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Five-Year Summary of *In Vitro* Activity and Resistance Mechanisms of Linezolid against Clinically Important Gram-Positive Cocci in the United States from the LEADER Surveillance Program (2011 to 2015)

Michael A. Pfaller,[a,b] Rodrigo E. Mendes,[a] Jennifer M. Streit,[a] Patricia A. Hogan,[c] Robert K. Flamm[a]

JMI Laboratories, North Liberty, Iowa, USA[a]; University of Iowa, Iowa City, Iowa, USA[b]; Pfizer Inc., Collegeville, Pennsylvania, USA[c]

ABSTRACT This report describes linezolid susceptibility testing results for 6,741 Gram-positive pathogens from 60 U.S. sites collected during 2015 for the LEADER Program. In addition, the report summarizes linezolid *in vitro* activity, resistance mechanisms, and molecular typing obtained for 2011 to 2015. During 2015, linezolid showed potent activity in testing against *Staphylococcus aureus*, inhibiting >99.9% of 3,031 isolates at ≤2 μg/ml. Similarly, linezolid showed coverage against 99.2% of coagulase-negative staphylococci, 99.7% of enterococci, and 100.0% of *Streptococcus pneumoniae*, virdans group, and beta-hemolytic streptococcus isolates tested. The overall linezolid resistance rate remained a modest <1% from 2011 to 2015. Staphylococci, especially *Staphylococcus epidermidis*, showed a range of linezolid resistance mechanisms. Increased annual trends for the presence of *cfr* among *Staphylococcus aureus* isolates were not observed, but 64.3% (9/14) of the isolates with decreased susceptibility (MIC, ≥4 μg/ml) to linezolid carried this transferrable gene (2011 to 2015). The *cfr* gene was detected in 21.9% (7/32) of linezolid-resistant staphylococci other than *S. aureus* from 2011 to 2015. The *optrA* gene was noted in half (2/4) of the population of linezolid-nonsusceptible *Enterococcus faecalis* isolates from 2011 to 2015, while linezolid-nonsusceptible *Enterococcus faecium* isolates showed alterations predominantly (16/16) in the 23S rRNA gene (G2576T). This report confirms a long record of linezolid activity against Gram-positive isolates in the United States since regulatory approval in 2000 and reports the oxazolidinones evolving resistance mechanisms.

KEYWORDS LEADER, linezolid, oxazolidinones

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Address correspondence to Michael A. Pfaller, mike-pfaller@jmilabs.com.

Linezolid, the first member of the oxazolidinone class of antimicrobial agents, has demonstrated clinical effectiveness for treating respiratory tract and skin and soft tissue infections caused by a variety of Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), since its introduction in 2000 (1–4). The clinical data have been supported by the LEADER Surveillance Program, established in 2004 to detect emerging antimicrobial resistance among Gram-positive cocci (GPC) in the United States (5). For 12 consecutive years, this program has provided yearly information regarding linezolid resistance mechanisms, including the identification of new and emerging mechanisms (6–11).

Linezolid exerts its antibacterial activity by inhibiting protein synthesis by binding to the 23S subunit of the 50S ribosome (12). Resistance development appeared early in

TABLE 1 Summary of the linezolid nonsusceptibility rates documented during the LEADER Program for 2011 to 2015

Organism(s) (no. tested)	% linezolid nonsusceptibility[a]					
	2011	2012	2013	2014	2015	2011–2015
S. aureus (15,177)	0.1	<0.1	0.1	0.1	<0.1	0.1
Coagulase-negative staphylococci (3,815)	1.2	0.9	0.5	0.6	0.8	0.8
Enterococci (4,849)	0.4	0.5	0.6	0.7	0.3	0.5
S. pneumoniae (5,221)	0.0	0.0	0.0	0.0	0.0	0.0
Viridans group streptococci (1,601)	0.7	0.0	0.3	0.0	0.0	0.1
Beta-hemolytic streptococci (4,100)	0.0	0.0	0.0	0.0	0.0	0.0

[a]Percentages of linezolid nonsusceptibility for 2011 to 2015 were adapted from Mendes et al. (17), Flamm et al. (11), and this study.

clinical use in staphylococci and enterococci through ribosomal mutation in the 23S rRNA (6, 13). Subsequently, an rRNA methyltransferase was identified that conferred resistance to linezolid and other antimicrobial agents (7, 9, 14, 15; see https://doi-org.ezproxy.library.tufts.edu/10.1093/jac/dkx023). This *cfr* rRNA methyltransferase has the potential to mobilize, and, although it has been detected among an expanding number of GPC, it is still not the dominant mechanism of linezolid resistance among clinical GPC (5). The *optrA* gene, an additional mobile element, was reported in 2015 and confers oxazolidinone resistance (16).

