

## Revised Abstract

**Objectives:** Over 75% of the bacterial super infections identified by the CDC as causal or co-morbidity factors in the deaths of pediatric patients with pneumonia secondary to the H1N1 virus are methicillin-resistant *S. aureus* (MRSA) or *S. pneumoniae*. Few pediatric drugs are available to cover both these deadly pathogens. Linezolid is the only approved oxazolidinone (although other drugs from this class are in development) for use against gram-positive bacteria that cause serious pneumonia, including streptococci, vancomycin-resistant enterococci (VRE), and MRSA. The Tigecycline Evaluation Surveillance Trial (TEST) has been monitoring susceptibility of linezolid globally since 2004. This study reports the activity of linezolid from 2007 through 2009 against selected gram-positive aerobes in North America. **Methods:** 270 gram-positive aerobic pathogens from respiratory sources were collected and identified in pediatric patients ( $\leq 16$  years) from more than 220 sites in Canada and the United States over the 3 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 summarized in the following table:

Organism	N	%Sus	mcg/ml		
			MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>E. faecalis</i>	9	100	1	2	$\leq 0.5$ - 2
<i>S. aureus</i>	77	100	2	4	1 - 4
<i>S. aureus</i> , MRSA	19	100	2	4	1 - 4
<i>S. aureus</i> , MSSA	58	100	2	4	1 - 4
<i>S. agalactiae</i>	14	100	1	1	$\leq 0.5$ - 2
<i>S. pneumoniae</i>	170	100	1	1	$\leq 0.5$ - 2

**Conclusions:** Although some reports of linezolid resistance are published, they are rare, and this surveillance detected no *in vitro* resistant strains in this pediatric population. Linezolid demonstrates a remarkable consistency in activity against most gram-positive pathogens. Continued monitoring of linezolid activity against these pathogens is warranted.

## Introduction

Linezolid is the only approved oxazolidinone (although other drugs from this class are in development) for use against gram-positive bacteria that cause serious pneumonia, including streptococci, vancomycin-resistant enterococci (VRE), and MRSA. Linezolid is used in multiple indications for the treatment of Gram-positive infections including the treatment of infections in the pediatric population. The Tigecycline Evaluation Surveillance Trial (TEST) has been monitoring susceptibility of linezolid globally since 2004. This study reports the activity of linezolid from 2007 through 2009 against selected Gram-positive aerobes from pediatric respiratory sources in North America.

## 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 2007 - 2009 North America.

**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) or FDA (3), where appropriate.

## References

- Clinical and Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in *Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Clinical and Laboratory Standards Institute, *Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement*, in CLSI document M100-S20. 2010: CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Tygacil®. 2009. Federal Drug Administration, Product Information. Pfizer, Inc., Collegeville, PA, USA.

## Acknowledgements

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Figure 1. Origins of the pediatric respiratory isolates

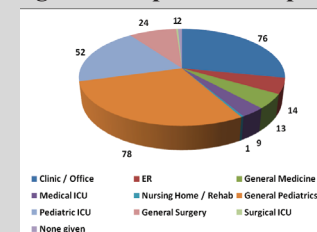


Table 1. In vitro activity of linezolid and comparators against 9 isolates of *E. faecalis* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	0.5	1	0	0	0	0.5	1
Ampicillin	1	1	100	0	0	0.5	1
Ceftriaxone	>64	>64	0	0	0	64	>64
Levofloxacin	0.5	1	100	0	0	0.5	1
Linezolid	1	2	100	0	0	$\leq 0.5$	2
Meropenem	4	8	0	0	0	0.25	8
Minocycline	8	>8	22.2	33.3	44.4	1	>8
Penicillin	2	4	100	0	0	0.5	4
Pip / Tazo	2	4	0	0	0	2	4
Tigecycline	0.12	0.25	100	0	0	0.06	0.25
Vancomycin	1	2	100	0	0	0.25	2

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

Table 2. In vitro activity of linezolid and comparators against 77 isolates of *S. aureus* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	1	8	81.8	0.0	18.2	0.12	>8
Ampicillin	8	>16	15.6	0.0	84.4	$\leq 0.06$	>16
Ceftriaxone	4	32	76.6	15.6	7.8	2	>64
Levofloxacin	0.25	8	77.9	2.6	19.5	$\leq 0.06$	>32
Linezolid	2	4	100.0	0.0	0.0	1	4
Meropenem	$\leq 0.12$	2	93.5	2.6	3.9	$\leq 0.12$	>16
Minocycline	$\leq 0.25$	0.5	100.0	0.0	0.0	$\leq 0.25$	2
Penicillin	8	>8	13.0	0.0	87.0	$\leq 0.06$	>8
Pip / Tazo	1	>16	87.0	0.0	13.0	$\leq 0.25$	>16
Tigecycline	0.12	0.25	100.0	0.0	0.0	0.06	0.5
Vancomycin	1	1	100.0	0.0	0.0	$\leq 0.12$	2

