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Linezolid Experience and Accurate Determination of Resistance (LEADER) Program 2006: Emerging Oxazolidinone and Inducible Clindamycin Resistances

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ABSTRACT

Background: LEADER has completed 3 years (2004-2006) of USA surveillance for linezolid (LZD), the first oxazolidinone class agent to be licensed for use in clinical practice. LZD has emerged as a valuable alternative for infections caused by resistant (R) Gram-positive (GP) organisms, such as methicillin-R *S. aureus* (MRSA), drug-resistant *S. pneumoniae* (DRSP) and vancomycin-resistant enterococci (VRE).

Methods: 5,374 GP pathogens isolated in 50 USA medical centers (MCs) were sent to a central laboratory for identification confirmation and CLSI broth microdilution susceptibility (S) testing. Sites were distributed throughout the 9 census regions and participants submitted 100 isolates in the following organism groups (no.): *S. aureus* (SA; 2,913), coagulase-negative staphylococci (CoNS; 808), enterococci (ENT, 547), *S. pneumoniae* (SPN; 546), viridans group (VGS; 189) and ß-haemolytic streptococci (BHS; 371). Molecular studies were also performed to identify R mechanisms and clonality within or between MCs.

Results: Table. LZD activity in the USA by year

Organisms (no., all years)	% non-susceptible or resistant 2004	2005	2006
S. aureus (8,806)	0.00	0.03	0.03
CoNS (1,834)	0.20	1.13	1.61
Enterococci (1,954)	0.80	0.64	1.83
All streptococci[a] (1,979)	0.00	0.00	0.00
All organisms (14,573)	0.14	0.24	0.45

a. Includes: SPN (1,419), VGS (189) and BHS (371).

One MRSA strain was detected as non-S to LZD, and only 3 SA had a LZD MIC of 4 µg/ml (susceptible breakpoint). MRSA rates in US regions ranged from 49% to 66%. 13 CoNS from 8 different MCs were LZD-R along with another 10 ENT isolates (VRE rate was 28.0%). All ENT or CoNS with characterized R had previously described G2576T mutations and clonality within MCs was common. No R was observed among streptococci. Inducible clindamycin (CC)-R was 39.4% among erythromycin-R, CC-S SA strains.

Conclusions: LZD displayed sustained activity throughout the 50 USA medical centers and 9 census regions with a high S rate (99.45%). No evidence of LZD MIC creep was detected among indicated species. Rare LZD-R was noted among enterococci and CoNS with a slight year-to-year increase.

INTRODUCTION

The LEADER Program has two years of experience (2004, 2005) providing United States (USA) resistance surveillance information for linezolid, the first oxazolidinone class agent to be licensed for use in clinical practice. Linezolid has been used primarily to treat Gram-positive pathogens associated with complicated skin and soft tissue infections (cSSTI) and nosocomial pneumonias, after its USA-Food and Drug Administration approval in early 2000. Linezolid has emerged as a viable alternative for infections caused by Gram-positive organisms that are resistant to conventional drugs, such as methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae* (DRSP) and vancomycin-resistant enterococci (VRE). Therefore, it is prudent to monitor the potency and potential emerging resistance to oxazolidinones as the use of this agent increases, in volume and geographic distributions.

The linezolid 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. Among the rare cases of linezolid resistance reported to date for staphylococci and enterococci, G2576 or T2500 target site mutations have been the typical mechanism.

The 2002 and 2003 ZAAPS Program monitored linezolid resistance in countries around the world including the USA. Since 2004, the ZAAPS Program surveyed only the "rest of world" (not USA) while the USA was separated (LEADER) and expanded to 50 sample sites. This report summarizes the LEADER program (2006) findings from laboratories distributed evenly across the USA. A total of 5,374 strains (107.5% compliance to protocol) were tested in this resistance surveillance initiative.

