

Revised Abstract

Objectives: Linezolid has shown excellent activity against gram-positive organisms since its introduction over a decade ago. The Tigecycline Evaluation and Surveillance Trial (TEST) examines the susceptibility of pathogens isolated from a wide variety of infectious processes worldwide to multiple antimicrobial agents. This report focuses on *in vitro* susceptibility of gram-positive pathogens to linezolid over the past 7 years. **Methods:** From 2004-2010, 3,206 gram-positive isolates from multiple infection sources were collected at 37 sites in 8 Asian countries. MICs were performed at each site following CLSI guidelines using commercially-prepared broth microdilution panels. Results were interpreted according to CLSI breakpoints. **Results:** The % susceptible, MIC₉₀, and geometric mean (GM) MIC for linezolid are shown in the following table.

	% Susceptible / MIC ₅₀ (mg/L) / GM MIC (mg/L)						
	2004	2005	2006	2007	2008	2009	2010
<i>E. faecalis</i>	100/2/1.58 (41)	100/2/1.37 (42)	100/2/1.49 (92)	100/2/1.43 (127)	100/2/1.39 (46)	100/2/1.48 (89)	100/2/1.24 (42)
<i>E. faecium</i> (including 76 VRE)	100/2/1.19 (12)	100/2/1.17 (13)	100/2/1.47 (67)	100/2/1.45 (74)	100/2/1.51 (49)	100/2/1.57 (78)	100/2/1.41 (24)
<i>S. aureus</i> (including 2 VISA)	100/4/1.89 (112)	100/2/1.34 (59)	100/4/1.68 (272)	100/2/1.67 (333)	100/2/1.91 (175)	100/2/1.76 (266)	100/4/1.84 (110)
MSSA	100/4/2.10 (73)	100/2/2.00 (19)	100/4/1.78 (151)	100/2/1.72 (183)	100/2/1.98 (65)	100/4/1.94 (90)	100/4/2.09 (61)
MRSA	100/2/1.56 (39)	100/2/1.11 (40)	100/2/1.55 (121)	100/2/1.88 (150)	100/2/1.98 (110)	100/2/1.67 (176)	100/2/1.57 (49)
<i>S. agalactiae</i>	100/1/0.98 (31)	100/1/0.71 (18)	100/1/0.98 (98)	100/1/0.98 (127)	100/1/0.95 (67)	100/2/1.06 (103)	100/1/0.94 (31)
<i>S. pneumoniae</i>	100/1/0.69 (52)	100/1/0.66 (47)	100/1/0.65 (140)	100/1/0.62 (146)	100/1/0.82 (113)	100/1/0.81 (100)	10 of 10 ⁹ /0.57 (10)
PSSP	100/1/0.64 (33)	100/1/0.70 (29)	100/1/0.65 (48)	100/1/0.62 (51)	100/2/0.87 (36)	100/1/0.73 (49)	6 of 6 ⁹ /0.56 (6)
PISP	100/1/0.74 (16)	8 of 8 ⁹ /0.65 (8)	100/1/0.62 (40)	100/1/0.62 (30)	100/1/0.79 (18)	100/1/0.62 (13)	--/--/-- (0)
PRSP	3 of 3 ⁹ /1.00 (3)	10 of 10 ⁹ /0.57 (10)	100/1/0.67 (65)	100/1/0.63 (59)	100/1/0.79 (38)	100/2/1.00 (4)	4 of 4 ⁹ /0.60 (4)

Conclusions: Linezolid was universally active against all gram-positive isolates collected in Asia between 2004 and 2010, including VRE, MRSA, and PRSP. MIC₉₀ values ranged between 1 and 4 mcg/ml across species.

Introduction

Linezolid, a member of the oxazolidinone class of drugs, has shown excellent activity against gram-positive organisms since its introduction over a decade ago. Its spectrum of *in vitro* activity covers all clinically important aerobic gram-positive bacteria, including antibiotic resistant strains, such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus*, and penicillin-resistant *Streptococcus pneumoniae*. The Tigecycline Evaluation and Surveillance Trial (TEST) has been monitoring the susceptibility of linezolid globally since 2004. This report focuses on *in vitro* susceptibility of gram-positive pathogens to linezolid over the past 7 years.

Materials & Methods

- Isolates were derived from blood (28%), respiratory tract (23%), bodily fluids (14%), urine (11%), wounds (9%) and various other infection sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected between 2004 and 2010 from 37 medical centers in 8 countries in Asia. The number of participating sites per country ranged from 8 in China and India, 7 in South Korea, 5 in Taiwan, 3 in Pakistan and Singapore, 2 in Thailand, and 1 in Malaysia. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc., located in Schaumburg, IL, USA.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. Antimicrobial agents were supplied by the panel manufacturers MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, Cleveland, OH).
- Quality control (QC) of broth microdilution panels followed manufacturers' and CLSI guidelines using *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines [2].
- MIC interpretive criteria followed published breakpoints defined by CLSI [2].
- Differences in linezolid MICs between individual countries and Asia overall were assessed using the Conover-Iman procedure (essentially a t-test on ranked MIC values) with Bonferroni correction.

