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Summary of Linezolid Activity and Resistance Mechanisms Detected during the 2012 LEADER Surveillance Program for the United States

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This study summarizes the linezolid susceptibility testing results for 7,429 Gram-positive pathogens from 60 U.S. sites collected during the 2012 sampling year for the LEADER Program. Linezolid showed potent activity when tested against 2,980 *Staphylococcus aureus* isolates, inhibiting all but 3 at ≤2 μg/ml. Similarly, linezolid showed coverage against 99.5% of enterococci, as well as for all streptococci tested. These results confirm a long record of linezolid activity against U.S. Gram-positive isolates since regulatory approval in 2000.

During more than a decade of clinical use, linezolid has demonstrated clinical effectiveness for treating infections caused by a variety of Gram-positive pathogens (1–4). The clinical data have been supported by the LEADER Surveillance Program established in 2004, which has monitored the activity, spectrum and susceptibility/resistance rates of this oxazolidinone in the United States for eight consecutive years (5, 6). Table 1 summarizes the linezolid nonsusceptibility rates documented during the 8-year LEADER Program, which illustrates the low rates observed for the monitored species and groups of Gram-positive organisms. In this study, we report the results obtained during the ninth consecutive (2012) year of the LEADER Program by applying centralized testing by reference microdilution methods.

A total of 7,429 Gram-positive pathogens cultured in 60 U.S. medical centers (in 37 states) located in all nine U.S. Census Bureau Regions, including 7 medical centers specializing in children's health care, were submitted to JMI Laboratories (North Liberty, IA). Isolates were primarily identified by the participating laboratory, and the identifications were confirmed by the reference monitoring laboratory (JMI Laboratories) by using standard algorithms and Vitek 2 (bioMérieux, Hazelwood, MO), supported by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS; Bruker Daltonics, Bremen, Germany).

Isolates were tested for susceptibility by broth microdilution following the methods in Clinical and Laboratory Standards Institute (CLSI) document M07-A9 (7). Testing was performed using panels manufactured by Thermo Fisher Scientific (Cleveland, OH). Isolates with initial linezolid MIC results at ≥4 μg/ml were submitted to additional testing using customized frozen-form panels, molecular characterization of resistance mechanisms, and epidemiology typing, as previously described (8–10). Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. Validation of the MIC values was performed by concurrent testing of CLSI-recommended quality control reference strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619) (11). MIC interpretations were based on the CLSI document M100-S23 (2013) breakpoint criteria, as available (11). Isolates resistant to erythromycin but susceptible to

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TABLE 1 Summary of the linezolid nonsusceptibility rates documented during the 9-year LEADER surveillance program

Organism (no. of isolates tested)	% with linezolid nonsusceptibility in[a]:								
	2004	2005	2006	2007	2008	2009	2010	2011	2012
S. aureus (27,827)	0.00	0.03	0.03	0.06	0.10	0.15	0.06	0.10	0.03
CoNS[b] (6,984)	0.20	1.13	1.61	1.76	1.64	1.47	1.48	1.18	0.93
Enterococci (7,608)	0.80	0.64	1.83	1.13	0.55	0.49	1.10	0.34	0.53
S. pneumoniae (6,311)	0.00	0.00	0.00	0.00	0.00	0.00	0.12[c]	0.00	0.00
Viridans group streptococci (2,381)	NT	NT	0.00	0.00	0.00	0.00	0.00	0.19[c]	0.00
Beta-hemolytic streptococci (3,980)	NT	NT	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total (54,911)	0.14	0.24	0.45	0.44	0.36	0.34	0.38	0.19	0.17

[a] Percentage of linezolid nonsusceptibility results for the 2004 to 2010, 2011, and 2012 sampling years were adapted from Flamm et al. (5), Flamm et al. (6) and this study, respectively. NT, not tested.
[b] CoNS, coagulase-negative staphylococci.
[c] One *S. pneumoniae* isolate (MIC, 4 μg/ml) with alterations in L4 (Q67K and G69V) and one *S. sanguinis* isolate (MIC, 32 μg/ml) with multiple mutations in the 23S rRNA and L22 (5, 8).

clindamycin were subjected to the CLSI broth microdilution inducible clindamycin resistance screening test (11).