MATERIALS AND METHODS

The medical centers were selected to represent all nine USA Bureau of Census geographic zones or regions (5-7 sites/region) as follows: Pacific (California [3], Hawaii [1], Washington [3]), Mountain (Arizona [2], Colorado [2], Utah [1]), West North Central (Iowa [1], Kansas [1], Missouri [2], Nebraska [1]), West South Central (Arkansas [1], Texas [4]), East North Central (Illinois [1], Indiana [1], Michigan[1], Ohio [2], Wisconsin [2]), East South Central (Alabama [1], Kentucky [2], Tennessee [2]), New England (Connecticut [1], Maine [1], Massachusetts [2], Vermont [1]), Middle Atlantic (Pennsylvania [1], New York [3], New Jersey [2]), and South Atlantic (Florida [2], Maryland [1], North Carolina [1], Virginia [1]).

Each medical center was instructed to forward 100 organisms with the following species distribution: *S. aureus* (50 strains, approximate one-half MRSA), coagulase-negative staphylococci (CoNS; 20 strains), enterococci (10 strains), *S. pneumoniae* (10 strains), and ß-haemolytic streptococci and viridans group streptococci (five strains each). The strains should be dominantly from bacteremias although isolates from documented pneumonia, cutaneous wound infections and urinary tract infections were acceptable. The forwarded clinical isolates (5,374) were distributed among the following organism groups: *S. aureus* (2,913), CoNS (808), enterococci (547), *S. pneumoniae* (546), viridans group streptococci (189) and ß-haemolytic streptococci (371).

All tests were performed in a GLP reference laboratory (JMI Laboratories, North Liberty, Iowa) using Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) broth microdilution methods and published interpretive criteria. Linezolid-resistant isolates were confirmed with the linezolid Etest (AB BIODISK, Solna, Sweden) and disk diffusion susceptibility testing. Molecular testing was performed on linezolid-resistant isolates to identify the 23S rRNA target site mutations and potential clonality using PFGE, automated ribotyping and various PCR procedures. Also, *S. aureus* strains found to be resistant to erythromycin and susceptible to clindamycin were screened by the CLSI D-test method to detect inducible clindamycin resistance.

RESULTS

- A total of 2,913 *S. aureus* strains were tested by the reference broth microdilution method with sample sizes varying from 262 (New England) to 442 (East North Central) isolates per region. MRSA rates could not be accurately determined as sites were instructed to send approximately 50%. Participant sites complied closely to the request and the overall MRSA rate was 56.6%; range 49.2% (West North Central) to 66.3% (East North Central).
- The linezolid MIC_{90} for *S. aureus* was 2 µg/ml, however, when the MRSA and MSSA was examined separately, the modal linezolid MIC for MRSA was lower (1 µg/ml) compared to the MSSA strains (2 µg/ml). This observation has also been noted with MRSA from the non-USA 2006 ZAAPS Program. A single linezolid-resistant MRSA strain was isolated (Seattle, Washington; MIC, 8 µg/ml with a G2576T mutation). The linezolid percentage susceptibility for the 2,913 *S. aureus* was 99.97%.
- The all region CoNS linezolid MIC_{90} was 1 µg/ml and no significant differences were noted in linezolid MIC distributions when comparing oxacillin-resistant and -susceptible isolates. Thirteen CoNS isolates had a linezolid MIC of >8 µg/ml (non-susceptible) and these strains were detected in 7 of the 9 census regions, in 6 different states, and in 8 medical centers. These species included *S. epidermidis* (11 strains) and *S. haemolyticus* (two strains). Table 3 illustrates that two epidemic clusters were identified in hospitals in New Jersey (pattern B1/54.4) and Wisconsin (pattern A/328.5).
- Among enterococcal strains, the ampicillin-susceptible rate was only 67.8% and VRE rates varied by USA census region from 11.3% (Pacific) to 49.3% (East North Central). The VRE rate for the entire enterococcal sample was 28.0% and the VanA resistance phenotype represented 88.2% of these VRE isolates.

