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Linezolid Experience and Accurate Determination of Resistance (LEADER) Program for 2012: Regional Activity of Linezolid and Comparator Compounds

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ABSTRACT

Background: Linezolid (LZD) remains the only marketed oxazolidinone antimicrobial available in the USA since its approval in 2000. It is active against Gram-positive (GP) organisms that are resistant (R) to conventional drugs, such as MRSA, drug-R *S. pneumoniae* (DRSP) and vancomycin-R enterococci (VRE). The Linezolid Experience and Accurate Determination of Resistance (LEADER) Program has monitored LZD-R rates in the USA through the collection of nearly 55,000 isolates since 2004.

Methods: A total of 7,429 GP pathogens were submitted from 60 medical centers in 37 states (representing all 9 Census Regions). The organism groups (no. overall) were: *S. aureus* (SA; 2,980), coagulase-negative staphylococci (CoNS; 753), enterococci (ENT; 937), *S. pneumoniae* (SPN; 1273), viridans group (VGS; 526), and β-haemolytic streptococci (BHS; 960). CLSI broth microdilution susceptibility (S) testing was performed. LZD-R isolates were confirmed by Etest (bioMerieux, Hazelwood, MO) and CLSI disk diffusion methods. PCR and sequencing was performed to detect mutations in 23S rRNA, L3, L4, and L22 proteins, and an acquired gene (*cfr*).

Results: LZD activity against GP organisms remains high (99.83% S). The $MIC_{50/90}$ for SA was at 1/2 μg/ml. MRSA rates varied by region from 35.1 to 58.7%. Only one SA isolate was LZD-R (MSSA; LZD MIC, 32 μg/ml; G2576T and L3 alteration) and two MRSA (LZD MIC, 4 μg/ml) contained the *cfr* gene (Indiana and Illinois). Among CoNS, seven isolates (0.92% of all strains [1.18% in 2011 and 1.48% in 2010]) demonstrated linezolid MIC results of ≥8 μg/ml. Four *E. faecium* (≥8 μg/ml; G2576T mutations; 0.4% of ENT) were LZD non-S. LZD was active against all SPN with a $MIC_{50/90}$ of 1/1 μg/ml. Penicillin-R rates for SPN ranged from 12.4 to 32.3% and ceftriaxone–non-S varied by region from 2.7 to 13.8%. For VGS and BHS, compromised S was noted for erythromycin, clindamycin and tetracycline, while LZD MIC values were dominantly 1 μg/ml ($MIC_{50/90}$, 1 μg/ml).

Conclusion: LZD demonstrated excellent activity with a S rate of 99.83% with no evidence of MIC creep when compared to previous years (2004-2011) of the LEADER Program. While rates of MRSA and DRSP vary moderately between USA Census Regions, LZD-R in the USA remains below 1.0% in all regions. Surveillance networks should be maintained to detect emerging R types to LZD and geographic variances.

INTRODUCTION

The Linezolid Experience and Accurate Determination of Resistance (LEADER) surveillance program has monitored linezolid (an oxazolidinone) activity, spectrum and resistance rates through a structured collection of nearly 55,000 isolates in the United States (USA) since 2004. Linezolid remains the only Food and Drug Administration (FDA) approved and marketed oxazolidinone antimicrobial available in the USA since 2000. The oxazolidinone mechanism of action has been described as selective binding to the 50S ribosomal subunit of the 23S rRNA molecule with resultant inhibition of protein synthesis.

Linezolid is used to treat uncomplicated and complicated skin and skin structure infections (cSSSI) and nosocomial pneumonia caused by Gram-positive pathogens. Linezolid is also indicated for the treatment of vancomycin-resistant *Enterococcus faecium* infections. This compound has emerged as a valuable treatment option against Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae* (DRSP) and vancomycin-resistant enterococci (VRE) that are resistant to conventional drugs.

METHODS

Bacterial strain collection. Sixty medical centers were selected to represent the nine USA Census Regions. Each recruited medical center was instructed to forward ≥100 organisms with the following species or genus distribution: *S. aureus* (50 strains) coagulase-negative staphylococci (CoNS; 15 strains), enterococci (15 strains), *S. pneumoniae* (10 strains), β-haemolytic streptococci (5 strains) and viridans group streptococci (5 strains). The strains were predominantly from bacteremias, although isolates from pneumonia (respiratory tract), cutaneous wound infections or cSSSI, and urinary tract infections were acceptable.

A total of 7,429 GP pathogens were submitted to JMI Laboratories and distributed among the following organism groups: *S. aureus* (2,980 strains), CoNS (753), enterococci (937), *S. pneumoniae* (1,273), viridans group streptococci (526), and β-haemolytic streptococci (960).

