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Antimicrobial Activity of Oxazolidinones (Linezolid) and Streptogramins (Quinupristin/Dalfopristin) Tested Against Nearly 40,000 Gram-Positive Isolates in the Global SENTRY Antimicrobial Surveillance Program (1997-2000).

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AMENDED ABSTRACT

Background: Resistance (R) among Gram-positive cocci (GPC) has escalated in the last decade to levels necessitating the development and use of new drug classes, oxazolidinones (linezolid-LZD) and streptogramins (Quinupristin/Dalfopristin-Q/D). The SENTRY Program has monitored these classes before, during, and after the release by various regulatory agencies since 1997.

Methods: Nearly 40,000 GPC were tested against > 30 drugs by reference broth microdilution methods (NCCLS 2002) between 1997-2000 in 4 SENTRY regions Asia-Western Pacific (APAC), Europe (EU), Latin America (LA), and North America (NA). The tested strains were 30,780 staphylococci (7,261 MRSA and 6,345 MR-CoNS); 6,898 enterococci (590 VRE) and 2,047 streptococci (283 PEN-I or R pneumococci). Strains were from hospitalized patients with infection sites of blood, lung, SST or urine with strains tested centrally by regional monitors in Australia and USA.

Results: Among staphylococci, LZD was active against all isolates (MICs, 2-4 µg/ml) regardless of susceptibility patterns of other agents. Similar results were noted for vancomycin (1 VISA in Hong Kong), teicoplanin (1 VISA strain and resistant CoNS-0.8-4.0%) and Q/D (<1% R, greatest among CoNS). Gatifloxacin had the widest spectrum of activity among fluoroquinolones (FQ) against S. aureus (1.5%-9.2% R) and CoNS (0.8-4.0%). LZD was also active against all enterococci (MIC_{50} and MIC_{90}, 2 µg/ml). Q/D was only active against 75.3% of VRE. The VRE rate was highest in NA (12.4%) > EU (3.2%) > LA (1.6%) > APAC (1.3%). Van A patterns were most prevalent in all regions except APAC (54% van B). Among streptococci, LZD was consistently active (MIC_{50}, 1 µg/ml) as were the glycopeptides and Q/D. Variable PEN-R was observed by regions: EU (32.5%) > APAC (15.1%) > LA (13.8%) > NA (9.6%), but macrolide R was highest in EU (40.3%) for pneumococci. Ciprofloxacin-R at ≥ 4 µg/ml in streptococcal strains were noted worldwide highest in vir.gr. strepts (18.4-25.6%). 96.4% of LZD MICs were at 1-4 µg/ml.

Conclusions: LZD remained active (MIC, ≤ 4 µg/ml) against all GPC strains tested in the SENTRY Program (1997-2000). Q/D, glycopeptides and newer FQ compounds were less effective in vitro. It remains a prudent practice to continue R surveillance programs to detect emerging LZD patterns and recognize significant regional variations in R rates.

INTRODUCTION

Linezolid (LZD) represents the first of a new class of antimicrobials, oxazolidinones, to become clinically available in the last 35 years. It was approved in the United States during April of 2000, and was indicated for the treatment of patients with infections caused by Gram-positive bacteria. The initial approved labeling for LZD included; 1) adults with nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, vancomycin-resistant enterococcus infections, and methicillin (oxacillin)-resistant *Staphylococcus aureus*. The approval provided cautious optimism in light of the growing resistance among Gram-positive cocci, which have necessitated the rapid development of newer agents such as LZD, streptogramin combinations (Quinupristin/Dalfopristin-Q/D) and novel agents (everninomycins, lipopeptides, glycylcyclines etc.) to combat the resistance. The release of LZD, though a welcome one in order to provide effective therapy for VRE, also provided a growing need for careful surveillance of in order to avoid further growth in resistance patterns.

The SENTRY Antimicrobial Surveillance Program was initiated in 1997, with the primary purpose being to monitor antimicrobial resistance trends of both nosocomial and community-acquired pathogens over large geographic areas. Currently, over 80 sentinel hospitals throughout the SENTRY Program network share bacterial isolates with designated central laboratories in order to assure validated reference identification and susceptibility testing methods. The purpose of this report is to provide baseline data on more then 30,000 Gram-positive cocci obtained through the SENTRY Program in order to compare susceptibility results obtained for the newer oxazolidinone, LZD with other agents used in the treatment of infections caused by *S. aureus*, coagulase-negative staphylococci, enterococci, *Streptococci pneumoniae*, viridans group streptococci, and ß-haemolytic streptococci.

