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NOTES

Activity of Linezolid against 3,251 Strains of Uncommonly Isolated Gram-Positive Organisms: Report from the SENTRY Antimicrobial Surveillance Program[▽]

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Linezolid was tested against 32 species of uncommonly isolated gram-positive organisms (3,251 strains) by reference MIC methods and found to be highly active (MIC_{50} range, 0.25 to 2 μg/ml; MIC_{90} range, 0.25 to 2 μg/ml). Only one isolate (viridans group streptococcus; 0.03% of tested strains) was resistant to linezolid.

Linezolid, the only oxazolidinone used in clinical practice, has demonstrated potent activity against gram-positive pathogens, including resistant variants such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococcal species, vancomycin-resistant enterococci, and β-hemolytic streptococci (8, 14, 15). The oxazolidinone action against these organisms has been described as bacteriostatic, and premarketing surveillance trials have shown that nearly all the indicated pathogens (>99.9%) are susceptible (2–5, 12, 15). Subsequent postmarketing resistance-monitoring studies (ZAAPS, LEADER, SENTRY Antimicrobial Surveillance Program) have discovered linezolid-resistant isolates among staphylococci, enterococci, and some viridans group streptococci species (1, 9, 13, 16). However, the rates of occurrence have remained far less than 1% but are occasionally more frequent among some species (coagulase-negative staphylococci, *Enterococcus faecium*), with long-term therapy (≥6 weeks), or in cases in which infection control practices are suspected to have been compromised (18, 20).

Regulatory agencies and the Clinical and Laboratory Standards Institute (CLSI) have established indications for linezolid use and breakpoint interpretive criteria of ≤2 μg/ml as susceptible for streptococci or enterococci and ≤4 μg/ml for staphylococci (7). Resistance has been defined at ≥8 μg/ml for enterococci (7). These criteria are very helpful for clinical laboratories in guiding therapy for serious gram-positive infections; however, linezolid may be a treatment option for numerous nonindicated gram-positive pathogens, due to potential intolerance of other agents or frank resistance. To address this therapeutic possibility, we expanded the knowledge and spectrum of linezolid activity by studying the compound against 32 gram-positive species that were uncommonly isolated from contemporary patients with clinical infections.

The organisms were obtained from the SENTRY Antimicrobial Surveillance Program (1999-2006) from isolates cultured in North America, Latin America, and Europe (10). All strains were processed according to a central reference laboratory study design, using CLSI M7-A7 broth microdilution methods and interpretive criteria (6, 7, 11). Cation-adjusted Mueller-Hinton broth was supplemented with 2 to 5% lysed horse blood when fastidious species were tested (6, 7). To interpret the susceptibility of the rarer species, established breakpoints for organisms of the same genus (e.g., streptococci or enterococci) were applied for comparison purposes only. All organisms for which the MIC of linezolid was ≥8 μg/ml were tested by PCR techniques for rRNA target mutations commonly associated with oxazolidinone resistance (14, 16). Also, tests with staphylococci and enterococci for which the MIC of linezolid was 4 μg/ml were repeated to establish the reproducible MICs that occurred near the published breakpoints (7). Concurrent quality control (QC) testing was performed with CLSI-recommended strains (6, 7). All QC results were within established MIC ranges (7).

A total of 3,251 organisms were analyzed, including *Aerococcus* spp. (22), *Bacillus* spp. (202; two species groups); *Corynebacterium* spp. (342; five species); enterococci (378; six species); *Listeria monocytogenes* (137); *Micrococcus luteus* (29); *Rothia mucilaginosa* (18); β-hemolytic streptococci, not group A or B (865; three serogroups); and viridans group streptococci (1,258; 12 species) (Tables 1 and 2). All identifications were initially made at the participant sites and were confirmed at the central laboratory by conventional reference methods and commercial systems (Vitek and Vitek 2; bioMerieux, Hazelwood, MO).

Table 1 shows the distribution of the MIC of linezolid for the tested strains and the MIC_{50} and MIC_{90} values for 1,128 isolates of gram-positive cocci. Among these species, the *Corynebacterium* spp. (unspeciated, *C. amycolatum*, *C. jeikeium*, *C. pseudodiphtheriticum*, and *C. striatum*) were most susceptible

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TABLE 1. Potency and spectrum of activity of linezolid against 1,128 strains of uncommonly isolated gram-positive organisms

Organism (no. tested)	Cumulative % inhibited at indicated MIC (μg/ml):							MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.06	0.12	0.25	0.5	1	2	4		
Aerococcus spp. (22)	0.0	0.0	4.5	31.8	63.6	100.0		1	2
Bacillus spp. (142)	0.7	0.7	4.9	31.7	97.2	100.0		1	1
B. cereus (60)	1.7	1.7	3.3	30.0	98.3	100.0		1	1
Corynebacterium spp. (236)	2.1	13.6	68.2	92.4	99.6	100.0		0.25	0.5
Corynebacterium amycolatum (11)	0.0	27.3	100.0					0.25	0.25
Corynebacterium jeikeium (59)	1.7	5.1	67.8	98.3	100.0			0.25	0.5
Corynebacterium pseudodiphtheriticum (11)	0.0	0.0	36.4	90.9	100.0			0.5	0.5
Corynebacterium striatum (25)	0.0	12.0	88.0	100.0				0.25	0.5
Enterococcus avium (116)	0.0	0.0	0.0	4.3	52.6	99.1	100.0	1	2
Enterococcus casseliflavus (65)	0.0	0.0	0.0	0.0	23.1	96.9	100.0	2	2
Enterococcus durans (49)	0.0	0.0	2.0	8.2	32.7	100.0		2	2
Enterococcus gallinarum (119)	0.0	0.0	0.0	1.7	30.3	99.2	100.0	2	2
Enterococcus hirae (16)	0.0	0.0	0.0	0.0	37.5	100.0		2	2
Enterococcus raffinosus (13)	0.0	0.0	0.0	0.0	46.2	100.0		2	2
Listeria monocytogenes (137)	0.0	0.0	0.0	0.7	29.2	100.0		2	2
Micrococcus luteus (29)	0.0	0.0	3.4	75.9	100.0	-		0.5	1
Rothia mucilaginosa (18)	0.0	5.6	16.7	83.3	94.4	100.0		0.5	1

