolates with HLR to gentamicin were resistant to ciprofloxacin in comparison to 33% of *E. faecium* strains with no HLR to gentamicin ( $P < 0.005$ ). The high linkage between fluoroquinolone resistance and gentamicin resistance is unexplained; there were no geographic trends because these strains were found in every country. It is also unlikely that clonal spread of a single organism resulted in wide-spread resistance in 27 countries.

**Glycopeptides.** Resistance to vancomycin was high (MIC,  $\geq 256 \mu\text{g/ml}$ ) in 18 strains with the *vanA* gene (two *E. faecalis* and 16 *E. faecium* strains) and one with *vanB* (*E. faecium*); resistance was moderate (MIC, 8 to 32  $\mu\text{g/ml}$ ) in four *E. faecium* strains (containing *vanB*) and 27 strains with *vanC* (26 *E. gallinarum* and 1 *E. casseliflavus* strain). The *vanA*-containing strains were resistant to teicoplanin (MIC, 16 to 25  $\mu\text{g/ml}$ ). Vancomycin resistance was seldom linked with gentamicin resistance, in contrast with findings in other parts of the world (1, 6, 18). Except towards the *vanA*-containing strains, teicoplanin was the most active glycopeptide, being eight times or more as active as vancomycin and LY 333328. There was no cross-resistance between vancomycin and LY 333328 (Table 3).

**Everninomicin.** The activity of everninomicin was comparable to that of LY 333328, with the MICs ranging from 0.03 to 2  $\mu\text{g/ml}$ .

**Quinupristin-dalfopristin.** The MICs of quinupristin-dalfopristin ranged from 0.03 to 64  $\mu\text{g/ml}$ . Overall, *E. faecalis* strains were less susceptible than strains of *E. faecium* and other species (12, 13), yet development of increased resistance by *E. faecium* during therapy is a matter of concern (3).

LY 333328, everninomicin, and quinupristin-dalfopristin were the only compounds tested which inhibited enterococci independently of their susceptibilities to gentamicin and vancomycin. The MICs at which 90% of the isolates were inhibited that we found for LY 333328, everninomicin, and quinupristin-dalfopristin were in the range reported by others (8, 15, 16, 17). These drugs compared favorably with teicoplanin in activity against *vanA* strains.

Multiresistance is not uncommon, but our percentages were much higher than those given by others (16). Multiresistance and cross-resistance result in limitations in clinical use, especially by loss of synergistic combinations which are often needed for enterococcal infections. New agents like LY 333328, everninomicin, and quinupristin-dalfopristin, which do not (or do not yet) display cross-resistance are therefore of great value.

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