Although linezolid resistance in GPC has evolved during the 12-year history of LEADER to include new species and resistance mechanisms, the overall linezolid resistance rate has remained modest at <1% (10, 11, 17). Table 1 summarizes the linezolid nonsusceptibility rates documented in the United States during the last 5 years of the LEADER Program, illustrating the low rates observed for the monitored species and groups of GPC. In this report, we present the 2015 U.S. LEADER Program results and compare them with the 2011–2014 results. The comparisons focus on linezolid *in vitro* activity, resistance mechanisms, and molecular typing among GPC.

RESULTS AND DISCUSSION

All *S. aureus* isolates tested during 2015 (n = 3,031), except 1 isolate displaying an MIC value at 8 μg/ml, were inhibited by linezolid at ≤2 μg/ml (Tables 2, 3, and 4). Daptomycin, vancomycin, teicoplanin, tigecycline, and trimethoprim-sulfamethoxazole demonstrated high antimicrobial coverage (100% susceptibility) against MRSA, while levofloxacin (67.6% resistance), erythromycin (84.0%), and clindamycin (26.9 and 16.4% constitutive and inducible resistance, respectively) showed high resistance rates (Table 3). In the last 5 years of the LEADER Program, *S. aureus* isolates with decreased susceptibility (MIC, ≥4 μg/ml) to linezolid showed the presence of *cfr*, mutations in the 23S rRNA gene and/or L3 gene, and/or a combination of these resistance mechanisms (Table 4). Although no annual trends seem to exist for the presence of *cfr*, 64.3% (9/14) of the *S. aureus* isolates with decreased susceptibility to linezolid carried this gene during the 2011–2015 interval. This genetic presence remains of particular importance due to this species causing community- and hospital-acquired infections and because 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) (18, 19). The proximity to the breakpoint may make detecting this mobile resistance determinant difficult, which emphasizes the importance of active surveillance.

Nearly all (99.2%) coagulase-negative staphylococci (CoNS) were inhibited by linezolid at ≤2 μg/ml; however, 7 (0.8%) CoNS isolates displayed MIC values of >16 μg/ml during 2015 (Tables 2 and 4). Tigecycline, linezolid, and daptomycin were the most potent agents tested against CoNS isolates, followed by vancomycin and teicoplanin. Other agents had limited activity (40.5% to 86.7% susceptibility; Table 3). For 2011 to 2015, LEADER Program *S. epidermidis* isolates represented the vast majority of CoNS species (96.9%; 31/32) that displayed a linezolid resistance phenotype (Table 4).

TABLE 2 Antimicrobial activity of linezolid tested against the main organisms and organism groups of isolates included during 2015

Organisms/no. of isolates	No. of isolates (cumulative %) at MIC (μg/ml) of:									MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	0.06	0.12	0.25	0.5	1	2	4	8	>8		
Staphylococcus aureus (3,031)		3 (0.1)	23 (0.9)	1186 (40.0)	1773 (98.5)	45 (>99.9)	0 (>99.9)	1 (100.0)		1	1
Methicillin susceptible (1,640)		2 (0.1)	9 (0.7)	571 (35.5)	1023 (97.9)	35 (100.0)				1	1
Methicillin resistant (1,391)		1 (0.1)	14 (1.1)	615 (45.3)	750 (99.2)	10 (99.9)	0 (99.9)	1 (100.0)		1	1
Coagulase-negative staphylococci (924)		4 (0.4)	103 (11.6)	562 (72.4)	240 (98.4)	8 (99.2)	0 (99.2)	0 (99.2)	7 (100.0)	0.5	1
Methicillin susceptible (381)		3 (0.8)	48 (13.4)	232 (74.3)	97 (99.7)	1 (100.0)				0.5	1
Methicillin resistant (543)		1 (0.2)	55 (10.3)	330 (71.1)	143 (97.4)	7 (98.7)	0 (98.7)	0 (98.7)	7 (100.0)	0.5	1
Enterococcus spp. (973)			26 (2.7)	267 (30.1)	605 (92.3)	72 (99.7)	1 (99.8)	2 (100.0)		1	1
E. faecalis (676)			11 (1.6)	192 (30.0)	429 (93.5)	43 (99.9)	1 (100.0)			1	1
E. faecium (270)			14 (5.2)	65 (29.3)	164 (90.0)	25 (99.3)	0 (99.3)	2 (100.0)		1	1
Streptococcus pneumoniae (850)			3 (0.4)	193 (23.1)	620 (96.0)	34 (100.0)				1	1
Penicillin intermediate (MIC, $\geq$0.12 and $\leq$1 μg/ml) (249)			1 (0.4)	45 (18.5)	198 (98.0)	5 (100.0)				1	1
Penicillin resistant (MIC, $\geq$2 μg/ml) (64)				30 (46.9)	33 (98.4)	1 (100.0)				1	1
Viridans group streptococci (236)	4 (1.7)	2 (2.5)	8 (5.9)	134 (62.7)	88 (100.0)					0.5	1
Beta-hemolytic streptococci (727)				180 (24.8)	547 (100.0)					1	1

