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First Annual Report from the Worldwide ZAAPS Oxazolidinone Resistance and Usage Surveillance Program (2002)

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AMENDED ABSTRACT

Background: Linezolid (LZD), the first clinically used oxazolidinone (OXA), was introduced into practice (USA) in April 2001. Prior OXA surveillance results indicated no resistant (R) Gram-positive pathogens, however R cases have emerged in 2002 among *S. aureus* and enterococci. The ZAAPS Program monitors for the occurrence of OXA-R across 4 continents.

Methods: A total of 200 Gram-positive species samples were collected in 2002 from 54 laboratories in North America (3 nations/33 sites), Europe (6/16), South America (1/2), South Korea (1/1) and Taiwan (1/2). All 7,971 tests were performed in a central laboratory using reference methods (NCCLS, M7-A6). LZD-use statistics were collected from USA sites and correlated to emergence of OXA-R strains.

Results: The results follow in the table:

Organism (no. tested)	MIC$_{90}$ (μg/ml)/% susceptible (S) North America	South America	Europe	Far East	Mode MIC (no. at mode)
S. aureus (3,687))	2/>99.9[a]	2/100	2/100	2/100	2 (2,521)
Coag-neg staph (870)	2/>99.9[a]	2/100	1/100	1/100	1 (657)
Enterococci (1,070)	2/99.8[a]	2/100	2/100	2/100	2 (635)
ß-haem strept (387)	1/100	1/100	1/100	1/100	1 (344)
vir. gr. strept (187)	1/98.4[a]	1/100	1/100	1/100	1 (133)
S. pneumoniae (1,770)	1/100	1/100	1/100	1/100	1 (840)
All isolates (7,971)	-	-	-	-	1 (3,496)

a. 4 isolates from the USA (4 states; 4 species) with G2576U mutations.

No significant variation in LZD potency was noted between geographic regions by species or in the MIC distribution and over time compared to the premarketing ZAPS studies. LZD-use data was obtained for 2.8 million patient hospital days (USA; 10,472 beds). Overall, LZD use was 0.4 DDD/100 pt days (range, 0.1 - 1.1). Among LZD-R cases (4), only 2 patients had prior LZD exposure and hospital use rates were 0.1, 0.1, 0.4, 0.5 DDD/100 pt days. No correlation of total hospital LZD use and R was detected.

Conclusions: LZD was active against 99.95% of tested Gram-positive organism in the ZAAPS Program (2002). Four LZD-R strains were detected (USA only) representing different species (*S. aureus*, CoNS, vir. gr. streptococci and *E. faecium*). OXA-R remains rare and post-marketing surveillance appears capable of detecting emerging R risk.

INTRODUCTION

Increasing antimicrobial resistance in staphylococci, streptococci and enterococci has been well documented over the last two decades for the most commonly utilized antimicrobial agents (oxacillin, penicillin, vancomycin). These increasing antimicrobial resistance rates have necessitated the search for novel agents and new antimicrobial classes. One of the newer antimicrobial classes is the oxazolidinones with the release of linezolid into clinical practice in April 2000. Linezolid has become an excellent therapeutic alternative for the treatment of serious infections involving Gram-positive organisms.

The Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program has been developed to monitor for the emergence of linezolid resistance in > 50 medical centers in North America, Europe, South America, Korea and Taiwan. To date, most linezolid resistance has been documented from individual cases with prior long-term exposure to linezolid, usually in North America.

Table 1. Distribution of organism identifications for the 2002 ZAAPS sample indexed by nation of origin (7,971 strains).

Nation (no. medical centers)	No of strains ß-streptococci	vir. gr. streptococci	*S. pneumoniae*	Enterococci	*S. aureus*	CoNS	Total
Canada (5)	54	23	235	105	417	106	940
United States (25)	262	61	1,127	650	2,478	454	5,032
Mexico (3)	4	9	2	44	83	58	200
Brazil (2)	6	5	22	17	115	35	200
France (4)	9	12	40	15	92	32	200
Germany (3)	4	2	84	34	55	21	200
Italy (3)	0	0	45	37	83	35	200
Spain (3)	6	5	39	36	81	33	200
Sweden (1)	8	7	87	23	43	32	200
United Kingdom (2)	15	15	51	21	93	5	200
Korea (1)	0	18	38	40	51	52	199
Taiwan (2)	19	30	0	48	96	7	200
TOTAL (54)	387	187	1,770	1,070	3,687	870	7,971

MATERIALS & METHODS

A total of 7,971 bacterial isolates (Table 1) were collected for the Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program. Each participant site forwarded a total of 200 Gram-positive strains for processing in 2002. The sites were divided into distinct regions which included: North America (three nations/33 sites), Europe (six nations/16 sites), South America (one nation/two sites) and the Far East (two nations/three sites). Isolate groups were *Staphylococcus aureus* (3,687 strains), coagulase-negative staphylococci (870 strains), ß-haemolytic streptococci (387 strains), viridans group streptococci (187 strains), *Streptococcus pneumoniae* (1,770 strains) and enterococci (1,070 strains).