All *S. aureus* isolates tested (2,980) were inhibited by linezolid at ≤2 μg/ml, except for two and one isolates displaying MIC values at 4 and 32 μg/ml, respectively (Tables 2, 3, and 4). The former isolates carried the *cfr* gene, while the latter strain had mutations in the 23S rRNA and the L3 ribosomal protein (Table 4). Daptomycin, vancomycin, gentamicin, and trimethoprim-sulfamethoxazole demonstrated high levels of antimicrobial coverage (≥97.0% susceptible) when tested against methicillin-resistant *S. aureus* (MRSA), while ciprofloxacin (66.1% resistance), erythromycin (88.4%), and clindamycin (25.4 and 12.3% constitutive and inducible resistance, respectively) showed high resistance rates (Table 3). Nearly all (99.1%) coagulase-negative staphylococci (CoNS) were also inhibited by linezolid at ≤2 μg/ml, whereas seven (0.9%) isolates displayed MIC values of 16 to 128 μg/ml (Tables 2 and 4). Linezolid and daptomycin, followed by vancomycin, were the most potent agents tested against CoNS. Other agents had limited activities (36.5 to 85.0% susceptible) (Table 3).

Linezolid was equally potent when tested against both *E. faecalis* and *E. faecium* ($MIC_{50/90}$, 1/2 μg/ml for both) (Table 2), and linezolid-nonsusceptible enterococci showed a 23S rRNA mutation at position G2576 (Table 4). In addition, one *E. faecium* isolate from New Orleans was *cfr* positive, which represents the first detection of *cfr* in enterococci in the United States. All *E. faecalis* isolates except one remained susceptible to ampicillin, and totals of 73.7% (191/259) and 3.6% (23/640) of the *E. faecium* and *E. faecalis* isolates, respectively, were vancomycin resistant (data not shown). Overall, linezolid ($MIC_{50/90}$, 1/2 μg/ml) and daptomycin ($MIC_{50/90}$, 1/2 μg/ml) were equally potent when tested against the U.S. collection of enterococci, whereas other agents showed narrower antimicrobial coverage (49.1 to 77.7% susceptible) (Table 3). Linezolid ($MIC_{50/90}$, 1/1 μg/ml) showed uniform potency when tested against *S. pneumoniae* and other streptococcal groups of organisms (Tables 2 and 3). Moreover, ceftriaxone, levofloxacin, and vancomycin had good antimicrobial coverage (≥91.5% susceptible).

The linezolid resistance mechanisms detected among selected isolates corroborate those documented in previous LEADER reports (5, 6, 12–15), including *cfr* and G2576 alterations in *S. aureus*, multiple mutations in 23S rRNA and ribosomal proteins in CoNS, which translate into higher linezolid MIC values, and the G2576 modification in enterococci. The presence of *cfr* in *S. aureus* remains of particular importance due to the role of this species in causing community- and hospital-acquired infections and the fact that these organisms often display a linezolid MIC result at the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for susceptibility (i.e., ≤4 μg/ml) (11, 16). This may further facilitate the spread of this mobile resistance determinant, emphasizing the importance of active surveillance. Additional genetic analysis demonstrated the presence of clonally related *S. epidermidis* isolates in a single site in North Carolina, as well as isolates with pulsed-field gel electrophoresis (PFGE) profiles similar to those observed during previous years of the LEADER Program, suggesting persistence of resistant lineages within institutions (New Jersey and Tennessee) (see Table 4).

This report confirms high susceptibility rates for linezolid when tested against isolates from U.S. hospitals during 2012 and

TABLE 2 Linezolid MIC distribution when tested against species and groups of Gram-positive cocci isolated in the United States and submitted to the LEADER Surveillance Program, 2012