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

Table 3. In vitro activity of linezolid and comparators against 19 isolates of methicillin-resistant *S. aureus* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	8	>8	26.3	0.0	73.7	4	>8
Ampicillin	>16	>16	0.0	0.0	100.0	0.5	>16
Ceftriaxone	32	>64	10.5	57.9	31.6	8	>64
Levofloxacin	4	32	26.3	0.0	73.7	0.25	>32
Linezolid	2	4	100.0	0.0	0.0	1	4
Meropenem	2	>16	73.7	10.5	15.8	0.5	>16
Minocycline	$\leq 0.25$	$\leq 0.25$	100.0	0.0	0.0	$\leq 0.25$	0.5
Penicillin	>8	>8	0.0	0.0	100.0	1	>8
Pip / Tazo	16	>16	47.4	0.0	52.6	2	>16
Tigecycline	0.12	0.5	100.0	0.0	0.0	0.06	0.5
Vancomycin	1	1	100.0	0.0	0.0	0.5	1

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

## Results

Table 4. In vitro activity of linezolid and comparators against 14 isolates of *S. agalactiae* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	0.06	0.12	0	0	0	$\leq 0.03$	0.12
Ampicillin	0.12	0.12	100	0	0	$\leq 0.06$	0.25
Ceftriaxone	0.06	0.12	100	0	0	$\leq 0.03$	0.12
Levofloxacin	1	1	100	0	0	0.25	1
Linezolid	1	1	100	0	0	$\leq 0.5$	2
Meropenem	$\leq 0.12$	$\leq 0.12$	100	0	0	$\leq 0.12$	$\leq 0.12$
Minocycline	8	>8	0	0	0	$\leq 0.25$	>8
Penicillin	$\leq 0.06$	0.12	100	0	0	$\leq 0.06$	0.12
Pip / Tazo	$\leq 0.25$	0.5	0	0	0	$\leq 0.25$	0.5
Tigecycline	0.03	0.06	100	0	0	0.03	0.12
Vancomycin	0.5	0.5	100	0	0	0.25	1

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

Table 5. In vitro activity of linezolid and comparators against 170 isolates of *S. pneumoniae* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	0.06	8	74.7	12.4	12.9	$\leq 0.03$	8
Ampicillin	0.12	8	0.0	0.0	0.0	$\leq 0.06$	16
Azithromycin	0.25	>64	54.1	0.0	45.9	$\leq 0.03$	>64
Ceftriaxone	0.06	1	92.4	4.7	2.9	$\leq 0.03$	8
Clarithromycin	0.06	>64	54.1	1.2	44.7	$\leq 0.015$	>64
Clindamycin	0.06	>64	75.3	0.0	24.7	$\leq 0.015$	>64
Erythromycin	0.25	>64	51.8	1.2	47.1	$\leq 0.015$	>64
Imipenem	1	1	25.0	0.0	75.0	$\leq 0.12$	1
Levofloxacin	1	1	99.4	0.0	0.6	0.12	8
Linezolid	1	1	100.0	0.0	0.0	$\leq 0.5$	2
Meropenem	$\leq 0.12$	1	63.3	9.0	27.7	$\leq 0.12$	4
Minocycline	0.5	8	0.0	0.0	0.0	$\leq 0.25$	>8
Penicillin	0.12	4	44.7	21.8	33.5	$\leq 0.06$	8
Pip / Tazo	$\leq 0.25$	4	0.0	0.0	0.0	$\leq 0.25$	8
Tigecycline	0.03	0.12	90.0	0.0	10.0	$\leq 0.008$	0.12
Vancomycin	0.25	0.5	100.0	0.0	0.0	$\leq 0.12$	1

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

Table 6. In vitro activity of linezolid and comparators against 57 isolates of penicillin-resistant *S. pneumoniae* from pediatric respiratory sources

Drug	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus*	%Int	%Res	Min MIC	Max MIC
Amox / Clav	4	8	24.6	36.8	38.6	0.5	8
Ampicillin	4	8	0.0	0.0	0.0	1	16
Azithromycin	64	>64	12.5	0.0	87.5	0.12	>64
Ceftriaxone	1	2	77.2	14.0	8.8	0.25	8
Clarithromycin	64	>64	12.5	0.0	87.5	0.03	>64
Clindamycin	>64	>64	25.0	0.0	75.0	0.03	>64
Erythromycin	>64	>64	12.5	0.0	87.5	0.12	>64
Imipenem	1	1	0.0	0.0	100.0	1	1
Levofloxacin	1	1	58.3	0.0	1.8	0.12	8
Linezolid	$\leq 0.5$	1	100.0	0.0	0.0	$\leq 0.5$	2
Meropenem	1	1	3.7	16.7	79.6	$\leq 0.12$	4
Minocycline	4	>8	0.0	0.0	0.0	$\leq 0.25$	>8
Penicillin	4	4	0.0	0.0	100.0	2	8
Pip / Tazo	4	8	0.0	0.0	0.0	1	8
Tigecycline	0.03	0.06	96.5	0.0	3.5	$\leq 0.008$	0.12
Vancomycin	0.25	0.5	100.0	0.0	0.0	0.25	1

\* Susceptibility defined by CLSI (M100-S20, Jan 2010), where available; Tigecycline susceptibility defined by FDA (Tygacil®, 2009).

## Conclusions

- All isolates were susceptible to linezolid in this study.
- Linezolid exhibited consistent activity against all Gram-positives from pediatric sources.
- Activity of linezolid was not affected by resistance to other antimicrobials.