

Revised Abstract

Objectives: Linezolid has shown excellent activity against gram-positive organisms since its introduction a decade ago. The Tigecycline Evaluation Surveillance Trial (TEST) has been monitoring susceptibility of linezolid globally since 2004. This report compares the activity of linezolid from 2004 through 2008 against selected gram-positive aerobes. **Methods:** More than 49,000 gram-positive aerobic pathogens were collected and identified from more than 1400 sites in 57 countries over the 5 year span of the study. MICs of linezolid were determined by broth microdilution using CLSI guidelines. Linezolid susceptibilities were interpreted using CLSI breakpoints. **Results:** Results are presented below (MIC₉₀%Sus/h):

Organism	2004	2005	2006	2007	2008
<i>E. faecalis</i>	2/99.6/1093	2/99.5/1266	2/99.9/1619	2/99.9/2195	2/99.9/1820
<i>E. faecium</i>	2/98.2/396	2/99.3/427	2/99.4/651	2/99.2/707	2/99.5/768
VREs	2/98.2/216	2/97.7/280	2/98.8/327	2/98.5/336	2/99.6/240
<i>S. aureus</i>	4/100/2525	2/100/2931	4/100/3612	4/100/4944	4/100/4377
MRSA	4/100/1158	2/100/1412	4/100/1531	4/100/2028	2/100/1493
MSSA	4/100/1367	2/99.9/1519	4/99.9/2081	4/99.9/2916	4/100/2884
<i>S. agalactiae</i>	1/100/926	1/100/1036	1/100/1454	1/100/1908	1/100/1634
<i>S. pneumoniae</i>	1/100/1411	1/100/1539	1/99.9/1923	1/99.9/2306	1/100/1881

Conclusions: Linezolid demonstrates remarkable consistency in activity for most gram-positive pathogens over the 5 year study period. Small, apparent increases in %Sus for linezolid against the enterococci from 2004 to 2008 did not reach the level of significance (p>0.05). Continued monitoring of linezolid activity against this pathogen is warranted.

Introduction

Linezolid is a synthetic antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to several other antibiotics. A member of the oxazolidinone class of drugs, linezolid is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). The main indications of linezolid are infections of the skin and soft tissues and pneumonia (particularly hospital-acquired pneumonia), although off-label use for a variety of other infections is becoming popular.

The current study investigated the activity of linezolid during 2004 through 2008 against a wide range of Gram-positive pathogens as part of the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) and highlights the consistent activity of the agent and very low resistance rates.

Materials & Methods

▪ **Clinical isolates:** Isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from the period 2004 - 2008 and originated from Africa, Asia, Europe, Latin America, Middle East, North America and the South Pacific.

▪ **Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using plates manufactured by Trek Diagnostics, following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing (1). Susceptibility was determined using clinical breakpoints published by the CLSI (2).

References

1. CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eighth Edition. CLSI document M07-A8. 2010: Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
2. CLSI, Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. CLSI document M100-S20. 2010: Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

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Results

Table 1. In vitro activity of linezolid against *E. faecalis* during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	1093	2	2	99.63	0.37	0	≤0.5	4
2005	1266	2	2	99.45	0.24	0.32	≤0.5	>8
2006	1619	2	2	99.94	0.06	0	≤0.5	4
2007	2195	2	2	99.86	0.09	0.05	≤0.5	8
2008	1820	2	2	99.95	0.05	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 2. In vitro activity of linezolid against *E. faecium* during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	396	2	2	98.23	1.26	0.51	≤0.5	>8
2005	427	2	2	99.3	0.47	0.23	≤0.5	8
2006	651	2	2	99.39	0.61	0	≤0.5	4
2007	707	2	2	99.15	0.42	0.42	≤0.5	>8
2008	768	2	2	99.48	0.52	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 3. In vitro activity of linezolid against vancomycin enterococci during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	216	2	2	98.15	1.39	0.46	1	>8
2005	280	2	2	97.86	0.71	1.43	≤0.5	>8
2006	327	2	2	98.78	1.22	0	≤0.5	4
2007	336	2	2	98.51	0.89	0.60	≤0.5	8
2008	240	2	2	99.58	0.42	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 4. In vitro activity of linezolid against *S. aureus* during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	2525	2	4	100	0	0	≤0.5	4
2005	2931	2	2	99.97	0	0.03	≤0.5	8
2006	3612	2	4	99.97	0	0.03	≤0.5	>8
2007	4944	2	4	99.98	0	0.02	≤0.5	>8
2008	4377	2	4	100	0	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 5. In vitro activity of linezolid against MRSA during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	1158	2	4	100	0	0	≤0.5	4
2005	1412	2	2	100	0	0	≤0.5	4
2006	1531	2	4	100	0	0	≤0.5	4
2007	2028	2	4	100	0	0	≤0.5	4
2008	1493	2	2	100	0	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 6. In vitro activity of linezolid against MSSA during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	1367	2	4	100	0	0	≤0.5	4
2005	1519	2	2	99.93	0	0.07	≤0.5	8
2006	2081	2	4	99.95	0	0.05	≤0.5	>8
2007	2916	2	4	99.97	0	0.03	≤0.5	>8
2008	2884	2	4	100	0	0	≤0.5	4

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 7. In vitro activity of linezolid against *S. agalactiae* during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	926	1	1	100	0	0	≤0.5	2
2005	1036	1	1	100	0	0	≤0.5	2
2006	1454	1	1	100	0	0	≤0.5	2
2007	1908	1	1	100	0	0	≤0.5	2
2008	1634	1	1	100	0	0	≤0.5	2

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Table 8. In vitro activity of linezolid against *S. pneumoniae* during 2004 to 2008.

Year	N	MIC ₅₀	MIC ₉₀	% Sus*	% Int	% Res	Min MIC	Max MIC
2004	1411	≤0.5	1	100	0	0	≤0.5	2
2005	1539	≤0.5	1	100	0	0	≤0.5	2
2006	1923	≤0.5	1	99.95	0	0.05	≤0.5	4
2007	2306	≤0.5	1	99.96	0	0.04	≤0.5	4
2008	1881	1	1	100	0	0	≤0.5	2

* Susceptibility of Linezolid defined by CLSI (M100-S10, 2010). P-value >0.05 over 5 years, based on Cochrane-Armitage Trend Test.

Conclusions

- Linezolid demonstrated consistently high *in vitro* activity against all Gram-positive species over the five year study period, including resistant phenotypes such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Minor variations in the *in vitro* activity of linezolid did not reach the level of significance (p>0.05) for any species or resistant phenotype.
- Although linezolid resistance in enterococci and *S. aureus* are reported, the overall incidence of resistance remains extremely low and sporadic. No linezolid-resistant MRSA or *S. agalactiae* are reported in this large global surveillance.