References

- Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eighth Edition. CLSI document M07-A8. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA.

Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline European Surveillance Trial program group. This study was sponsored by Pfizer Inc.

Results

Figure 1: Countries of origin for the sample of 3,206 gram-positive isolates from Asia.

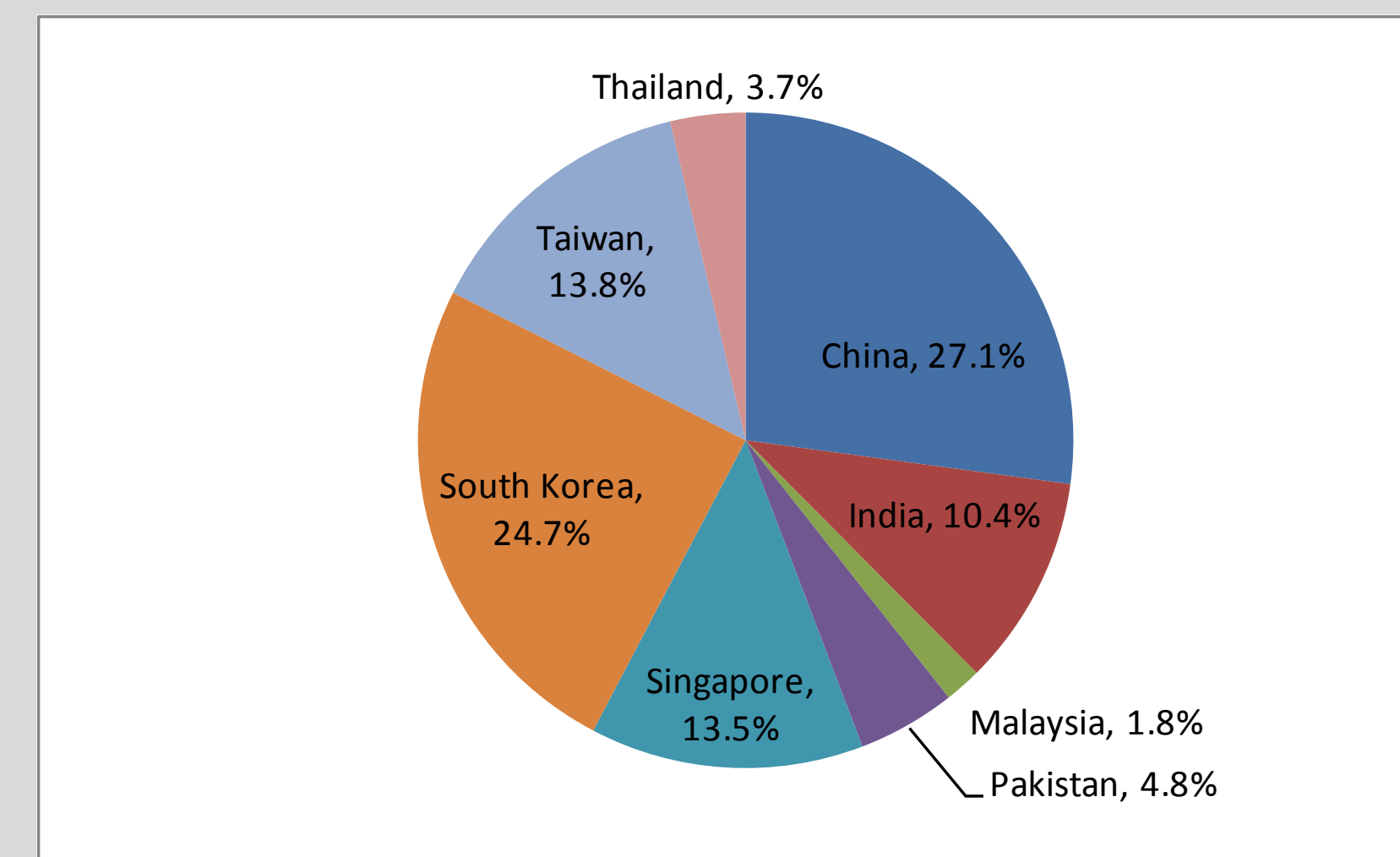


Table 1. *In vitro* activity of linezolid against 3,206 gram-positive isolates from Asia, 2004-2010.