TABLE 3 Comparative activity of linezolid tested against 6,741 Gram-positive pathogens isolated during the 2015 LEADER Program

Organism/resistance group (no. tested) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI (%S/%R)[a]
S. aureus				
Oxacillin susceptible (1,640)				
Linezolid	1	1	≤0.12 to 2	100.0/0.0
Vancomycin	0.5	1	≤0.12 to 2	100.0/0.0
Teicoplanin	≤0.5	≤0.5	≤0.5 to 8	100.0/0.0
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—
Erythromycin	0.25	>8	≤0.06 to >8	64.6/28.1
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	94.4/5.4
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.9/3.2
Tigecycline[b]	0.06	0.12	≤0.015 to 0.5	100.0/—
Gentamicin	≤1	≤1	≤1 to >8	98.6/1.3
Levofloxacin	0.12	4	≤0.03 to >4	88.5/11.2
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	99.4/0.6
Oxacillin resistant (1,391)				
Linezolid	1	1	≤0.12 to >8	99.9/0.1
Vancomycin	0.5	1	≤0.12 to 2	100.0/0.0
Teicoplanin	≤0.5	≤0.5	≤0.5 to 8	100.0/0.0
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—
Erythromycin	>8	>8	≤0.06 to >8	12.5/84.0
Clindamycin	≤0.25	>2	≤0.25 to >2	72.6/26.9
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	94.2/4.8
Tigecycline[b]	0.06	0.12	≤0.015 to 0.5	100.0/—
Gentamicin	≤1	≤1	≤1 to >8	96.1/3.8
Levofloxacin	4	>4	0.12 to >4	30.7/67.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 to >4	97.2/2.8
Coagulase-negative staphylococci				
Oxacillin susceptible (381)[c]				
Linezolid	0.5	1	≤0.12 to 2	100.0/0.0
Vancomycin	0.5	2	≤0.12 to 2	100.0/0.0
Teicoplanin	≤0.5	4	≤0.5 to 8	100.0/0.0
Daptomycin	0.25	0.5	≤0.12 to 1	100.0/—
Erythromycin	0.12	>8	≤0.06 to >8	65.6/32.3
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	91.1/7.9
Tetracycline	≤0.5	1	≤0.5 to >8	92.4/6.0
Tigecycline[b]	0.06	0.12	≤0.015 to 0.5	100.0/0.0
Gentamicin	≤1	≤1	≤1 to >8	97.4/2.4
Levofloxacin	0.25	4	≤0.03 to >4	84.8/14.2
Trimethoprim-sulfamethoxazole	≤0.5	2	≤0.5 to >4	90.3/9.7
Oxacillin resistant (543)[d]				
Linezolid	0.5	1	≤0.12 to >8	98.7/1.3
Vancomycin	1	2	≤0.12 to 2	100.0/0.0
Teicoplanin	2	4	≤0.5 to 16	99.3/0.0
Daptomycin	0.5	0.5	≤0.12 to 1	100.0/—
Erythromycin	>8	>8	≤0.06 to >8	22.8/74.2
Clindamycin	≤0.25	>2	≤0.25 to >2	57.8/39.0
Tetracycline	≤0.5	>8	≤0.5 to >8	82.7/16.0
Tigecycline[b]	0.06	0.25	0.03 to 0.5	100.0/0.0
Gentamicin	≤1	>8	≤1 to >8	65.9/30.8
Levofloxacin	>4	>4	≤0.03 to >4	39.8/57.6
Trimethoprim-sulfamethoxazole	1	>4	≤0.5 to >4	63.5/36.5
Enterococcus spp.[e] (973)				
Linezolid	1	1	≤0.25 to 8	99.7/0.2
Ampicillin	1	>8	≤0.5 to >8	76.6/23.4
Vancomycin	1	>16	≤0.5 to >16	78.3/21.6
Teicoplanin	≤2	>16	≤2 to >16	79.1/18.4
Daptomycin	1	2	≤0.25 to >8	99.8/—
Tigecycline[b]	0.06	0.12	≤0.015 to 0.5	99.8/0.0
Levofloxacin	1	>4	≤0.5 to >4	59.3/39.0
Piperacillin-tazobactam	4	>16	≤2 to >16	76.3/23.4
S. pneumoniae (850)				
Linezolid	1	1	0.25 to 2	100.0/—