Antimicrobial susceptibility test methods. All susceptibility tests were performed using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods (frozen- and dry-form 96-well plates; CLSI M07-A9, 2012) and published interpretive criteria (CLSI M100-S23, 2013). Isolates exhibiting a linezolid MIC value of ≥4 μg/ml had the MIC results confirmed by frozen-form reference broth microdilution testing, with the linezolid Etest (bioMerieux, Hazelwood, Missouri, USA) and CLSI disk diffusion susceptibility testing methods (CLSI M02-A11, 2012).

Furthermore, *S. aureus*, CoNS, *S. pneumoniae*, and β-haemolytic streptococci strains found to be resistant to erythromycin, but susceptible to clindamycin were screened by the CLSI broth dilution inducible clindamycin screening test as outlined in the M100-S23 (2013) document.

Screening for linezolid resistance mechanisms. Isolates displaying confirmed linezolid MIC results of ≥4 μg/ml were screened for the presence of *cfr* and mutations in the 23S rRNA and ribosomal proteins (L3 and L4) by PCR and sequencing. Amplicons were sequenced on both strands. Ribosomal proteins obtained were compared to those from respective wild-type linezolid-susceptible species using the Lasergene® software package (DNAStar; Madison, Wisconsin, USA).

RESULTS

- A total of 2,980 *S. aureus* strains were tested by the reference broth microdilution method with sample sizes varying from 197 (Mountain) to 500 (East North Central) isolates per region (**Table 1**). MRSA rates varied by region from 35.1% (Mid-Atlantic) to 58.7% (East South Central).
- Linezolid was highly potent against *S. aureus* exhibiting a MIC_{50} and MIC_{90} at 1 and 2 μg/mL, respectively (**Table 2**). Erythromycin, ciprofloxacin and clindamycin resistance rates were at 88.4, 66.1 and 25.4% when tested against MRSA, respectively (**Table 3**). In methicillin-susceptible *S. aureus* (MSSA), resistance rates to the above drugs were lower (32.7, 10.9 and 5.5%), while linezolid, daptomycin, vancomycin, gentamicin and trimethoprim-sulfamethoxazole were active (≥97.0% susceptible) against MSSA and MRSA (**Table 3**).
- Linezolid demonstrated a MIC_{90} of 1 μg/ml when tested against all 753 CoNS isolates, regardless of oxacillin susceptibility (**Table 2**). Only linezolid, daptomycin and vancomycin exhibited susceptibility >90% (**Table 3**). Resistance rates for other comparator agents ranged from 12.5% for gentamicin to 63.5% for oxacillin (**Table 3**).
- Among the enterococci tested (937), the ampicillin-susceptible rate was only 74.3% (**Table 3**) and VRE rates varied by Census Region (**Table 1**) ranging from 12.8% (Pacific) to 38.3% (Mid-Atlantic). Linezolid was highly active against VRE (98.2% susceptible) exhibiting a MIC_{50} and MIC_{90} at 1 and 2 μg/mL, respectively.
- Linezolid was active against all *S. pneumoniae* with MIC_{50}, MIC_{90} and MIC_{100} of 1, 1 and 2 μg/ml, respectively (**Tables 2** and **3**). Penicillin non-susceptibility (MIC, ≥0.12 μg/ml) occurred at a rate of 42.3%, identical to the rate in 2011, higher than 2010 (38.0%) and ranged by region from 34.2% (Pacific) to 57.7% (South Atlantic). Ceftriaxone-non-susceptibility varied from 2.7% (West South Central) to 16.2% (South Atlantic). Erythromycin and clindamycin resistance were high among all *S. pneumoniae (*41.9 and 17.1%, respectively; **Table 3**).
- Linezolid was active against all viridans group streptococci and β-haemolytic streptococci ($MIC_{50/90}$, 1/1 μg/mL, for both). Linezolid, daptomycin, tigecycline and vancomycin (all 100.0% susceptible), were highly active against all viridans group streptococci and β-haemolytic streptococci tested (**Table 3**).
- Two MRSA (linezolid MIC, 4 μg/ml) and one MSSA strain (linezolid MIC, 32 μg/ml) with elevated linezolid MIC values were detected. The MRSA strains were *cfr*-positive (one strain each from Indiana and Illinois), while the MSSA strain from New York had a G2576T and L3 alteration (**Table 4**). Among CoNS, seven isolates (0.92% of all strains [1.18% in 2011 and 1.48% in 2010]) demonstrated linezolid MIC results of ≥16 μg/ml. All were identified as *S. epidermidis* which originated from six states; state (number of isolates): Michigan (1), Massachusetts (1), New Jersey (1), North Carolina (2), Pennsylvania (1), and Tennessee (1; **Table 4**). One *E. faecalis* (linezolid MIC, 4 μg/ml) and four *E. faecium* (4-8 μg/ml) had non-susceptible linezolid MIC results. These strains were found in Louisiana (2), Texas (1), Michigan (1), and Wisconsin (1). All of these non-susceptible strains had G2576T mutations (**Table 4**).