  Linezolid and daptomycin were the most active agents tested with susceptibility rates at 97.4% and 99.8%, respectively. A total of 10 enterococci (seven *E. faecium* and three *E. faecalis*; 8 states) had a linezolid MIC at >8 µg/ml (Tables 1-3). Clonal analyses indicated that where more than one linezolid-resistant enterococcal strain was documented in the LEADER program site sample, a clonal outbreak was highly probable (Table 4).
- High-level penicillin resistance (MIC, ≥2 µg/ml) among pneumococci occurred at a rate of 13.2% (range 6.3% [Pacific] to 23.1% [West North Central]) and erythromycin resistance (MIC, ≥1 µg/ml) was two-to three-fold higher than penicillin rates at 30.2% (range, 16.3% [Pacific] to 48.1% [West North Central]). Ciprofloxacin MIC values at ≥4 µg/ml [Chen et al. 1999] accounted for 2.7% of the *S. pneumoniae*, a statistic indicating possible single-step mutations (usually in *parC*).

  Linezolid was active against all *S. pneumoniae* (MIC_{50} and MIC_{90}, 1 µg/ml) and only 1.6% of strains had a MIC at 2 µg/ml (susceptible breakpoint), see Table 2.

Table 1. Linezolid activity compared to 14 other agents when tested in the LEADER Program (USA, 2006), 5,374 strains.

Pathogen (no. tested)/antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category: Susceptible/Resistant
S. aureus (2,913)				
Linezolid	2	2	0.25-8	>99.9 / -
Ciprofloxacin	0.5	>4	≤0.03->4	52.5 / 45.6
Clindamycin	≤0.25	>2	≤0.25->2	75.0 / 24.8
Daptomycin	0.25	0.5	≤0.06-2	99.9 / -
Erythromycin	>2	>2	≤0.25->2	34.0 / 65.8
Gentamicin	≤2	≤2	≤2->8	96.8 / 2.9
Oxacillin[a]	>2	>2	≤0.25->2	43.4 / 56.6
Quinupristin/dalfopristin	0.5	0.5	≤0.25-2	99.9 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	97.3 / 2.7
Vancomycin	1	1	0.25-4	99.9 / 0.0
Coagulase-negative staphylococci (808)				
Linezolid	1	1	≤0.06->8	98.4 / -
Ciprofloxacin	4	>4	≤0.03->4	42.2 / 56.9
Clindamycin	≤0.25	>2	≤0.25->2	59.9 / 38.4
Daptomycin	0.25	0.5	≤0.06-1	100.0 / -
Erythromycin	>2	>2	≤0.25->2	28.8 / 70.8
Gentamicin	≤2	>8	≤2->8	71.3 / 15.4
Oxacillin[a]	>2	>2	≤0.25->2	23.1 / 76.9
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-2	99.3 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	61.9 / 38.1
Vancomycin	1	2	≤0.12-2	100.0 / 0.0
Enterococci (547)				
Linezolid	1	2	0.25->8	97.4 / 1.8
Ampicillin[a]	≤1	>16	≤1->16	67.8 / 32.2
Ciprofloxacin	4	>4	≤0.03->4	46.4 / 51.6
Daptomycin	1	2	≤0.06->8	99.8 / -
Gentamicin (high-level)	≤500	>1000	≤500->1000	76.2 / 23.8
Quinupristin/dalfopristin	>2	>2	≤0.25->2	31.1 / 63.8
Streptomycin (high level)	≤1000	>2000	≤1000->2000	68.2 / 31.8
Teicoplanin	≤2	>16	≤2->16	72.8 / 24.7
Vancomycin	1	>16	0.25->16	71.7 / 28.0
S. pneumoniae (546)				
Linezolid	1	1	≤0.06-2	100.0 / -
Amoxicillin/clavulanic acid	≤1	2	≤1-16	90.8 / 6.2
Ceftriaxone	≤0.25	1	≤0.25-8	98.0 / 0.5
Ciprofloxacin	1	2	0.25->4	(2.7)[b]
Clindamycin	≤0.25	>2	≤0.25->2	84.2 / 15.2
Erythromycin	≤0.25	>2	≤0.25->2	69.4 / 30.2
Levofloxacin	1	1	≤0.5->4	99.6 / 0.4
Penicillin	≤0.03	2	≤0.03-8	67.0 / 13.2
Vancomycin	≤1	≤1	≤1	100.0 / -
Viridans group streptococci (189)				
Linezolid	0.5	1	≤0.06-1	100.0 / -
Ceftriaxone	≤0.25	1	≤0.25-32	95.2 / 3.7
Ciprofloxacin	1	4	≤0.03->4	(12.7)[b]
Clindamycin	≤0.25	>2	≤0.25->2	88.4 / 11.1
Daptomycin	0.25	0.5	≤0.06-1	100.0 / -
Erythromycin	1	>2	≤0.25->2	45.0 / 54.0
Levofloxacin	1	2	≤0.5->4	93.1 / 5.8
Penicillin[a]	0.06	1	≤0.015-4	72.5 / 3.7
Vancomycin	0.5	1	≤0.12-1	100.0 / -
ß-haemolytic streptococci (371)				
Linezolid	1	1	0.12-2	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -
Ciprofloxacin	0.5	1	0.06->4	(1.9)[b]
Clindamycin	≤0.25	>2	≤0.25->2	86.5 / 12.4
Daptomycin	0.12	0.25	≤0.06-0.5	100.0 / -
Erythromycin	≤0.25	>2	≤0.25->2	70.6 / 28.8
Levofloxacin	≤0.5	1	≤0.5->4	98.4 / 1.1
Penicillin[a]	0.03	0.06	≤0.015-0.12	100.0 / -
Vancomycin	0.5	0.5	≤0.12-1	100.0 / -