Organism[a] (no. of isolates [n = 7,429])	No. (cumulative %) of isolates inhibited at linezolid MIC (μg/ml) of:								MIC (μg/ml)	
	≤0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
S. aureus (2,980)	1 (0.0)	5 (0.2)	290 (9.9)	2,354 (88.9)	327 (99.9)	2 (>99.9)	0 (>99.9)	1 (100.0)	1	2
Oxacillin susceptible (1,537)	0 (0.0)	3 (0.2)	140 (9.3)	1,207 (87.8)	186 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	1	2
Oxacillin resistant (1,443)	1 (0.1)	2 (0.2)	150 (10.6)	1,147 (90.1)	141 (99.9)	2 (100.0)			1	1
CoNS (753)	2 (0.3)	106 (14.3)	449 (74.0)	184 (98.4)	5 (99.1)	0 (99.1)	0 (99.1)	7 (100.0)	0.5	1
Enterococcus spp. (937)	0 (0.0)	9 (1.0)	112 (12.9)	695 (87.1)	116 (99.5)	1 (99.6)	3 (99.9)	1 (100.0)	1	2
E. faecalis (640)	0 (0.0)	8 (1.3)	71 (12.3)	482 (87.7)	78 (99.8)	1 (100.0)			1	2
E. faecium (259)	0 (0.0)	1 (0.4)	32 (12.8)	185 (84.5)	37 (98.8)	0 (98.8)	3 (99.6)	1 (100.0)	1	2
S. pneumoniae (1,273)	6 (0.5)	36 (3.3)	408 (35.3)	800 (98.2)	23 (100.0)				1	1
VGS (526)	12 (2.3)	26 (7.2)	217 (48.5)	260 (97.9)	11 (100.0)				1	1
BHS (960)	1 (0.1)	2 (0.3)	258 (27.2)	699 (100.0)					1	1

[a] CoNS, coagulase-negative staphylococci; VGS, viridans group streptococci; BHS, beta-hemolytic streptococci.

TABLE 3 Antimicrobial activities and spectra of linezolid and comparator agents when tested against species and groups of Gram-positive cocci isolated in the United States and submitted to the LEADER Surveillance Program, 2012

Organism(s), antimicrobial agent (no. of isolates tested [n = 7,429])	MIC (μg/ml)			%S/%I/%R by CLSI criteria[a]
	MIC_{50}	MIC_{90}	Range	
S. aureus isolates				
Oxacillin resistant (1,443)				
Linezolid	1	2	0.25–4	100.0/0.0/0.0
Ciprofloxacin	>4	>4	0.06–>4	32.5/1.4/66.1
Clindamycin	≤0.25	>2	≤0.25–>2	74.4/0.2/25.4 (12.3)[b]
Erythromycin	>16	>16	≤0.12–>16	9.6/2.0/88.4
Gentamicin	≤1	≤1	≤1–>8	97.0/0.1/2.9
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	98.3/0.0/1.7
Daptomycin	0.25	0.5	0.06–2	99.9/—/—
Vancomycin	1	1	0.25–2	100.0/0.0/0.0
Oxacillin susceptible (1,537)				
Linezolid	1	2	0.25–>8	99.9/0.0/0.1
Ciprofloxacin	0.25	>4	≤0.03–>4	87.2/1.9/10.9
Clindamycin	≤0.25	≤0.25	≤0.25–>2	94.3/0.2/5.5 (13.8)[b]
Erythromycin	0.25	>16	≤0.12–>16	63.3/4.4/32.7
Gentamicin	≤1	≤1	≤1–>8	99.0/0.3/0.7
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	99.5/0.0/0.5
Daptomycin	0.25	0.5	≤0.06–2	99.9/—/—
Vancomycin	1	1	0.25–2	100.0/0.0/0.0
CoNS[c] (753)				
Linezolid	0.5	1	≤0.12–>8	99.1/0.0/0.9
Oxacillin	1	>2	≤0.25–>2	36.5/0.0/63.5
Ciprofloxacin	0.25	>4	≤0.03–>4	62.2/0.5/37.3
Clindamycin	≤0.25	>2	≤0.25–>2	73.4/2.8/23.8 (9.6)[b]
Erythromycin	>16	>16	≤0.12–>16	39.6/2.1/58.3
Gentamicin	≤1	>8	≤1–>8	85.0/2.5/12.5
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5—>4	72.6/0.0/27.4
Daptomycin	0.25	0.5	≤0.06–2	99.9/—/—
Vancomycin	1	2	≤0.12–4	100.0/0.0/0.0
Enterococci[d] (937)				
Linezolid	1	2	0.25–>8	99.5/0.1/0.4
Ampicillin	1	>8	0.5–>8	74.3/0.0/25.7
Ciprofloxacin	2	>4	0.25–>4	49.1/6.8/44.1
Piperacillin-tazobactam	4	>64	1–>64	74.3/—/—
Daptomycin	1	2	≤0.06–4	100.0/—/—
Teicoplanin	≤2	>16	≤2–>16	77.7/1.0/21.3
Vancomycin	1	>16	0.25–>16	76.6/0.5/22.9
S. pneumoniae (1,273)				
Linezolid	1	1	≤0.12–2	100.0/—/—
Amoxicillin-clavulanic acid	≤1	4	≤1–>8	86.4/3.7/9.9
Ceftriaxone	≤0.06	1	≤0.06–8	91.5/7.3/1.2
Ciprofloxacin	1	2	0.12–>4	—/—/—
Clindamycin	≤0.25	>2	≤0.25–>2	82.2/0.7/17.1 (1.3)[b]
Erythromycin	≤0.12	>16	≤0.12–>16	57.4/0.7/41.9
Levofloxacin	1	1	0.25–>4	99.2/0.1/0.7
Penicillin[e]	≤0.06	4	≤0.06–8	57.7/24.1/18.2
Vancomycin	0.25	0.5	≤0.12–0.5	100.0/—/—
Viridans group streptococci[f] (526)				
Linezolid	1	1	≤0.12–2	100.0/—/—
Ceftriaxone	0.25	0.5	≤0.06–8	95.8/2.5/1.7
Ciprofloxacin	1	4	≤0.03–>4	—/—/—
Clindamycin	≤0.25	>2	≤0.25–>2	87.6/0.6/11.8
Erythromycin	0.5	16	≤0.12–>16	48.5/2.8/48.7