MATERIALS AND METHODS

Isolates in this study were recent clinical strains obtained through the SENTRY Antimicrobial Surveillance Program (1997-2000) which were from blood stream, respiratory and urinary tract as well as skin and soft tissue infections. A total of 30,336 Gram-positive isolates were evaluated which included *S.aureus* (17,011), coagulase-negative staphylococci (CoNS, 6,177) *Enterococcus* spp. (5,103), *S.pneumoniae* (1,057), beta-haemolytic streptococcus (633) and viridans-group streptococcus (355).

These strains were tested against a panel of eight or ten Gram-positive focused agents. These included linezolid, quinupristin/dalfopristin, vancomycin, teicoplanin, oxacillin or ampicillin or penicillin, erythromycin (staphylococci and streptococci), clindamycin (staphylococci), mupirocin (staphylococci), ciprofloxacin, gatifloxacin (staphylococci and streptococci), and high-level gentamicin and streptomycin (enterococcus only). In addition to the common pathogenic species or species groups discussed, four other Gram-positive species were tested including *Bacillus* spp., *Corynebacterium* spp., *Listeria* spp., and *Micrococcus* spp. These strains were evaluated against the linezolid and quinupristin/dalfopristin only. All strains were tested by reference broth microdilution methods recommended by the NCCLS using dry form panels supplied by TREK Diagnostics (West Lake, OH). Organisms from pure culture plates were suspended into a Mueller-Hinton broth media to equal a 0.5 McFarland standard and further diluted and inoculated into the antibiotic containing wells to equal approximately $5x10^4$ CFU/ml. Panels were incubated in an ambient environment for 24 hours, depending on the species. The panels were read for the lowest drug concentration, which visually inhibited growth of the organism which determined the minimum inhibitory concentration (MIC) for each antimicrobial agent. Concomitant processing of ATCC quality control strains including *S.aureus* ATCC 29213, *E.faecalis* ATCC 29212 and *S.pneumoniae* ATCC 49619.

RESULTS

- LZD demonstrated excellent activity against all staphylococcal strains evaluated with no resistance reported in each of the four regions through 2000. A LZD-susceptible single heteroresistant variation of VISA (Hong Kong) was identified. Additionally, LZD was active against all enterococci isolates tested at ≤ 4 µg/ml, with MIC_{90} results being 2 µg/ml and resistance rates being nil for all four geographic regions. The activity of LZD against pneumococcal strains (MIC_{90}, 1 µg/ml; 100% susceptible) was the same in all four regions.
- LZD, Q/D, vancomycin, and teicoplanin demonstrated excellent activity against both the viridans group streptococci and beta haemolytic streptococcal isolates. There were no resistant isolates in any of the four geographical regions for these four agents.
- Q/D demonstrated good activity against pneumococci strains with MICs ranging from 0.25 to 1 µg/ml. Although Q/D had MICs ranging from 0.12-0.5 µg/ml against all staphylococcal strains, a minimal degree of resistance to *S. aureus* was observed of <0.1% and 0.8% for APAC and EU, respectively.
- Vancomycin and teicoplanin showed varying activity against enterococcal isolates. Teicoplanin demonstrated lower MIC ranges then vancomycin, and lower rates of resistance of 0.6% (APAC), 2.2% (EU), 1.4% (LA), and 9.1% for NA as compared to 1.3% (APAC), 3.2% (EU), 1.6% (LA), and 12.4% (NA) for vancomycin.
- Glycopeptides against pneumococcal strains showed MICs for vancomycin ranging from 0.25 to 0.5 µg/ml and no resistance in three geographical areas. In the APAC, the resistance rate was 0.4%, and was attributed to one isolate which had a MIC of 2 µg/ml.
- Among the fluoroquinolones tested, gatifloxacin demonstrated a lower resistance rate for the viridans group streptococci (0%-3.7%) compared to ciprofloxacin (18.4%-25.6%), and for the beta haemolytic streptococci, (0%-0.3%) versus (0%-0.6%), respectively. Gatifloxacin also showed low overall resistance rates to the *S. aureus* strains with rates as high as 9.2% for NA, to as low as 1.5% for EU. MIC values for ciprofloxacin ranged from 0.25 to >2 µg/ml, with resistance rates of 30.1% to 39.7%. Gatifloxacin possessed the lowest overall fluoroquinolone resistance rates against the CoNS. Gatifloxacin had better activity against pneumococcal strains with MICs at 0.25-0.5 µg/ml versus ciprofloxacin at 1-2 µg/ml. The resistance rates for gatifloxacin were 0% (EU), 0.5% (NA), 0.6% (LA), 1.6% (APAC) versus 3.9% (EU), 1.4% (NA), 1.7% (LA), and 3.3% (APAC), for ciprofloxacin.
- Resistance rates for penicillin (≥2 µg/ml) among *S. pneumoniae* varied markedly by region: 9.6% (NA), 13.8% (LA), 15.1% (APAC), and 32.5% (EU).
- Erythromycin demonstrated a favorable MIC_{90} (≤ 0.06 µg/ml) for pneumococcal isolates collected from LA, with resistant rates of only 7.7%. Marked variations in resistance rates amongst the remaining regions was discovered; 29.4% (APAC), 40.3% (EU), and 14.6% (NA). Erythromycin did not obtain the level of activity of that reported for penicillin, for the viridans group and the ß-haemolytic streptococci.
- Linezolid demonstrated excellent activity against bacterial strains that were resistant to comparator drugs such as penicillin-resistant *S. pneumoniae*, oxacillin-resistant *S. aureus*, oxacillin-resistant CoNS, and vancomycin-resistant enterococci.
- Linezolid demonstrated complete activity against *Bacillus* spp, *Cornybacterium* spp, *Listeria* spp, and *Micrococcus* spp.