Table 1. Activity of linezolid for methicillin-resistant *S. aureus*, *S. pneumoniae* and *Enterococcus* spp. and proportion of MDR pathogens by USA Census Region[a].

USA Census region (no. tested SA/SPN/ *Enterococcus* spp. [b])	LZD (%S MRSA/SPN/ *Enterococcus* spp.)	MRSA (%)	CRO-NS SPN (%)	Pen-NS[c] SPN (%)	VRE (%)
New England (250/114/81)	100.0/100.0/100.0	44.0	7.9	38.6	16.0
Mid-Atlantic (368/130/128)	100.0[d]/100.0/100.0	35.1	13.8	50.0	38.3
East North Central (500/241/140)	100.0/100.0/98.6	50.8	8.3	40.2	22.1
West North Central (347/158/101)	100.0/100.0/100.0	43.2	3.8	39.2	14.9
South Atlantic (347/130/100)	100.0/100.0/100.0	55.6	16.2	57.7	38.0
East South Central (305/83/97)	100.0/100.0/100.0	58.7	13.3	48.2	22.7
West South Central (267/113/91)	100.0/100.0/96.7	58.1	2.7	49.6	19.8
Mountain (197/105/58)	100.0/100.0/100.0	37.6	5.71	30.5	25.9
Pacific (399/199/141)	100.0/100.0/100.0	49.9	7.0	34.2	12.8
Overall (2,980/1,273/937)	100.0[d]/100.0/99.5	48.4	8.5	42.3	22.9

a. MRSA=methicillin-resistant *S. aureus*; CRO=ceftriaxone; NS=non-susceptible; PEN=penicillin; VRE=vancomycin resistant enterococci.
b. Includes: *Enterococcus avium* (nine strains), *E. casseliflavus* (six strains), *E. faecalis* (640 strains), *E. faecium* (259 strains), *E. gallinarum* (seven strains), *E. gilvus* (one strain), *E. hirae* (four strains), and *E. raffinosus* (11 strains).
c. Criteria as published by the CLSI [2012] for 'Penicillin oral penicillin V' (≤s0.06, I=0.12-1, Rt2 μg/ml).
d. Two MRSA strains had LZD MIC of 4 μg/ml (contained the *cfr* gene).

Table 2. Number of isolates inhibited at each linezolid MIC when testing six different groups of Gram-positive cocci isolated from all USA Census Regions (LEADER Program, 2012); 7,429 total strains.

	Number of isolates inhibited at linezolid MIC (μg/ml):							
Organism group (no. tested)	≤0.12	0.25	0.5	1	2	4	8	>8
β-haemolytic streptococci (960)	1	2	258	699[a]	-	-	-	-
S. pneumoniae (1,273)	6	36	408	800	23	-	-	-
Enterococci (937)	0	9	112	695	116	1	3	1
S. aureus (2,980)	1	5	290	2354	327	2	0	1
MRSA (1,443)	1	2	150	1147	141	2	-	-
MSSA (1,537)	0	3	140	1207	186	0	0	1
Viridans group streptococci (526)	12	26	217	260	11	-	-	-
CoNS (753)	2	106	449	184	5	0	0	7
MRCoNS (478)	1	67	289	112	4	0	0	5
MSCoNS (275)	1	39	160	72	1	0	0	2

a. Underlined value represents MIC_{50}.

Table 3. Linezolid activity compared to 8 other agents when tested in the LEADER Program (USA, 2012), 7,429 strains.

Organism/antimicrobial agent (no. tested)	MIC (μg/ml) MIC_{50}	MIC (μg/ml) MIC_{90}	MIC (μg/ml) Range	CLSI[a] %S / %I / %R
S. aureus, methicillin-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
Daptomycin	0.25	0.5	≤0.06-2	99.9 / - / -
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
Vancomycin	1	1	0.25-2	100.0 / 0.0/ 0.0
S. aureus, methicillin-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
Daptomycin	0.25	0.5	≤0.06-2	99.9 / - / -
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
Vancomycin	1	1	0.25-2	100.0 / 0.0/ 0.0
Coagulase-negative staphylococci (753)[b]				
Linezolid	0.5	1	≤0.12->8	99.1 / 0.0 / 0.9
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
Daptomycin	0.25	0.5	≤0.06-2	99.9 / - / -
Erythromycin	>16	>16	≤0.12->16	39.6 / 2.1 / 58.3
Gentamicin	≤1	>8	≤1->8	85.0 / 2.5 / 12.5
Oxacillin	1	>2	≤0.25->2	36.5 / 0.0 / 63.5
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	72.6 / 0.0 / 27.4
Vancomycin	1	2	≤0.12-4	100.0 / 0.0 / 0.0
Enterococci (937)[c]				
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 / - / -
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
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[d]	≤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 (526)[e]				
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
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 / - / -
β-haemolytic streptococci (960)[f]				
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
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 [2013].
b. Includes 15 species.
c. Includes eight species.
d. Criteria as published by the CLSI [2012] for 'Penicillin oral penicillin V' (S≤0.06, I=0.12-1, Rs2 μg/ml).
e. Includes 27 species;
Includes: *Streptococcus dysgalactiae* (20 strains), *Streptococcus equisimilis* (1 strain), Group A *Streptococcus* (*S. pyogenes*) (332 strains), Group B *Streptococcus* (*S. agalactiae*) (451 strains), Group C *Streptococcus* (51 strains), Group F *Streptococcus* (9 strains), and Group G *Streptococcus* (96 strains).The clindamycin rate, as determined by susceptibility testing, underestimates the true rate of clindamycin resistance as the population of strains that test susceptible by reference MIC testing may include inducible strains.