	% Susceptible / MIC ₅₀ (mg/L) / GM MIC (mg/L)						
	2004	2005	2006	2007	2008	2009	2010
<i>E. faecalis</i>	100/2/1.58 (41)	100/2/1.37 (42)	100/2/1.49 (92)	100/2/1.43 (127)	100/2/1.39 (46)	100/2/1.48 (89)	100/2/1.24 (42)
<i>E. faecium</i> (including 76 VRE)	100/2/1.19 (12)	100/2/1.17 (13)	100/2/1.47 (67)	100/2/1.45 (74)	100/2/1.51 (49)	100/2/1.57 (78)	100/2/1.41 (24)
<i>S. aureus</i> (including 2 VISA)	100/4/1.89 (112)	100/2/1.34 (59)	100/4/1.68 (272)	100/2/1.67 (333)	100/2/1.91 (175)	100/2/1.76 (266)	100/4/1.84 (110)
MSSA	100/4/2.10 (73)	100/2/2.00 (19)	100/4/1.78 (151)	100/2/1.72 (183)	100/2/1.98 (65)	100/4/1.94 (90)	100/4/2.09 (61)
MRSA	100/2/1.56 (39)	100/2/1.11 (40)	100/2/1.55 (121)	100/2/1.88 (150)	100/2/1.88 (110)	100/2/1.67 (176)	100/2/1.57 (49)
<i>S. agalactiae</i>	100/1/0.98 (31)	100/1/0.71 (18)	100/1/0.98 (98)	100/1/0.98 (127)	100/1/0.95 (67)	100/2/1.06 (103)	100/1/0.94 (31)
<i>S. pneumoniae</i>	100/1/0.69 (52)	100/1/0.66 (47)	100/1/0.65 (140)	100/1/0.62 (146)	100/1/0.82 (113)	100/1/0.81 (100)	10 of 10 ⁹ /0.57 (10)
PSSP	100/1/0.64 (33)	100/1/0.70 (29)	100/1/0.65 (48)	100/1/0.62 (51)	100/2/0.87 (36)	100/1/0.73 (49)	6 of 6 ⁹ /0.56 (6)
PISP	100/1/0.74 (16)	8 of 8 ⁹ /0.65 (8)	100/1/0.62 (40)	100/1/0.62 (30)	100/1/0.79 (18)	100/1/0.62 (13)	--/--/-- (0)
PRSP	3 of 3 ⁹ /1.00 (3)	10 of 10 ⁹ /0.57 (10)	100/1/0.67 (65)	100/1/0.63 (59)	100/1/0.79 (38)	100/2/1.00 (4)	4 of 4 ⁹ /0.60 (4)

*For n≤10, %Susceptible and MIC₅₀ are not reported; results are shown as susceptible n of total n. VRE=vancomycin-resistant enterococci; VISA=vancomycin-intermediate *S. aureus*.

Table 2. Cumulative percentage of recent isolates inhibited by linezolid, 2009-10 (MIC₉₀ shaded in yellow).

Organism	Breakpoints (S I R)	MIC (mg/L)			
		≤0.5	1	2	4
<i>E. faecalis</i>	≤2 4 ≥8	6.1	45.8	100	
<i>E. faecium</i>	≤2 4 ≥8	2	36.3	100	
<i>S. aureus</i>	≤4 -- ≥8	0	27.9	88.8	100
MSSA	≤4 -- ≥8	0	20.5	79.5	100
MRSA	≤4 -- ≥8	0	32.9	95.1	100
<i>S. agalactiae</i>	≤2 -- --	6.7	89.6	100	
<i>S. pneumoniae</i>	≤2 -- --	44.5	90.9	100	
PSSP	≤2 -- --	50.9	98.2	100	
PISP	≤2 -- --	69.2	100		
PRSP	≤2 -- --	28.6	78.6	100	

S=Susceptible; I=Intermediate; R=Resistant (CLSI M100-S21 guidelines).

Table 3. Geometric mean MIC by country and for Asia overall, 2004-10.

	<i>E. faecalis</i>	<i>E. faecium</i>	<i>S. aureus</i>	<i>S. agalactiae</i>	<i>S. pneumoniae</i>
Asia (479/317/1327/475/608)	1.43	1.47	1.73	0.98	0.7
China (141/84/373/128/144)	1.27*	1.25*	1.52*	0.96	0.60*
India (61/32/164/20/57)	1.26	1.22*	1.74	0.87	0.72
Malaysia (11/4/22/10/11)	1.88	1.41	2.74*	1.00	0.94*
Pakistan (23/13/62/24/33)	1.83*	1.45	2.74*	0.97	0.70
Singapore (78/18/175/65/97)	1.64*	1.65	1.87	1.04	0.78
South Korea (80/107/319/133/154)	1.44	1.66*	1.61*	0.97	0.75
Taiwan (67/49/164/75/89)	1.56	1.62	1.92*	0.99	0.64
Thailand (18/10/48/20/23)	1.47	1.41	1.92	0.97	0.76

*Asterisks denotes results significantly different from the overall Asian geometric mean MIC; green=significantly lower than the Asian average, red=significantly higher (p<0.05).

Conclusions

- Linezolid was universally active against all aerobic gram-positive isolates collected for this study in Asia between 2004 and 2010, including vancomycin-resistant enterococci, methicillin-resistant *S. aureus* (including two VISA strains), and penicillin-resistant *S. pneumoniae*. MIC₉₀ values ranged between 1 and 4 mcg/ml across species.
- The *in vitro* activity of linezolid varied slightly among countries, with China demonstrating statistically significantly lower geometric mean MICs than the Asian average against several species, and Malaysia and Pakistan showing significantly higher geometric mean MICs for two species; however, it is important to note again that 100% of isolates in all countries were susceptible to linezolid.