Isolates were tested against a Gram-positive panel including 22 antimicrobial agents; linezolid, amoxicillin/clavulanic, ampicillin, cefepime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, doxycycline, erythromycin, gentamicin, levofloxacin, nitrofurantoin, oxacillin, penicillin, quinupristin/dalfopristin, rifampin, streptomycin, teicoplanin, tetracycline, trimethoprim/sulfamethoxazole and vancomycin.

Susceptibility testing was performed on validated commercial dry-form reference broth microdilution panels supplied by TREK Diagnostics (Cleveland, OH) by methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS). An initial bacterial suspension equal to a 0.5 McFarland Standard was prepared for each isolate, diluted 1/200 then inoculated with a Sensititre autoinoculator into the panels to approximate 5 x 10^5 CFU/ml. After incubation in an ambient air environment at 35ºC for 20 - 24 hours, antimicrobial susceptibility was determined by visual inspection for growth and interpreted by NCCLS recommendations. Concurrent susceptibility quality control strains (*Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619) were tested.

Table 2. Comparisons of linezolid and nine other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for *S. aureus* (3,687 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	2	2	0.25-16	>99.9	[b]
Ciprofloxacin	0.5	>4	≤0.25->4	59.9	39.2
Clindamycin	0.12	>8	≤0.06->8	69.0	30.9
Erythromycin	1	>8	≤0.06->8	49.6	49.5
Gentamicin	≤2	8	≤2->8	89.9	9.7
Oxacillin	0.5	>8	≤0.06->8	62.0	38.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-8	99.8	0.1
Tetracycline	≤4	≤4	≤4->8	90.8	8.4
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.9	5.1
Vancomycin	1	1	0.25-2	100.0	0.0

a. Susceptibility interpretive criteria of the NCCLS [2003].
b. One linezolid-resistant strain was observed (MIC, 16 μg/ml): with a G2576U mutation.

Table 3. Comparisons of linezolid and nine other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for CoNS (870 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	1	2	≤0.25-2	>99.9	[b]
Ciprofloxacin	>2	>2	≤0.25->2	46.4	51.3
Clindamycin	0.12	>8	≤0.06->8	58.6	41.1
Erythromycin	>8	>8	≤0.06->8	29.0	67.8
Gentamicin	≤2	>8	≤2->8	57.3	32.7
Oxacillin	4	>8	≤0.06->8	22.1	77.9
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-2	99.8	0.0
Tetracycline	≤4	>8	≤4->8	85.1	14.7
Trimethoprim/Sulfamethoxazole	≤0.5	>2	≤0.5->2	55.6	44.4
Vancomycin	2	2	≤0.12-4	100.0	0.0

a. Susceptibility interpretive criteria of the NCCLS [2003].
b. One linezolid-resistant strain was detected (MIC, > 8 μg/ml): with a G2576U mutation.

Table 4. Comparisons of linezolid and nine other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for ß-haemolytic streptococci (387 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	1	1	≤0.06-2	100.0	-
Cefepime	≤0.12	≤0.12	≤0.12-2	99.7	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Clindamycin	≤0.06	0.25	≤0.06->8	91.0	9.0
Erythromycin	≤0.06	4	≤0.06->8	79.1	20.7
Levofloxacin	0.5	1	0.25->4	99.7	0.3
Penicillin	0.03	0.06	≤0.015-0.25	99.2	-
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0	0.0
Tetracycline	>8	>8	≤4->8	42.1	56.3
Vancomycin	0.5	0.5	≤0.12-1	100.0	-

a. Susceptibility interpretive criteria of the NCCLS [2002].

RESULTS AND DISCUSSION

- Against the *Staphylococcus* species (Table 2 and 3) linezolid demonstrated a MIC$_{90}$ at 2 μg/ml and only vancomycin had a greater percent susceptibility rate than linezolid.
- Complete coverage (100.0% susceptibility) was observed for linezolid, ceftriaxone, quinupristin/dalfopristin and vancomycin against the ß-haemolytic streptococci (Table 4).
- Linezolid, quinupristin/dalfopristin and vancomycin were 100.0% active and amoxicillin/clavulanic, cefepime, ceftriaxone and levofloxacin demonstrated ≥ 95.0% susceptibility rates against the *S. pneumoniae* isolates (Table 5).
- No antimicrobial agent achieved 100.0% susceptibility against the viridans group streptococci, but linezolid (99.5% susceptible), vancomycin (98.9% susceptible) and quinupristin/dalfopristin (97.9% susceptible) were most active in vitro (Table 6).
- Against the Enterococcus spp. isolates tested (Table 7), linezolid potency (MIC$_{90}$, 2 μg/ml) and susceptibility (99.9%) was superior compared to the next best antimicrobial agents, glycopeptides (85.5 - 87.7% susceptible) and chloramphenicol (85.4% susceptible).
- Four linezolid resistant isolates (two staphylococci, one streptococcus, one enterococcus) were isolated in four medical centers (Texas, New York, Kentucky, Iowa) in the US during the ZAAPS surveillance (G2576U mutations).
- Antimicrobial usage data collected from the US ZAAPS participant sites encompassed greater than 2.8 million patient hospital days from 10,472 beds.
- The average usage was 0.4 DDD/100 patient days with a range of 0.1 - 1.1 DDD/100 patient days.