(Continued on following page)

TABLE 3 (Continued)

Organism(s), antimicrobial agent (no. of isolates tested [n = 7,429])	MIC (μg/ml)			%S/%I/%R by CLSI criteria[a]
	MIC_{50}	MIC_{90}	Range	
Levofloxacin	1	2	≤0.12–>4	93.1/1.2/5.7
Penicillin	≤0.06	0.5	≤0.06–>8	73.6/24.1/2.3
Vancomycin	0.5	1	≤0.12–1	100.0/—/—
Beta-hemolytic streptococci[g] (960)				
Linezolid	1	1	≤0.12–1	100.0/—/—
Ceftriaxone	≤0.06	0.12	≤0.06–0.5	100.0/—/—
Ciprofloxacin	0.5	1	0.12–>4	—/—/—
Clindamycin	≤0.25	>2	≤0.25–>2	80.0/0.6/19.4 (5.5)[b]
Erythromycin	≤0.12	>16	≤0.12–>16	60.7/1.3/38.0
Levofloxacin	≤0.5	1	≤0.12–>4	98.9/0.2/0.9
Penicillin	≤0.06	≤0.06	≤0.06–0.12	100.0/—/—
Vancomycin	0.5	0.5	≤0.12–1	100.0/—/—

[a] Criteria as published by the CLSI (11). %S, percent susceptible; %I, percent intermediate; %R, percent resistant; —, breakpoint not available.
[b] Inducible clindamycin resistance rate among erythromycin-resistant, clindamycin-susceptible isolates as determined by the CLSI broth microdilution inducible clindamycin resistance screening test (11).
[c] Includes [organism (no. of isolates)] *S. auricularis* (1), *S. capitis* (35), *S. caprae* (9), *S. cohnii* (5), *S. epidermidis* (462), *S. haemolyticus* (30), *S. hominis* (53), *S. intermedius* (5), *S. lugdunensis* (78), *S. pasteuri* (2), *S. pettenkoferi* (9), *S. saprophyticus* (35), *S. schleiferi* (2), *S. simulans* (13), *S. warneri* (12), and coagulase-negative staphylococci whose species was not determined (2).
[d] Includes [organism (no. of isolates)] *E. avium* (9), *E. casseliflavus* (6), *E. faecalis* (640), *E. faecium* (259), *E. gallinarum* (7), *E. gilvus* (1), *E. hirae* (4), and *E. raffinosus* (11).
[e] Criteria used were as published by the CLSI for "Penicillin oral penicillin V" (susceptible, ≤0.06 μg/ml; intermediate, 0.12 to 1 μg/ml; and resistant, ≥2 μg/ml) (11).
[f] Includes 27 species.
[g] Includes [organism (no. of isolates)] *S. dysgalactiae* (20), *S. equisimilis* (1), group A *Streptococcus* (*S. pyogenes*; 332), group B *Streptococcus* (*S. agalactiae*; 451), group C *Streptococcus* species (51), group F *Streptococcus* (9), and group G *Streptococcus* species (96).