a. Criteria as published by the CLSI, ß-lactam susceptibility should be directed by the oxacillin test results with staphylococci. Enterococcal susceptibility was predicted by ampicillin results and penicillin was the agent used for streptococcal activity for selected ß-lactams.
b. Percentages in parentheses are the strains having a ciprofloxacin MIC at ≥4 µg/ml, possible QRDR mutations.

- Penicillin non-susceptibility (MIC, ≥0.25 µg/ml) was noted for 27.5% of viridans group streptococci tested. This resistance pattern minimally varied by census region from 21.9% (Mid-Atlantic) to 47.1% (Mountain). An unexpected finding was the elevated level of fluoroquinolone resistance as represented by levofloxacin (5.9%). Also, the ciprofloxacin MIC values at ≥4 µg/ml was a striking 12.7%. Linezolid MIC values among these streptococci were consistently between 0.25 and 1 µg/ml (MIC_{90}, 1 µg/ml, see Table 2).
- Significant resistances were identified for erythromycin (28.8%), clindamycin (12.4%) and tetracycline (49.3%) among ß-haemolytic streptococci. The constitutive MLS_B resistance patterns (erythromycin- and clindamycin-resistant) as a percentage of all macrolide-resistant strains by region were: Pacific (53.1%), Mountain (28.6%), West North Central (45.5%), West South Central (53.3%), East North Central (39.0%), East South Central (45.4%), New England (24.9%), Mid-Atlantic (30.7%), and South Atlantic (57.2%). These high (Southeast, Midwest and Pacific areas) and regionally different rates of MLS_B resistance patterns demonstrate the declining utility of this class. The linezolid MIC range was only 0.12-2 µg/ml with a clear modal MIC, MIC_{50} and MIC_{90} at 1 µg/ml (Table 3).
- In Table 4, the results for testing *S. aureus* strains of the erythromycin-resistant, clindamycin-susceptible (ERCS) phenotype to detect an inducible clindamycin resistance are displayed (1,181 tests). The CLSI D-test showed an overall resistance induction rate of 39.4% among ERCS phenotype *S. aureus*.
- Table 2 shows the overall activities of linezolid versus all tested strains for the six organism groups. Generally, linezolid MIC distributions are narrow with near 100.0% of results within three doubling dilutions. This characteristic of central tendencies for linezolid potency has been consistent within ZAPS, ZAAPS and LEADER program reports and publications for nearly six years.