(Continued on next page)

TABLE 3 (Continued)

Organism/resistance group (no. tested) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI (%S/%R)[a]
Penicillin[f]	≤0.06	1	≤0.06 to 4	96.7/0.0
Penicillin[g]	≤0.06	1	≤0.06 to 4	63.2/7.5
Amoxicillin-clavulanate	≤0.03	2	≤0.03 to 4	95.2/1.9
Ceftriaxone[h]	0.03	1	≤0.015 to >2	98.4/0.5
Vancomycin	0.25	0.25	≤0.03 to 0.5	100.0/—
Erythromycin	0.03	>2	≤0.015 to >2	56.5/42.9
Clindamycin	≤0.12	>1	≤0.12 to >1	85.0/14.4
Levofloxacin	1	1	0.25 to >4	99.3/0.7
Tetracycline	0.25	>4	≤0.12 to >4	80.1/19.7
Tigecycline[b]	0.03	0.06	0.015 to 0.12	99.9/—
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 to >4	74.7/14.0
Viridans group and other streptococci (236)[i]				
Linezolid	0.5	1	≤0.06 to 1	100.0/—
Penicillin	≤0.03	0.5	≤0.03 to >4	79.1/2.7
Ceftriaxone	0.12	0.5	≤0.03 to >4	97.3/1.8
Vancomycin	0.5	0.5	≤0.06 to 1	100.0/—
Daptomycin	0.5	0.5	≤0.06 to 1	100.0/—
Erythromycin	0.5	>4	≤0.03 to >4	46.7/48.4
Clindamycin	0.03	>2	≤0.015 to >2	83.1/16.4
Levofloxacin	1	2	≤0.03 to >4	92.4/7.1
Tetracycline	1	>8	≤0.25 to >8	56.4/39.6
Tigecycline[b]	0.03	0.06	≤0.008 to 0.25	100.0/—
Beta-hemolytic streptococci (727)[j]				
Linezolid	1	1	0.5 to 1	100.0/—
Penicillin	≤0.03	0.06	≤0.03 to 0.12	100.0/—
Ceftriaxone	≤0.03	0.06	≤0.03 to 0.25	100.0/—
Vancomycin	0.25	0.5	≤0.06 to 1	100.0/—
Daptomycin	0.12	0.5	≤0.06 to 1	100.0/—
Erythromycin	0.06	>4	≤0.03 to >4	60.8/38.2
Clindamycin	0.06	>2	≤0.015 to >2	78.7/20.9
Levofloxacin	0.5	1	0.06 to >4	99.3/0.3
Tetracycline	4	>8	≤0.25 to >8	49.7/48.8
Tigecycline[b]	0.06	0.06	0.015 to 0.25	100.0/—