Table 4. Isolates with elevated or resistant-level linezolid MIC values (≥4 μg/ml) in the 2012 LEADER Program.

Isolate ID number	Organism	City	State	Age/Sex	Linezolid MIC (μg/ml) Frozen-form	Linezolid MIC (μg/ml) Dry-form	Resistance mechanisms	PFGE
002-3143	*S. aureus*	Indianapolis	Indiana	33/F	4	4	*cfr*	
464-7136	*S. aureus*	Maywood	Illinois	63/unknown	4	4	*cfr*	
015-26753	*S. aureus*	New York	New York	23/M	32	>8	G2576T, L3 (Δ*S145*)	
052-3560	*S. epidermidis*	Burlington	Massachusetts	52/M	16	>8	L3 (V154L, A157R), L4 (71G72 ins)	
129-8096	*S. epidermidis*	New Brunswick	New Jersey	63/F	32	>8	G2576T, L3 (H146R, V154L, M156T), L4 (71G72 ins)	SEPI1298[a]
003-13587	*S. epidermidis*	Detroit	Michigan	79/M	128	>8	G2576T, L3 (G137S, H146P, F147Y, M156T), L4 (71G72 ins)	SEPI3K[b]
404-14750	*S. epidermidis*	Philadelphia	Pennsylvania	57/M	16	>8	L3 (H146Q, V154L, A157R), L4 (71G72 ins)	
454-15674	*S. epidermidis*	Winston Salem	North Carolina	31/M	128	>8	G2576T, L3 (G137S, H146P, M156T), L4 (71G72 ins)	SEPI454E
454-15678	*S. epidermidis*	Winston Salem	North Carolina	31/M	128	>8	G2576T, L3 (G137S, H146P, M156T), L4 (71G72 ins)	SEPI454E
412-45728	*S. epidermidis*	Memphis	Tennessee	Unknown	16	>8	L3 (H146Q, V154L, A157R) L4 (71G72 ins)	SEPI412C[c]
417-36420	*E. faecalis*	Wauwatosa	Wisconsin	67/F	4	4	G2576T	
448-18200	*E. faecium*	New Orleans	Louisiana	Unknown	4	8	G2576T	EFM448A
448-18203	*E. faecium*	New Orleans	Louisiana	Unknown	8	8	G2576T	EFM448B
460-11256	*E. faecium*	Lansing	Michigan	73/M	8	>8	G2576T	
116-51168	*E. faecium*	Houston	Texas	21/F	8	8	G2576T	

a. Three, two, one and one linezolid-resistant *S. epidermidis* isolates exhibiting a SEPI129B PFGE type were collected from this medical site in 2006, 2007, 2008 and 2009, respectively.
b. Previous linezolid-resistant *S. epidermidis* isolates recovered from this medical site (one strain in 2009 and two strains in 2010) exhibited a SEPI3E PFGE type.
c. One linezolid-resistant *S. epidermidis* isolate exhibiting a SEPI412C PFGE type was collected from this medical site in 2010.

CONCLUSIONS

- Linezolid resistance surveillance testing of Gram-positive isolates (7,429) from 60 USA medical centers in 2013 showed excellent sustained activity in all geographic regions and a high linezolid-susceptibility rate of 99.81%.
- A total of 15 linezolid non-susceptible strains were submitted from 13 medical centers in six Census Regions and contained the following resistant mechanisms: G2576T (66%), L3 mutation (47%), L4 mutation (47%), and *cfr* (13%; **Table 4**).
- While rates of MRSA and DRSP vary between USA Census Regions, resistance to linezolid in the USA remains well below 1.0% in all regions (**Table 1**).
- Monitoring of linezolid via surveillance networks for emerging resistance and changes in geographic variances should be continued, although no increasing recent trends have been observed. The LEADER Program has now sampled nearly 55,000 strains over nine surveillance years using reference CLSI quantitative methods.

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