sustained rates compared with the rates in previous surveillance years (Table 1). The low number of isolates nonsusceptible to linezolid relates to the fact that target site modifications, which are still the main mechanism of resistance, develop slowly due to the redundancy of rRNA in bacteria (17). The development (target site mutation) and acquisition (*cfr*) of resistance have been associated with linezolid exposure and/or prolonged treatment (8, 18, 19). Moreover, selection of isolates related to persistent clones within a given institution has also been described (10, 20). In addition, occasional outbreaks of *cfr*-carrying isolates, which have usually been contained after implementation of infection control measures, have recently been reported (9, 21). Nevertheless, it remains prudent to maintain such national and/or global surveillance programs, not only for monitoring the drug activity and

TABLE 4 Isolates with elevated or nonsusceptible linezolid MICs[a] observed during the 2012 LEADER Surveillance Program

Organism	Isolate	City	State	Linezolid MIC (μg/ml)	Resistance mechanism(s)	PFGE[b]
S. aureus	002-3143	Indianapolis	IN	4	*cfr*	
S. aureus	464-7136	Maywood	IL	4	*cfr*	
S. aureus	015-26753	New York	NY	32	G2576T; L3 (ΔS145)	
S. epidermidis	052-3560	Burlington	MA	16	L3 (V154L, A157R); L4 (71G72 ins)	
S. epidermidis	129-8096	New Brunswick	NJ	32	G2576T; L3 (H146R, V154L, M156T); L4 (71G72 ins[c])	SEPI129B[d]
S. epidermidis	003-13587	Detroit	MI	128	G2576T; L3 (G137S, H146P, F147Y, M156T); L4 (71G72 ins)	SEPI3K
S. epidermidis	404-14750	Philadelphia	PA	16	L3 (H146Q, V154L, A157R); L4 (71G72 ins)	
S. epidermidis	454-15674	Winston-Salem	NC	128	G2576T; L3 (G137S, H146P, M156T); L4 (71G72 ins)	SEPI454E
S. epidermidis	454-15678	Winston-Salem	NC	128	G2576T; L3 (G137S, H146P, M156T); L4 (71G72 ins)	SEPI454E
S. epidermidis	412-45728	Memphis	TN	16	L3 (H146Q, V154L, A157R); L4 (71G72 ins)	SEPI412C[e]
E. faecalis	417-36420	Wauwatosa	WI	4	G2576T	
E. faecium	448-18200	New Orleans	LA	4	G2576T	EFM448A
E. faecium	448-18203	New Orleans	LA	8	G2576T; *cfr*	EFM448B
E. faecium	460-11256	Lansing	MI	8	G2576T	
E. faecium	116-51168	Houston	TX	8	G2576T	

[a] Preliminary elevated or nonsusceptible MICs (≥4 μg/ml) (Thermo Fisher Scientific) were confirmed by using a customized frozen-form panel with an extended linezolid dilution range (i.e., 1 to 128 μg/ml).
[b] Pulsed-field gel electrophoresis (PFGE) types were assigned according to the organism code, comprised of the origin of the isolate (medical site number), followed by a capital letter (type) and a number (subtype), when applicable. Comparisons of PFGE profiles followed the criteria established by Tenover et al. (22).
[c] 71G72 ins, 71G72 insertion.
[d] Three, two, one, and one linezolid-resistant *S. epidermidis* isolates exhibiting an SEPI129B PFGE type were collected from this medical site during 2006, 2007, 2008, and 2009 sampling, respectively.
[e] One linezolid-resistant *S. epidermidis* isolate exhibiting an SEPI412C PFGE type was collected from this medical site in 2010.

spectrum but also for detecting the development and/or acquisition of resistance, such as *cfr* in *S. aureus* and *E. faecium*.

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