to linezolid, requiring a MIC_{50} of only 0.25 to 0.5 μg/ml. *M. luteus* and *R. mucilaginosa* strains were also very susceptible to linezolid (MIC_{50}, 0.5 μg/ml), as were *Aerococcus* spp. and the two groupings of *Bacillus* spp. (MIC_{50}, 1 μg/ml). Enterococci (not *E. faecalis* or *E. faecium*) were clearly less susceptible to linezolid (MIC_{50} and MIC_{90}, 2 μg/ml), but all MIC values for enterococci were ≤4 μg/ml, i.e., not resistant by CLSI criteria (7). No linezolid-resistant isolates were detected among the species summarized in Table 1.

The reference MIC values of linezolid for all streptococcal species of uncommon occurrence in documented clinical infections have been listed in Table 2. A very uniform pattern of linezolid susceptibility was noted, with MIC_{50} values ranging from 0.5 to 1 μg/ml and MIC_{90} values from 1 to 2 μg/ml. All species or serogroups demonstrated complete (100%) susceptibility (MIC, ≤2 μg/ml) except for a single strain of *Streptococcus oralis* previously reported from this program (10, 16). This organism had a G2576T rRNA mutation documented by PCR sequencing analysis (14, 19).

These in vitro results for linezolid document its wide potential clinical application to uncommonly isolated gram-positive species, and the infrequency of linezolid-resistant strains among the indicated species (1–5, 9, 12, 13, 15, 16) illustrates the continued clinical utility of the oxazolidinone class. However, when therapy with linezolid is considered, susceptibility tests should be performed by validated in vitro methods applying published interpretive criteria, if available (6, 7, 11). The results of such tests should be similar to those listed here for those rare species, and when MICs of linezolid of ≥8 μg/ml occur, the results should be confirmed by a reference labora-

TABLE 2. Potency and spectrum of activity of linezolid against uncommonly isolated species/serogroups of β-hemolytic (865 strains) and viridans group streptococci (1,258 strains)

Organism (no. tested)	Cumulative % inhibited at MIC (μg/ml):							MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	≤0.06	0.12	0.25	0.5	1	2	4		
β-Hemolytic streptococci									
Group C (199)	1.5	3.0	3.5	16.6	95.5	100.0		1	1
Group F (53)	0.0	1.9	3.8	39.6	96.2	100.0		1	1
Group G (613)	0.5	0.5	0.8	8.2	96.1	100.0		1	1
Viridans group streptococci									
S. anginosus (104)	2.9	2.9	7.7	33.7	96.2	100.0		1	1
S. bovis (223)[a]	0.0	0.0	2.7	23.8	87.2	100.0		1	2
S. constellatus (89)	1.1	3.4	12.4	42.7	98.9	100.0		1	1
S. gordonii (12)	0.0	0.0	0.0	33.3	100.0			1	1
S. intermedius (66)	0.0	0.0	0.0	24.2	87.9	100.0		1	2
S. mitis (341)	0.3	1.2	4.4	33.4	99.1	100.0		1	1
S. mutans (19)	0.0	0.0	0.0	36.8	89.5	100.0		1	2
S. oralis (139)	0.7	0.7	3.6	34.5	96.4	99.3	99.3[b]	1	1
S. parasanguis (21)	0.0	0.0	0.0	57.1	100.0			0.5	1
S. salivarius (91)	0.0	1.1	3.3	46.2	98.9	100.0		1	1
S. sanguinis (142)	0.0	0.7	4.2	36.6	97.9	100.0		1	1
S. vestibularis (11)	0.0	0.0	0.0	36.4	100.0			1	1

[a] Also known as *S. gallolyticus*.
[b] One strain with a G2576T mutation was documented as resistant.

tory using standardized methods (6, 7). Sahm et al. (21) recently noted discord between MIC values derived from the E-test (AB BIODISK, Solna, Sweden) and the reference broth microdilution method. Generally, the E-test MIC values of linezolid presented in this study were reliable for *S. aureus* testing but were consistently higher for enterococcal tests (21). Appropriate interpretations of endpoints for MIC values of linezolid require exclusion of trailing effects with the reference MICs and the application of an 80% inhibition endpoint to the hazy borders often seen with agar diffusion methods (disk diffusion and E-test) (6, 7, 17). These technical details must be considered along with acceptable concurrent QC results (7) to avoid the reporting of false linezolid resistance.

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