[a]Criteria employed were as published by the CLSI (18). %S/%R, percent susceptible/percent resistant; —, lack of resistant breakpoint.
[b]U.S. FDA breakpoints were applied for tigecycline.
[c]The organisms tested included *Staphylococcus auricularis* (2 isolates), *S. capitis* (36 isolates), *S. caprae* (10 isolates), *S. condimenti* (2 isolates), *S. epidermidis* (153 isolates), *S. hemolyticus* (12 isolates), *S. hominis* (32 isolates), *S. lugdunensis* (109 isolates), *S. pseudintermedius* (2 isolates), *S. saprophyticus* (2 isolates), *S. schleiferi* (2 isolates), *S. simulans* (11 isolates), and *S. warneri* (8 isolates).
[d]The organisms tested included *S. auricularis* (1 isolate), *S. capitis* (13 isolates), *S. cohnii* (5 isolates), *S. caprae* (2 isolates), *S. epidermidis* (402 isolates), *S. hemolyticus* (37 isolates), *S. hominis* (35 isolates), *S. lugdunensis* (6 isolates), *S. pettenkoferi* (4 isolates), *S. pseudintermedius/S. intermedius*/S. *delphini* (1 isolate), *S. saprophyticus* (22 isolates), *S. schleiferi* (1 isolate), *S. simulans* (9 isolates), and *S. warneri* (5 isolates).
[e]The organisms tested included *Enterococcus avium* (5 isolates), *E. casseliflavus* (6 isolates), *E. durans* (3 isolates), *E. faecalis* (676 isolates), *E. faecium* (270 isolates), *E. gallinarum* (11 isolates), *E. raffinosus* (1 isolate), and *E. thailandicus* (1 isolate).
[f]Criteria employed were as published by the CLSI for penicillin parenteral (nonmeningitis) (18).
[g]Criteria employed were as published by the CLSI for penicillin (oral penicillin V) (18).
[h]Criteria employed were as published by the CLSI for nonmeningitis (18).
[i]The organisms tested included *Streptococcus anginosus* (57 isolates), *S. anginosus* group (10 isolates), *S. australis* (2 isolates), *S. constellatus* (7 isolates), *S. cristatus* (2 isolates), *S. equinus* (1 isolate), *S. gallolyticus* (9 isolates), *S. gordonii* (2 isolates), *S. infantarius* (1 isolate), *S. infantis* (2 isolates), *S. intermedius* (9 isolates), *S. lutetiensis* (4 isolates), *S. mitis* (5 isolates), *S. mitis* group (8 isolates), *S. mitis/S. oralis* (47 isolates), *S. mutans* (3 isolates), *S. oralis* (33 isolates), *S. parasanguinis* (14 isolates), *S. salivarius* (6 isolates), *S. salivarius* group (4 isolates), *S. sanguinis* (8 isolates), and *S. vestibularis* (2 isolates).
[j]The organisms tested included *Streptococcus pyogenes* (297 isolates), *S. agalactiae* (341 isolates), *S. equi* (1 isolate), and *S. dysgalactiae* (89 isolates).

In addition, CoNS species possessed multiple combinations of linezolid resistance mechanisms, usually alterations in 23S rRNA, L3, and/or L4. The *cfr* gene was observed in 21.9% (7/32) of linezolid-resistant CoNS isolates during those 5 years.

Linezolid was equally potent against *Enterococcus faecalis* and *E. faecium* ($MIC_{50/90}$, 1/1 μg/ml for both; Table 2) during 2015. All *E. faecalis* isolates remained susceptible to ampicillin, and a total of 68.9% (186/270) and 3.2% (24/676) of *E. faecium* and *E. faecalis* isolates were vancomycin resistant, respectively (96.2% VanA phenotype; data not shown). Overall, tigecycline ($MIC_{50/90}$, 0.06/0.12 μg/ml) was the most potent agent against the U.S. collection of enterococci, followed by linezolid ($MIC_{50/90}$, 1/1 μg/ml)

TABLE 4 Isolates with elevated or nonsusceptible linezolid MIC values observed during the 2011–2015 LEADER Program

