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Experience with Linezolid in Vitro Coverage (% Susceptible) of *S. aureus* Pneumonia Isolates: Report From the SENTRY Antimicrobial Surveillance Program (1998-2009)

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Amended Abstract

Background: A decade ago linezolid, the first-in-class oxazolidinone, received regulatory approval for the therapy of multidrug-resistant Gram-positive pathogens including MRSA. Concurrently, the SENTRY Program initiated linezolid resistance (R) surveillance in 1998, continued to date. This analysis summarizes the worldwide monitoring of *S. aureus* (SA) isolated from patients with documented pneumonia.

Methods: SA from more than 150 hospitals on 5 continents were susceptibility (S) tested by CLSI M07-A8 methods and interpreted by M100-S20-U criteria for 10 agents. 12,219 pneumonia episodes were tabulated including 5,830 MRSA. Linezolid was compared to the broadest spectrum contemporary agents: levofloxacin (LEV), quinupristin/dalfopristin (Q/D), tetracycline (TC), tigecycline (TIG), trimethoprim/ sulfamethoxazole (T/S) and vancomycin (VAN; also represents teicoplanin). Clindamycin (CC) and erythromycin (ERY) were also tested.

Results: The MRSA rate in pneumonia patient isolates was 47.7% overall and the linezolid $MIC_{50/90}$ and MIC mode was at 2 µg/ml, with no variations for MSSA or for all SA. At the CLSI/EUCAST S breakpoint (≤4 µg/ml), >99.9% of SA were inhibited including all MSSA. Among comparison agents the rank order of coverage (%S) versus MRSA cases was: VAN = TIG (99.9%) > Q/D (99.3%)> T/S (87.9%) > TC (71.6%) > CC (27.6%) > LEV (9.2%) > ERY (6.8%). Only one MRSA strain from Arizona USA was linezolid-R (documented plasmidic *cfr* mechanism). Overall SA R rate was <0.01%.

Table

	Cum. % inhibited linezolid MIC (µg/ml)						
S. aureus group (no. tested)	≤0.25	0.5	1	2	4	8	% susceptible[a]
MSSA (6,389)	0.1	0.5	23.6	91.2	100.0	-	100.0
MRSA (5,830)	0.3	0.9	35.4	96.1	>99.9	100.0[b]	99.98
All (12,219)	0.2	0.7	29.2	93.5	>99.9	100.0	99.99

a. CLSI (2010) and EUCAST (2010) interpretive criteria.
b. MRSA with *cfr* resistance mechanism (Arizona).

Conclusion: The experience of a global, prevalence design R surveillance network (SENTRY Program) documented extremely rare occurrence of oxazolidinone R among collected MSSA or MRSA pneumonia cases (1 strain or <0.01%). This coverage rate remains comparable to that of VAN and TIG.

Introduction

Linezolid was the first oxazolidinone class agent studied and approved (2000) in the United States (USA) for clinical use (Diekema and Jones). Linezolid has been used to successfully treat Gram-positive pathogens causing complicated skin and skin structure infection (cSSSI) and nosocomial pneumonia (Kollef et al.; Wunderink et al.), after USA-Food and Drug Administration (FDA) review. This compound has emerged as a valuable and cost-effective (Estes and Orenstam; Luna and Navarro) parenteral/oral therapy for infections caused by emerging 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. The continued surveillance of the in vitro activity of linezolid allows the detection of emerging resistance and changes in susceptibility over time.

Oxazolidinone resistance surveillance was originally provided by the ZAPS Program (Ballow et al.) in the pre-launch period and then in 2002 and 2003 by the ZAAPS Program (Jones et al.), that sampled countries around the world including the USA. However, the subsequent 2004-2009 ZAAPS Program sampled only the “rest of the world” (non-USA), while the USA collection was separated into the LEADER Program (Farrell et al.). Concurrently, the global SENTRY Antimicrobial Surveillance Program monitored for linezolid resistances with documented occurrences observed shortly following clinical approval (Mutnick, et al.). Recent study results have documented that MRSA and DRSP have remained the most common contemporary pathogens isolated from hospital- and community-acquired pneumonia, respectively (Jones; Jones et al.); thus establishing linezolid as a desirable option for empiric or directed therapy (Luna and Navarro).