Table 2. Cumulative percentage inhibited results at each linezolid MIC when testing six different groups of Gram-positive cocci isolated for all USA Census regions (LEADER Program, 2006)[a].

Organism group (no. tested)	Cumulative % inhibited at linezolid MIC (µg/ml): ≤0.25	0.5	1	2	4	8	>8
Viridans group streptococci (189)	8.5	51.9	100.0	-	-	-	-
S. pneumoniae (546)	5.5	33.5	98.4	100.0	-	-	-
ß-haemolytic streptococci (371)	1.3	25.1	99.7	100.0	-	-	-
CoNS (808)	2.5	43.2	96.9	98.1	98.4	98.4	100.0[b]
Enterococci (547)	0.7	7.3	68.4	97.4	98.2	99.1[c]	100.0[c]
S. aureus (2,913)	0.2	1.3	49.7	99.9	>99.9	100.0[d]	-

a. Organism groups were ranked in decreasing order of susceptibility to the oxazolidinone.
b. 13 strains from Florida(3), Kentucky(1), Nebraska(1), New Jersey(3), Texas(3) and Wisconsin(2).
c. 10 strains from Arkansas(1), California(1), Florida(1), Illinois(1), New Jersey(1), Ohio(1), Tennessee(1) and Texas(3); *E. faecalis* (3) and *E. faecium* (7).
d. One strain from Seattle, Washington.

- Trends in linezolid resistance in the LEADER Program have been reported by Draghi et al. for organisms sampled in 2004 and 2005. The resistance rates have increased by roughly two-fold each year (Table 5), driven by resistances detected among the *E. faecium* and CoNS (*S. epidermidis* and *S. haemolyticus*) isolates. This recent rise in non-susceptibility has been fostered by documented clonal dissemination of mutant strains within the monitored hospitals (Table 3).

Table 3. *Enterococcus* spp. and CoNS isolates non-susceptible to linezolid (MIC values, ≥4 and ≥8 µg/ml, respectively) by reference testing.

Organism	Isolate	State (site)	Linezolid MIC	Mutation	PFGE	Ribotype	LEADER Report[a]	Clonal
E. faecium	533	Texas (1)	4	G2576T	A	258.320.3	Yes	Yes
E. faecium	534	Texas (1)	8	G2576T	A	258.320.3	Yes	Yes
E. faecium	575	Texas (1)	8	G2576T	A	258.320.3	Yes	Yes
E. faecium	538	Texas (1)	>8	G2576T	NT	258.319.5	Yes	-
E. faecium	1767	Arkansas	>8	G2576T	A	258.321.2	Yes	Yes
E. faecium	5534	Arkansas	>8	G2576T	A	258.321.2	No	Yes
E. faecium	5047	Ohio	>8	G2576T	B	NT	Yes	Yes
E. faecium	3817	Ohio	8	G2576T	B	NT	No	Yes
E. faecium	2067	New Jersey (2)	8	G2576T	NT	NT	Yes	-
E. faecium	2132	Illinois	8	G2576T	B	NT	Yes	-
E. faecalis	1000	California	8	G2576T	NT	NT	Yes	-
E. faecalis	1142	Tennessee	>8	G2576T	NT	NT	Yes	-
E. faecalis	2014	Florida (2)	>8	G2576T	NT	NT	Yes	-
S. epidermidis	5494	New Jersey (1)	>8	G2576T	B1	253.54.4	Yes	Yes
S. epidermidis	6431	New Jersey (1)	>8	G2576T	B1	253.54.4	Yes	Yes
S. epidermidis	512	Texas (1)	>8	Negative	A	105.1109.6	Yes	-
S. epidermidis	513	Texas (1)	>8	G2576T	B	105.328.5	Yes	-
S. epidermidis	692	Wisconsin	>8	G2576T	A	105.328.5	Yes	Yes
S. epidermidis	750	Wisconsin	>8	G2576T	A	105.328.5	Yes	Yes
S. epidermidis	805	Florida (1)	>8	Negative	NT	258.334.6	Yes	-
S. epidermidis	850	Florida (1)	>8	G2576T	A	105.1109.6	Yes	-
S. epidermidis	856	Florida (1)	>8	G2576T	NT	258.334.7	Yes	-
S. epidermidis	11107	Nebraska	>8	G2576T	NT	NT	Yes	-
S. epidermidis	7625	Texas (2)	>8	Negative	NT	NT	Yes	-
S. haemolyticus	2322	Kentucky	>8	G2576T	A	105.871.4	Yes	-
S. haemolyticus	2061	New Jersey (2)	>8	G2576T	NT	258.334.3	Yes	-