Organism	Yr	City	State	LZD MIC (μg/ml)[a]	Resistance mechanism(s) (mutation[s])	PFGE type[b]
S. aureus	2011	Akron	OH	4	*cfr*	SA4I
S. aureus	2011	Houston	TX	8	23S rRNA (G2576T)	
S. aureus	2011	Long Beach	CA	8	*cfr*; 23S rRNA (G2576T)	**SA146A**
S. aureus	2011	Louisville	KY	8	*cfr*	
S. aureus	2011	Milwaukee	WI	4	L3 (ΔS145)	
S. aureus	2012	Indianapolis	IN	4	*cfr*	
S. aureus	2012	Maywood	IL	4	*cfr*	
S. aureus	2012	New York	NY	32	23S rRNA (G2576T); L3 (ΔS145)	
S. aureus	2013	Detroit	MI	8	*cfr*	
S. aureus	2013	Long Beach	CA	32	*cfr*; 23S rRNA (G2576T); L3 (D159E, G152D)	**SA146A**
S. aureus	2014	Long Beach	CA	8	23S rRNA (G2576T)	**SA468A**
S. aureus	2014	Long Beach	CA	16	*cfr*; 23S rRNA (G2576T); L3 (ΔH146, P151L)	SA468B
S. aureus	2014	New Orleans	LA	4	*cfr*	
S. aureus	2015	Long Beach	CA	8	23S rRNA (G2576T)	**SA468A**
S. epidermidis	2011	Cleveland	OH	32	23S rRNA (G2576T); L3 (M156T, H146P, G137S, F147Y); L4 (71G72 ins[c])	
S. epidermidis	2011	Hackensack	NJ	64	23S rRNA (G2576T); L3 (V154L, M156T, H146R, G137D); L4 (71G72 ins)	
S. epidermidis	2011	Hershey	PA	64	23S rRNA (G2576T); L3 (V154L, M156T, H146R)	SEPI453C
S. epidermidis	2011	Houston	TX	64	23S rRNA (G2576T); L3 (M156T, H146P, G137S)	**SEPI116D**
S. epidermidis	2011	Houston	TX	16	L3 (V154L, H146Q, A157R); L4 (71G72 ins)	SEPI116E
S. epidermidis	2011	Memphis	TN	128	23S rRNA (G2576T); L3 (V154L, M156T, H146R); L4 (71G72 ins)	**SEPI436A**
S. epidermidis	2011	Memphis	TN	128	23S rRNA (G2576T); L3 (V154L, M156T, H146R); L4 (71G72 ins)	**SEPI436A**
S. epidermidis	2011	New Brunswick	NJ	64	23S rRNA (G2576T)	SEPI129I
S. epidermidis	2011	New Orleans	LA	64	23S rRNA (G2576T)	SEPI448F
S. epidermidis	2012	Burlington	MA	16	L3 (V154L, A157R); L4 (71G72 ins)	
S. epidermidis	2012	Detroit	MI	128	23S rRNA (G2576T); L3 (G137S, H146P, F147Y, M156T); L4 (71G72 ins)	**SEPI3K**
S. epidermidis	2012	Memphis	TN	16	L3 (H146Q, V154L, A157R); L4 (71G72 ins)	SEPI412C
S. epidermidis	2012	New Brunswick	NJ	32	23S rRNA (G2576T); L3 (H146R, V154L, M156T); L4 (71G72 ins)	SEPI129B
S. epidermidis	2012	Philadelphia	PA	16	L3 (H146Q, V154L, A157R); L4 (71G72 ins)	
S. epidermidis	2012	Winston-Salem	NC	128	23S rRNA (G2576T); L3 (G137S, H146P, M156T); L4 (71G72 ins)	**SEPI454E**
S. epidermidis	2012	Winston-Salem	NC	128	23S rRNA (G2576T); L3 (G137S, H146P, M156T); L4 (71G72 ins)	**SEPI454E**
S. epidermidis	2013	Detroit	MI	128	23S rRNA (G2576T); L3 (G137S, H146P, M156T); L4 (71G72 ins)	**SEPI3K**
S. epidermidis	2013	Houston	TX	64	23S rRNA (G2576T); L3 (H146R, M156T); L4 (71G72 ins)	SEPI116F
S. epidermidis	2013	Winston-Salem	NC	32	23S rRNA (G2576T); L3 (H146P, M156T)	**SEPI454E**
S. epidermidis	2014	Houston	TX	64	23S rRNA (G2576T); L3 (G137S, H146P, M156T); L4 (71G72 ins)	**SEPI116D**
S. epidermidis	2014	Houston	TX	128	*cfr*; L3 (H146Q, V154L, A157R); L4 (71G72 ins)	**SEPI116E**
S. epidermidis	2014	Long Beach	CA	128	*cfr*; L3 (G137S, H146Q, V154L, A157R); L4 (71G72 ins)	SEPI468B
S. epidermidis	2014	Memphis	TN	>128	*cfr*; 23S rRNA (G2576T); L4 (G137S, H146P, F147Y, M156T); L4 (71G72 ins)	SEPI412F
S. epidermidis	2014	San Francisco	CA	>128	*cfr*; L3 (H146Q, V154L, A157R); L4 (71G72 ins)	SEPI470A
S. epidermidis	2015	Houston	TX	128	*cfr*; 23S rRNA (C2534T); L3 (V154L, A157R); L4 (71G72 ins)	**SEPI116E**
S. epidermidis	2015	Houston	TX	>128	*cfr*; 23S rRNA (C2534T); L3 (H146Q, V154L, A157R)	**SEPI116E**
S. epidermidis	2015	Houston	TX	16	23S rRNA (C2534T); L3 (H146Q, V154L, A157R); L4 (71G72 ins)	**SEPI116E1**
S. epidermidis	2015	Houston	TX	16	L3 (V96D, H146Q, V154L, A157R); L4 (71G72 ins)	SEPI116G
S. epidermidis	2015	Long Beach	CA	16	23S rRNA (G2576T); L3 (V154L, M156T)	SEPI468C
S. epidermidis	2015	Memphis	KY	128	23S rRNA (G2576T); L3 (Q136L, H146R, M156T); L4 (71G72 ins)	SEPI412F
S. epidermidis	2015	Winston-Salem	NC	16	23S rRNA (G2576T); L3 (H146P, M156T)	**SEPI454E**
S. hominis	2014	Seattle	WA	8	*cfr*; L3 (M169L)	
S. sanguinis	2013	Aurora	CO	4	23S rRNA (G2576T); L4 (A22T)	
E. faecalis	2012	Wauwatosa	WI	4	23S rRNA (G2576T)	
E. faecalis	2013	Hershey	PA	8	23S rRNA (G2576T)	
E. faecalis	2014	Burlington	VT	8	*optrA*	
E. faecalis	2015	Milwaukee	WI	4	*optrA*	
E. faecium	2012	Houston	TX	8	23S rRNA (G2576T)	**EFM116B**
E. faecium	2012	Lansing	MI	8	23S rRNA (G2576T)	
E. faecium	2012	New Orleans	LA	4	23S rRNA (G2576T)	EFM448A
E. faecium	2012	New Orleans	LA	8	*cfr*(B); 23S rRNA (G2576T)	EFM448B
E. faecium	2013	Akron	OH	32	23S rRNA (G2576T)	
E. faecium	2013	Houston	TX	16	23S rRNA (G2576T)	EFM116C
E. faecium	2013	Los Angeles	CA	32	23S rRNA (G2576T)	EFM467A
E. faecium	2013	Maywood	IL	8	23S rRNA (G2576T)	
E. faecium	2013	New Orleans	LA	8	*cfr*(B); 23S rRNA (G2576T)	**EFM448B**
E. faecium	2014	Atlanta	GA	8	*cfr*(B); 23S rRNA (G2576T)	
E. faecium	2014	Charlottesville	VA	4	23S rRNA (G2576T)	
E. faecium	2014	Fairbanks	AK	8	23S rRNA (G2576T)	**EFM461A**