The oxazolidinone mechanism of action is selective binding to the 50S ribosomal subunit of the 23S rRNA molecule resulting in inhibition of protein synthesis. Among the reports of linezolid-resistant staphylococci and enterococci, the most common mechanism was target site mutation at G2576T, G2447T or T2504A (Meka and Gold). However, the relatively recent discovery of a mobile *cfr*-mediated resistance mechanism among *Staphylococcus* spp. (Long et al.) has become worrisome. In this report, we summarize longitudinal studies of linezolid activity against *S. aureus* strains isolated from patients hospitalized with pneumonia (SENTRY Program, 1998-2009).

Methods

Bacterial Strains Collected: A total of 12,219 *S. aureus* isolates were forwarded to the SENTRY Program (1998-2002, 2004-2009) from patients hospitalized with pneumonia. These pathogens came from 169 medical centers on five continents (four geographic surveillance regions; North America [54], Europe [43], Latin America [15] and Asia-Pacific [57]). The annual number of strains processed varied from 723 in 2005 to 1,671 in 2002 (1,111 strains/year). Of these *S. aureus* causing pneumonia, 5,830 were MRSA as determined by the CLSI MIC results (oxacillin) and cefoxitin disk methods. All identifications of *S. aureus* were made by two laboratories (local and monitoring investigators; JMI Laboratories, North Liberty, Iowa, USA) by standard manual tests, commercial systems (Vitek 2) and molecular methods, as needed.

Susceptibility Test Methods: All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). All *S. aureus* were tested in cation-adjust Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of quality control strains, including *S. aureus* ATCC 29213 and 25923, and *E. faecalis* ATCC 29212 (M100-S20-U, 2010). Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) and EUCAST (2010) criteria, when available.

Results

- Over 12,000 *S. aureus* strains isolated from patients hospitalized with pneumonia since 1998 worldwide (SENTRY Program) were susceptibility tested for linezolid and numerous comparison agents; nearly 6,000 were MRSA. Overall, 99.98% of these *S. aureus* strains were linezolid-susceptible (MIC, ≤4 µg/ml), see Table 1.
- MRSA and MSSA strains had identical linezolid MIC_{50}, MIC_{90} and modal MIC values (Tables 1-3). However, MRSA strains had markedly low susceptibility rates for some comparison agents including (rate for MRSA/MSSA): clindamycin (27.6/95.5%), erythromycin (6.8/76.8%), levofloxacin (9.2/93.0%), tetracycline (71.6/93.9%) and trimethoprim/ sulfamethoxazole (87.9/98.9%). Only linezolid (99.9-100.0% susceptible), quinupristin/dalfopristin (99.3-99.9%), teicoplanin (99.9-100.0%; less by EUCAST criteria at 96.3-98.8%) and vancomycin (99.9-100.0%) exhibited high-level coverage of these *S. aureus* strains.
- The only linezolid-non-susceptible strain occurred in a MRSA from Arizona, USA. This *S. aureus* had a *cfr* resistance gene producing a linezolid MIC of 8 µg/ml (Table 1).
- No trend toward greater linezolid resistance was found among these *S. aureus* causing pneumonia (data not shown).

Table 1. Linezolid MIC distributions for 12,219 *S. aureus* isolates cultured from lower respiratory tract specimens by the SENTRY Antimicrobial Surveillance Program (169 medical centers on five continents; 1998-2009).