Table 5. Activity of linezolid and quinupristin/dalfopristin against 291 strains of *Bacillus* spp., *Corynebacterium* spp., *Listeria* spp., and *Micrococcus spp.*

Organism (no. tested)/antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% susceptible/resistant[a]
Bacillus spp. (90)				
Linezolid	1	1	0.25-2	100.0/0.0
Quinupristin/Dalfopristin	0.5	2	0.25->8	84.4/6.7
Corynebacterium spp. (102)				
Linezolid	0.25	0.5	0.12-1	100.0/0.0
Quinupristin/Dalfopristin	0.12	0.5	≤0.06-4	96.1/1.0
Listeria spp. (39)				
Linezolid	2	2	1-2	100.0/0.0
Quinupristin/Dalfopristin	1	2	0.25-2	89.7/0.0
Micrococcus spp. (60)				
Linezolid	1	1	0.5-2	100.0/0.0
Quinupristin/Dalfopristin	≤0.06	0.25	≤0.06-1	100.0/0.0

a. Linezolid susceptible at ≤ 2 µg/ml and resistant at ≥ 8 µg/ml; and Quinupristin/Dalfopristin susceptible at ≤ 1 µg/ml and resistant at ≥ 4 µg/ml [NCCLS, 2002].

Table 1. Antimicrobial potency and spectrum of linezolid compared to nine other agents tested against 23,188 medical center isolates of staphylococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region (no. tested):[a] APAC		EU		LA		NA	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R[c]	MIC50/90b	% Rc	$MIC_{50/90}$[b]	% Rc	$MIC_{50/90}$[b]	% Rc
S. aureus (n)		(2416)		(3090)		(2248)		(9257)
Linezolid	2/4	0.0	2/2	0.0	2/4	0.0	2/4	0.0
Quinupristin/Dalfopristin	0.25/0.5	<0.1	0.25/0.5	0.8	0.25/0.5	0.0	0.25/0.5	0.0
Vancomycin	1/1	<0.1[d]	1/1	0.0	1/1	0.0	1/1	0.0
Teicoplanin	0.5/1	<0.1	0.5/2	<0.1	1/2	0.1	0.5/1	<0.1
Oxacillin	1/>8	44.8	0.5/>8	28.0	0.5/>8	35.1	0.5/>8	31.4
Erythromycin	1/>8	49.9	0.5/>8	34.9	0.5/>8	43.3	1/>8	44.2
Clindamycin	0.25/>8	35.5	0.12/>8	23.4	0.25/>8	32.3	0.25/>8	26.5
Ciprofloxacin	0.5/>2	39.7	0.25/>2	30.6	0.5/>2	32.7	0.5/>2	30.1
Gatifloxacin	0.12/4	4.6	0.06/4	1.5	0.12/4	1.7	0.12/4	9.2
Mupirocin	≤8/≤8	3.8	≤8/≤8	5.2	≤8/≤8	1.5	≤8/≤8	6.1
CoNS[e] (n)		(748)		(1729)		(902)		(2798)
Linezolid	1/2	0.0	1/2	0.0	1/2	0.0	1/2	0.0
Quinupristin/Dalfopristin	0.12/0.5	0.1	0.25/0.5	0.3	0.25/0.5	0.2	0.25/0.5	0.2
Vancomycin	1/2	0.0	2/2	0.0	2/2	0.0	2/2	0.1
Teicoplanin	2/16	2.5	2/8	0.8	2/16	3.3	2/8	2.2
Oxacillin	8/>8	78.1	8/>8	74.0	8/>8	76.6	8/>8	74.0
Erythromycin	>8/>8	55.3	>8/>8	62.2	>8/>8	61.6	>8/>8	70.7
Clindamycin	0.12/>8	38.2	0.12/>8	37.5	0.25/>8	42.9	0.25/>8	40.0
Ciprofloxacin	0.25/>2	34.6	0.5/>2	41.6	0.5/>2	40.2	0.5/>2	42.5
Gatifloxacin	0.12/2	1.9	0.12/2	1.8	0.12/2	0.8	0.25/4	4.0
Mupirocin	≤8/>16	16.3	≤8/>6	14.2	≤8/>16	25.7	≤8/>16	36.7