a. Yes = strain found in the LEADER Program sample, No = supplemental strain from the same medical center occurring in the same year and sampled for epidemiologic analysis only.

Table 4. Rates of inducible clindamycin-resistant *S. aureus* detected among 50 medical centers in 31 states (nine USA Census regions or zones) in 2006.

Region	State (no. sites)	D-tests[a] No.	% positive (range)
Pacific	California (3)	61	27.9 (10.0-52.6)
	Hawaii (1)	24	4.2 (4.2)
	Washington (3)	96	21.9 (7.8-52.2)
Mountain	Arizona (2)	30	26.7 (16.7-25.0)
	Colorado (2)	32	34.4 (0.0-52.4)
	Utah (1)	45	31.1 (31.1)
West North Central	Iowa (1)	37	62.2 (62.2)
	Kansas (1)	13	38.5 (38.5)
	Missouri (2)	57	28.1 (21.2-37.5)
	Nebraska (1)	19	31.6 (31.6)
West South Central	Arkansas (1)	38	23.7 (23.7)
	Texas (4)	68	26.5 (12.5-50.0)
East North Central	Illinois (1)	20	25.0 (25.0)
	Indiana (1)	22	50.0 (50.0)
	Michigan (1)	20	45.0 (45.0)
	Ohio (2)	48	58.3 (46.4-85.0)
	Wisconsin (2)	47	31.9 (23.5-36.7)
East South Central	Alabama (1)	33	15.2 (15.2)
	Kentucky (2)	49	42.9 (35.3-60.0)
	Tennessee (2)	69	34.8 (26.7-41.0)
New England	Connecticut (1)	28	39.3 (39.3)
	Maine (1)	14	78.6 (78.6)
	Massachusetts (2)	48	79.2 (66.7-91.7)
	Vermont (1)	25	60.0 (60.0)
Middle Atlantic	New Jersey (2)	42	52.4 (44.8-69.2)
	New York (3)	51	60.8 (50.0-70.0)
	Pennsylvania (1)	19	36.8 (36.8)
South Atlantic	Florida (2)	56	35.7 (30.0-42.3)
	Maryland (1)	24	62.5 (62.5)
	North Carolina (1)	18	55.6 (55.6)
	Virginia (1)	28	57.1 (57.1)

a. D-test as performed by the CLSI disk diffusion method (M2-A9, 2006; M100-S17, 2007).

Table 5. Three year trends in linezolid non-susceptibility results in the LEADER Program (2004-2006) and this report.