Table 5. Comparisons of linezolid and 11 other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for *S. pneumoniae* (1,770 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	1	1	≤0.25-2	100.0	-
Amoxicillin/Clavulanate	≤2	≤2	≤2-16	95.0	2.9
Cefepime	≤0.12	1	≤0.12-8	96.7	0.6
Ceftriaxone	≤0.25	1	≤0.25-8	97.5	1.5
Clindamycin	≤0.06	>8	≤0.06->8	88.5	11.0
Erythromycin	≤0.25	>8	≤0.25->8	74.5	24.4
Levofloxacin	1	1	≤0.03->4	99.1	0.8
Penicillin	≤0.03	2	≤0.03->4	71.3	15.8
Quinupristin/Dalfopristin	0.5	0.5	≤0.06-1	100.0	0.0
Tetracycline	≤4	>16	≤4->16	82.8	17.2
Trimethoprim/Sulfamethoxazole	≤0.5	4	≤0.5->4	71.1	24.7
Vancomycin	0.25	0.5	≤0.12-1	100.0	-

a. Susceptibility interpretive criteria of the NCCLS [2003].

Table 6. Comparisons of linezolid and nine other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for viridans group streptococci (187 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	1	1	≤0.25-8	99.5	[b]
Cefepime	≤0.12	1	≤0.12->16	89.3	4.8
Ceftriaxone	≤0.25	2	≤0.25->32	88.2	5.9
Clindamycin	≤0.06	0.5	≤0.06->8	89.2	9.1
Erythromycin	≤0.06	>8	≤0.06->8	62.6	33.2
Levofloxacin	1	1	0.12->4	96.7	2.2
Penicillin	0.06	2	≤0.015-16	72.2	6.4
Quinupristin/Dalfopristin	0.5	1	≤0.06-4	97.9	0.5
Tetracycline	≤4	>8	≤4->8	63.6	36.4
Vancomycin	0.5	0.5	≤0.12-2	98.9[c]	-

a. Susceptibility interpretive criteria of the NCCLS [2003].
b. A linezolid-resistant viridans group strain was detected (MIC, 8 μg/ml) with a G2576U mutation.
c. Two strains had a MIC of 2 μg/ml (e.g. one $\log_2$ dilution greater than the NCCLS breakpoint).

CONCLUSIONS

- Linezolid remains an excellent therapeutic option for complicated Gram-positive organism infections with only 0.05% resistance discovered in this worldwide ZAAPS Program sample.
- Oxazolidinone susceptibility testing and monitoring should be performed within medical centers utilizing these antimicrobial agents, especially on clinical isolates from patients receiving prolonged therapy.
- Local and international surveillance programs like ZAAPS are vital to monitor the emergence and dissemination of new or novel resistance mechanisms to recently introduced antimicrobial agents.
- Low oxazolidinone resistance rates were documented in enterococci, staphylococci and streptococci species infections.
- Linezolid usage rates in the medical centers with linezolid-resistant isolates varied from 0.1 to 0.5 DDD/100 patient days, and demonstrated no correlation between increased usage and the emergence of the resistant isolates.

Table 7. Comparisons of linezolid and 11 other antimicrobials tested as part of the ZAAPS protocol in all nations (2002) for enterococci (1,070 strains).

Antimicrobial agent	MIC (μg/ml) 50%	90%	Range	% by category[a] Susceptible	Resistant
Linezolid	2	2	0.25->8	99.9	0.1[b]
Ampicillin	≤2	>16	≤2->16	79.6	20.4
Chloramphenicol	8	>16	≤2->16	85.4	13.1
Doxycycline	>4	>4	≤0.5->4	47.6	52.4
Gentamicin[c]	≤500	>1000	≤500->1000	67.1	-
Levofloxacin	2	>4	≤0.03->4	50.9	47.7
Nitrofurantoin	≤32	>32	≤32->32	82.4	0.2
Quinupristin/Dalfopristin	8	>8	0.12->8	21.9	72.2
Rifampin	2	>2	≤0.25->2	32.5	40.2
Streptomycin[c]	≤1000	>2000	≤1000->2000	60.3	-
Teicoplanin	≤0.12	16	≤0.12->16	87.7	9.6
Vancomycin	1	>16	≤0.12->16	85.5	14.0

a. Susceptibility interpretive criteria of the NCCLS [2003].
b. One linezolid-resistant strain was isolated (MIC, > 8 μg/ml): with a G2576U mutation.
c. High-level resistance screen. Susceptible result predicts synergistic killing when combined with a cell-wall active agent.

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