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml.
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. One heteroresistant variation of VISA (Hong Kong).

Table 2. Antimicrobial potency and spectrum of linezolid compared to seven other agents tested against 5,103 medical center isolates of enterococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region (no. tested):[a] APAC (533)		EU (1125)		LA (375)		NA (3070)	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c
Linezolid	2/2	0.0	2/2	0.0	2/2	0.0	2/2	0.0
Quinupristin/Dalfopristin	8/>8	75.8	8/>8	67.1	8/>8	79.4	8/>8	72.0
Vancomycin	1/2	1.3	1/2	3.2	1/2	1.6	1/>16	12.4
Teicoplanin	0.25/0.5	0.6	0.25/0.5	2.2	0.25/0.5	1.4	0.25/1	9.1
Ampicillin	1/>16	16.7	1/>16	16.2	1/4	4.5	1/>16	20.8
Gentamicin[d]	≤500/>1000	32.3	≤500/>1000	30.2	≤500/>1000	20.1	≤500/>1000	30.8
Streptomycin[d]	≤1000/>2000	31.5	≤1000/>2000	44.5	≤1000/>2000	32.5	≤1000/>2000	39.3
Ciprofloxacin	0.5/>4	25.7	0.25/>4	28.9	0.5/>4	19.9	1/>4	44.2

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml).
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. High-level screening for synergy only.

Table 3. Antimicrobial potency and spectrum of linezolid compared to seven other agents tested against 2,045 medical center isolates of streptococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region (no. tested):a APAC		EU		LA		NA	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c	$MIC_{50/90}$[b]	% R^c
S. pneumoniae (n)		(245)		(77)		(181)		(554)
Linezolid	1/1	0.0	1/1	0.0	1/1	0.0	1/1	0.0
Quinupristin/Dalfopristin	0.5/1	0.0	0.25/0.5	0.0	0.5/0.5	0.0	0.25/0.5	0.0
Vancomycin	0.5/0.5	0.4[d]	0.25/0.5	0.0	0.5/0.5	0.0	0.25/0.5	0.0
Teicoplanin	≤0.12/≤0.12	0.0	≤0.12/≤0.12	0.0	≤0.12/≤0.12	0.0	≤0.12/≤0.12	0.0
Penicillin	0.03/2	15.1	0.25/2	32.5	≤0.015/2	13.8	≤0.015/1	9.6
Erythromycin	≤0.06/>8	29.4	≤0.06/>8	40.3	≤0.06/≤0.06	7.7	≤0.06/2	14.6
Ciprofloxacin	1/2	(3.3)[e]	1/2	(3.9)[e]	1/2	(1.7)[e]	1/2	(1.4)[e]
Gatifloxacin	0.25/0.5	1.6	0.25/0.5	0.0	0.25/0.5	0.6	0.25/0.5	0.5
viridans gr. strept. (n)		(98)		(53)		(42)		(162)
Linezolid	1/1	0.0	1/1	0.0	1/2	0.0	1/1	0.0
Quinupristin/Dalfopristin	1/1	0.0	0.5/1	0.0	0.5/1	0.0	0.5/1	0.0
Vancomycin	1/1	0.0	0.5/1	0.0	0.5/1	0.0	0.5/1	0.0
Teicoplanin	≤0.12/≤0.12	0.0	≤0.12/0.25	0.0	≤0.12/0.25	0.0	≤0.12/0.25	0.0
Penicillin	0.06/1	6.1	0.06/1	5.7	0.06/0.5	2.3	0.06/1	1.2
Erythromycin	≤0.06/>8	27.6	≤0.06/>8	41.5	≤0.06/2	32.6	≤0.06/4	36.4
Ciprofloxacin	1/>2	(18.4)[e]	2/>2	(22.6)[e]	2/>2	(25.6)[e]	2/>2	(19.1)[e]
Gatifloxacin	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	2.3	0.25/0.5	3.7
ß-haemolytic strept. (n)		(185)		(31)		(92)		(325)
Linezolid	1/1	0.0	1/1	0.0	1/1	0.0	1/1	0.0
Quinupristin/Dalfopristin	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	0.0
Vancomycin	0.5/0.5	0.0	0.5/0.5	0.0	0.5/0.5	0.0	0.5/0.5	0.0
Teicoplanin	≤0.12/0.25	0.0	≤0.12/≤0.12	0.0	≤0.12/0.25	0.0	≤0.12/0.25	0.0
Penicillin	≤0.015/0.06	0.0	0.03/0.06	0.0	≤0.015/0.06	0.0	0.03/0.06	0.0
Erythromycin	≤0.06/2	10.8	≤0.06/0.25	9.7	≤0.06/≤0.06	2.2	≤0.06/2	23.1
Ciprofloxacin	0.5/1	(0.5)[e]	0.5/1	(0.0)[e]	0.5/1	(0.0)[e]	0.5/1	(0.6)[e]
Gatifloxacin	0.25/0.25	0.0	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.25	0.3