Organisms (no. tested)	% linezolid non-susceptible or resistant 2004	2005	2006
S. aureus (8,806)	0.00	0.03	0.03
CoNS (1,834)	0.20	1.13	1.61
Enterococci (1,954)	0.80	0.64	1.83
S. pneumoniae (1,419)	0.00	0.00	0.00
viridans group streptococci (189)	NT[a]	NT	0.00
ß-haemolytic streptococci (371)	NT	NT	0.00
All organisms (14,573)	0.14	0.24	0.45

a. NT = not tested.

CONCLUSIONS

- The introduction of the oxazolidinone, linezolid, greatly facilitated the therapy of infections caused by Gram-positive pathogens resistant to other antimicrobial classes and rates of resistance must be placed in perspective by structured, prospective risk management surveillance programs that sample routine, invasive isolates across wide geographic areas and additionally incorporate molecular evaluations of resistance mechanisms and local epidemiology.
- Linezolid MIC population distributions remained unchanged without evidence of "MIC creep" among indicated species. Inducible clindamycin resistance among ERCS phenotype *S. aureus* strains was 39.4%. Observed differences or variations among medical centers will require local D-tests of each strain to appropriately guide clindamycin therapy.
- Linezolid resistances were noted among enterococci (10 of 547 strains; 1.83%) and CoNS (13 of 808 strains; 1.61%). These rates represent slight increases compared to 2004 and 2005 LEADER results; and the all organism linezolid-non-susceptible rates increased from 0.14% (2004) to 0.24% (2005) to 0.45% (2006).
- Resistances to other highly active Gram-positive focused agents were also documented that included daptomycin non-susceptibility (MIC, >1 µg/ml; 0.1%) among *S. aureus* and enterococci, teicoplanin-intermediate CoNS strains (data not shown), VISA isolates (0.1%), quinupristin/dalfopristin non-susceptible strains (*S. aureus*, CoNS and *E. faecium*; 0.4%), and levofloxacin-resistant streptococci (highest among viridans group streptococci at 5.8%).
- Concurrent molecular epidemiology and mechanisms of resistance testing for the linezolid-resistant strains implicated epidemic or endemic clonal dissemination in many of the monitored medical centers (Table 3).

SELECTED REFERENCES

1. Anderegg TR, Sader HS, Fritsche TR, Ross JE, Jones RN (2005). Trends in linezolid susceptibility patterns: Report from the 2002-2003 worldwide Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program. *Int J Antimicrob Agents* 26: 13-21.
2. Chen DK, McGeer A, de Azavedo JC, Low DE (1999). Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. Canadian Bacterial Surveillance Network. *N Engl J Med* 341: 233-239.
3. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute. (2007). *M100-S17, Performance standards for antimicrobial susceptibility testing, 17th informational supplement*. Wayne, PA: CLSI.
5. Clinical and Laboratory Standards Institute. (2006). *M2-A9. Performance standards for antimicrobial disk susceptibility tests; approved standard - ninth edition.* Wayne, PA: CLSI.
6. Diekema DJ, Jones RN (2001). Oxazolidinone antibiotics. *Lancet* 358: 1975-1982.
7. Draghi DC, Sheehan DJ, Hogan P, Sahm DF (2005). In vitro activity of linezolid against key gram-positive organisms isolated in the United States: Results of the LEADER 2004 surveillance program. *Antimicrob Agents Chemother* 49: 5024-5032.
8. Draghi DC, Sheehan DJ, Hogan P, Sahm DF (2006). Current antimicrobial resistance profiles among methicillin-resistant *Staphylococcus aureus* encountered in the outpatient setting. *Diagn Microbiol Infect Dis* 55: 129-133.
9. Ross JE, Anderegg TR, Sader HS, Fritsche TR, Jones RN (2005). Trends in linezolid susceptibility patterns in 2002: Report from the worldwide Zyvox Annual Appraisal of Potency and Spectrum Program. *Diagn Microbiol Infect Dis* 52: 53-58.
10. Zyvox Package insert. Pfizer 2004. Available at http://www.pfizer.com/pfizer/download/uspi_zyvox.pdf.