(Continued on next page)

TABLE 4 (Continued)

Organism	Yr	City	State	LZD MIC (μg/ml)[a]	Resistance mechanism(s) (mutation[s])	PFGE type[b]
E. faecium	2014	Fairbanks	AK	8	23S rRNA (G2576T)	**EFM461A1**
E. faecium	2014	Los Angeles	CA	16	23S rRNA (G2576T)	EFM467B
E. faecium	2015	Houston	TX	8	23S rRNA (G2576T)	EFM116D
E. faecium	2015	Seattle	WA	8	23S rRNA (G2576T); L3 (K95T)	

[a]Preliminarily determined elevated MIC values (≥4 μg/ml) were confirmed by using a customized frozen-form panel with an extended linezolid (LZD) dilution range (i.e., 1 to 128 μg/ml).
[b]Pulsed-field gel electrophoresis (PFGE) types were assigned according to the organism code, the origin of the isolate (medical site number), a capital letter (type), and a number (subtype), when applicable. Only PFGE profiles from same species isolates recovered from the same medical site were compared. PFGE types that included more than 1 isolate representing clonal dissemination are in bold.
[c]ins, insertion.

and daptomycin ($MIC_{50/90}$, 1/2 μg/ml). Other agents showed narrower antimicrobial coverage (59.3% to 79.1% susceptibility; Table 3). Alterations in the 23S rRNA remained important linezolid resistance mechanisms in enterococci during the 2011–2015 interval (Table 4). Three *E. faecium* isolates from New Orleans and Atlanta also carried the *cfr* variant *cfr*(B) (9); note that the newly described transferable *optrA* gene was found in 2 *E. faecalis* isolates from Vermont and Wisconsin in 2014 to 2015. This gene was first reported in enterococci from China in 2015 (16) and has been detected since then in human clinical specimens from several continents (8, 20–24).