S. aureus population (no. tested)	No. occurrences (cum. %) at each MIC (µg/ml):						% Susceptible[a]
	≤0.25	0.5	1	2	4	8	
All strains (12,219)	19(0.2)	64(0.7)	3487(29.2)	7858(93.5)	790(99.9)	1(100.0)[b]	99.99
Methicillin-susc. (6,389)	3(0.1)	28(0.5)	1474(23.6)	4322(91.2)	562(100.0)	-	100.0
Methicillin-R (5,830)	16(0.3)	36(0.9)	2013(35.4)	3536(96.1)	228(99.9)	1(100.0)[b]	99.98

a. Interpretive criteria of the CLSI (2010) and EUCAST (2010).
b. MRSA strain from the United States (Arizona) revealed a *cfr* oxazolidinone resistance mechanism.

Table 2. Linezolid activity compared to nine other agents when tested against 5,830 MRSA strains isolated from patients with pneumonia (SENTRY Antimicrobial Surveillance Program, 1998-2009).

	MIC (µg/ml)				% by category[a]
Antimicrobial agent	50%	90%	Mode	Range	Susceptible / Resistant
Linezolid	2	2	2	≤0.25-8	>99.9 / <0.1
Clindamycin	>2	>2	>2	≤0.25->2	27.6 / 72.3
Erythromycin	>2	>2	>2	≤0.25->2	6.8 / 92.9
Levofloxacin	>4	>4	>4	≤0.5->4	9.2 / 67.2
Quinupristin/dalfopristin	0.5	1	0.5	≤0.25->2	99.3 / 0.4
Teicoplanin	≤2	≤2	≤2	≤2->16	99.9 / 0.1
Tetracycline	≤4	>8	≤4	≤4->8	71.6 / 28.0
Tigecycline	≤0.12	0.25	≤0.12	≤0.12-1	99.9 / -[b]
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5	≤0.5->2	87.9 / 11.2
Vancomycin	1	1	1	≤0.12-4	99.9 / 0.0

a. Interpreted by CLSI criteria (M100-S20-U, 2010).
b. - = interpretive criteria are not established.

Table 3. Linezolid activity compared to nine other agents when tested against 6,389 MSSA strains isolated from patients with pneumonia (SENTRY Antimicrobial Surveillance Program, 1998-2009).

	MIC (µg/ml)				% by category[a]
Antimicrobial agent	50%	90%	Mode	Range	Susceptible/Resistant
Linezolid	2	2	2	≤0.25-4	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25	≤0.25->2	95.5 / 4.2
Erythromycin	0.5	>2	≤0.25	≤0.25->2	76.8 / 21.4
Levofloxacin	≤0.5	≤0.5	≤0.5	≤0.5->4	93.0 / 6.3
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25	≤0.25->2	99.9 / <0.1
Teicoplanin	≤2	≤2	≤2	≤2-4	100.0 /0.0
Tetracycline	≤4	>8	≤4	≤4->8	93.9 / 5.6
Tigecycline	≤0.12	0.25	≤0.12	≤0.12-1	99.9 / -[b]
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5	≤0.5->2	98.9 / 0.8
Vancomycin	1	1	1	≤0.12-2	100.0 / 0.0

a. Interpreted by CLSI criteria (M100-S20-U, 2010).
b. - = interpretive criteria are not established.

Conclusions

- Linezolid exhibited a stable potency against a worldwide collection of *S. aureus* associated with pneumonia (MIC_{50}, MIC_{90} and modal MIC at 2 µg/ml).
- Only one resistant strain harboring a *cfr* gene was found in the USA.
- Linezolid demonstrated a near-complete coverage (99.99% susceptible; Table 1) against these 12,219 *S. aureus* tested from 1998 through 2009.
- Via a broad and comprehensive in vitro surveillance sampling, linezolid remains an active agent as a therapeutic choice for pneumonias in hospitalized patients where MRSA is suspected. Few other agents (glycopeptides and quinupristin/dalfopristin) showed comparable activity.

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