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml.
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. One strain reproducibly having an MIC at 2 µg/ml (1.5 µg/ml by Etest).
e. Breakpoint of susceptible at ≤ 1 µg/ml and resistant at ≥ 4 µg/ml used for comparison purposes only.

Table 4. Impact of various resistances on the activity of linezolid.

Organism	Resistance pattern (no. tested)	Linezolid MIC (µg/ml) results: 50%	90%	Range	% by category:[a] Susceptible	Resistant
Enterococci	Vancomycin-susceptible (4664)	2	2	≤0.06-4	97.1	0.0
	Vancomycin-resistant (439)	2	2	0.5-4	97.5	0.0
S. pneumoniae	Penicillin-susceptible (774)	1	1	≤0.06-2	100.0	-
	Penicillin-intermediate (143)	1	1	0.12-2	100.0	-
	Penicillin-resistant (140)	1	1	0.5-2	100.0	-
S. aureus	Oxacillin-susceptible (11,120)	2	4	≤0.06-4	100.0	-
	Oxacillin-resistant (5,891)	2	4	0.25-4	100.0	-
CoNS[b]	Oxacillin-susceptible (1,432)	1	2	≤0.06-4	100.0	-
	Oxacillin-resistant (4,745)	1	2	≤0.06-4	100.0	-

a. MIC results interpreted by NCCLS [2002] criteria.
b. CoNS = coagulase-negative staphylococci.

CONCLUSIONS

- Linezolid demonstrated excellent activity against all Gram-positive bacteria tested in each of the four geographic regions, relative to comparator antimicrobials. Though the susceptibilities reported for linezolid were generally comparable to quinupristin/dalfopristin, vancomycin, and teicoplanin against most Gram-positive genera significant differences were apparent in favor of linezolid for enterococci.
- The frequent use of ciprofloxacin has continued to erode its susceptibilities to most of the Gram-positive cocci isolates tested, relative to the newer quinolones such as gatifloxacin.
- Penicillin continues to demonstrate good activity against some streptococci, but the resistance rates reported against *S. pneumoniae* (9.6%-32.5%) requires the availability of other agents such as the glycopeptides, the streptogramin combination, and linezolid.
- Before and one year after the release of linezolid in the US, it continues to be an effective agent to treat infections caused by Gram-positive cocci resistant to other previously effective agents. However, as has been shown in this as well as previous reports, continued vigilance is recommended in order to identify resistance patterns as they may develop against oxazolidinones.
- Cumulative results for linezolid demonstrated that 96% of MICs are in the range of 1 to 4 µ/ml. MIC results at ≥ 8 µ/ml indicate mutational resistance to this oxazolidinone.

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