Linezolid showed uniform potency against the 2015 collection of *Streptococcus pneumoniae* ($MIC_{50/90}$, 1/1 μg/ml), viridans group streptococci ($MIC_{50/90}$, 0.5/1 μg/ml), and beta-hemolytic streptococci ($MIC_{50/90}$, 1/1 μg/ml) (Tables 2 and 3). Moreover, ceftriaxone, levofloxacin, daptomycin, tigecycline, and vancomycin had good antimicrobial coverage (≥91.5% susceptibility) against these species (Table 3). The linezolid resistance phenotype among clinical streptococcal isolates remains rare in the literature, although studies have reported strains exhibiting target site alterations (5, 25–27).

Additional genetic analysis demonstrated the presence of clonally related strains, a feature noted among 20.0% of enterococcus isolates, 28.6% of *S. aureus* isolates, and 43.8% of CoNS isolates (Table 4). The higher occurrence of clonality among CoNS isolates is likely due to the ability of *S. epidermidis* to establish and persist in nosocomial environments (28).

This report confirms high susceptibility rates for linezolid against isolates from U.S. hospitals during 2015 and confirms sustained rates compared with previous surveillance years (Table 1). The low number of isolates nonsusceptible to linezolid relates to target site modifications, which remain the main resistance mechanism, developing slowly due to the redundancy of rRNA in bacteria (14). Isolates carrying target site mutations and/or *cfr* have been associated with prolonged drug exposure in at-risk patient populations, and these isolates can also disseminate due to breaks in infection prevention practices that lead to local outbreaks or endemic occurrences (25, 29–31). In addition, occasional outbreaks of *cfr*-carrying isolates have been reported; those outbreaks were usually contained after infection control measures were implemented (30, 32, 33). However, others reported unsuccessful results with respect to suppressing *cfr* isolates despite implementing control measures (34), which can be observed here by the presence of eventual clonal isolates recovered over time in the same institution (Table 4). Although the prevalence of *optrA* isolates remained low, the total number represented half of *E. faecalis* isolates that met the screening criteria in this study. Moreover, rapid *optrA* emergence has been reported worldwide (8). Therefore, maintaining such local/national and/or global surveillance programs is prudent to monitor the drug activity and spectrum and to detect resistance development and/or acquisition.

MATERIALS AND METHODS

Clinical isolates. A total of 6,741 GPC isolates cultured in 60 U.S. (37 states) medical centers, located in all 9 U.S. census divisions, were submitted to JMI Laboratories (North Liberty, Iowa, USA) during the 2015 LEADER survey. Participating laboratories primarily identified isolates that the reference monitoring laboratory (JMI Laboratories) confirmed by standard algorithms, and the results were supported by

matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing. Broth microdilution susceptibility testing of all isolates was performed in the reference monitoring laboratory and followed the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document (35). Bacterial inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. MIC values were validated by concurrently testing CLSI-recommended quality control reference strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619) (18). MIC interpretations were based on the CLSI M100-S27 (2017) breakpoint criteria, as available (18); however, tigecycline MIC results were interpreted using U.S. Food and Drug Administration criteria (36). Isolates resistant to erythromycin but susceptible to clindamycin were subjected to the CLSI broth microdilution inducible clindamycin resistance screening test (18, 35).

Detection of linezolid resistance mechanisms and epidemiologic typing. Isolates that showed elevated MIC results for linezolid (i.e., MIC, ≥4 μg/ml) were selected for further characterization at the central laboratory. The presence of *cfr* and *cfr*(B) and mutations in the 23S rRNA and ribosomal proteins (L3, L4, and L22) were investigated by PCR and sequencing of amplicons on both strands (25, 32, 37). In addition, isolates were screened for the newly described *optrA* gene (16). Isolates exhibiting decreased susceptibility to linezolid that were the same species and recovered from the same medical site underwent pulsed-field gel electrophoresis (7, 32, 37).

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