Analysis of MIC Relationships Between Tedizolid, Linezolid, and Vancomycin Tested Against *Staphylococcus aureus* and Enterococcal Clinical Isolates From US and European Hospitals (2014-2015)

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INTRODUCTION

- Antimicrobial resistance in bacterial pathogens is a worldwide challenge as it is associated with high morbidity and mortality rates
  - Multidrug-resistant patterns in Gram-positive and Gram-negative bacteria have resulted in infections that are difficult to treat or are even untreatable with conventional antimicrobials
  - Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates with decreased susceptibility to vancomycin and daptomycin have been reported
  - In addition, the often multidrug-resistant *Enterococcus faecium* organism that causes infections in hospitals in the United States has reached a prevalence similar to that of *Enterococcus faecalis,* with rates of vancomycin resistance between 68% and 80% (unpublished SENTRY data)
- This scenario has prompted the inclusion of MRSA and *E. faecium* among the so-called ESKAPE organisms (*E. faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.), which cause most nosocomial infections in the United States and are refractory to most clinically available agents
- Tedizolid has been approved for treatment of acute bacterial skin and skin structure infections (ABSSSI) in the United States, Europe, and Canada
  - Phase 3 clinical trials evaluating tedizolid use in nosocomial pneumonia are ongoing
- This study evaluated minimum inhibitory concentration (MIC) relationships between tedizolid and linezolid and between tedizolid and vancomycin against *S. aureus* and enterococci from US and European hospitals

MATERIALS AND METHODS

Bacterial strain collection

- A total of 10,666 *S. aureus* isolates and 2449 enterococci (1626 *E. faecalis* and 823 *E. faecium*) were collected during the Surveillance of Tedizolid Activity and Resistance (STAR) Program for 2014 and 2015 from the United States and Europe
- Isolates were initially identified by the participating laboratory and submitted to a central monitoring facility (JMI Laboratories, North Liberty, Iowa), where bacterial identifications were confirmed using standard algorithms and were supported by MALDI–TOF–MS (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
  - Testing was performed using reference 96-well panels manufactured by JMI Laboratories
  - MIC readings for tedizolid and linezolid were performed according to the CLSI guidelines (ie, the first well in which trailing begins without regard for pinpoint trailing in the wells)
- Quality assurance was performed by concurrent testing of CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213 and *E. faecalis* 29212); all QC results were within acceptable published ranges
- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (M100-S26)
  - Tigecycline MIC breakpoints were those found in the US Food and Drug Administration–approved package insert

RESULTS

- Tedizolid ($MIC_{50/90}$, 0.12/0.12 µg/mL; 100.0% susceptible) inhibited all *S. aureus* clinical isolates at ≤0.25 µg/mL, below the breakpoint for susceptibility (ie, ≤0.5 µg/mL). MIC_{50} and MIC_{90} results obtained for tedizolid against the MRSA and methicillin-susceptible subsets were equivalent to those obtained against the entire *S. aureus* population (**Tables 1** and **2**)

Table 1. Activity of tedizolid against contemporary *Staphylococcus aureus* and enterococcal clinical isolates from US and European hospitals

Organism	MIC, µg/mL		Number (cumulative %) Inhibited at MIC, µg/mL[‡§]							
Species/Phenotype (n)	50%	90%	≤0.015	0.03	0.06	0.12	0.25	0.5	1	>1
S. aureus (10,666)	0.12	0.12	1 (<0.1)	63 (0.6)	2416 (23.3)	**7680 (95.3)**	506 (100.0)			
MSSA (6678)	0.12	0.12	1 (<0.1)	35 (0.5)	1331 (20.5)	**4954 (94.7)**	357 (100.0)			
MRSA (3988)	0.12	0.12	0 (0.0)	28 (0.7)	1085 (27.9)	**2726 (96.3)**	149 (100.0)			
Enterococcus spp.[†] (2449)	0.12	0.25	0 (0.0)	7 (0.3)	120 (5.2)	**1416 (63.0)**	880 (98.9)	22 (99.8)	1 (99.9)	3 (100.0)
E. faecalis (1626)	0.12	0.25	0 (0.0)	2 (0.1)	48 (3.1)	**849 (55.3)**	710 (99.0)	15 (99.9)	1 (99.9)	1 (100.0)
E. faecium (823)	0.12	0.25	0 (0.0)	5 (0.6)	72 (9.4)	**567 (78.3)**	170 (98.9)	7 (99.8)	0 (99.8)	2 (100.0)
Vancomycin-susceptible (462)	0.12	0.25	0 (0.0)	3 (0.6)	32 (7.6)	**317 (76.2)**	107 (99.4)	3 (100.0)		
Vancomycin-resistant (359)	0.12	0.25	0 (0.0)	2 (0.6)	40 (11.7)	**248 (80.8)**	63 (98.3)	4 (99.4)	0 (99.4)	2 (100.0)

CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.
†Vancomycin-susceptible and -resistant according to the CLSI breakpoints of ≤4 µg/mL and ≥32 µg/mL, respectively.
‡MIC reading for tedizolid performed according to CLSI guidelines (the first well in which trailing begins without regard for pinpoint trailing in the wells).
§Tedizolid modal MIC shown in bold.

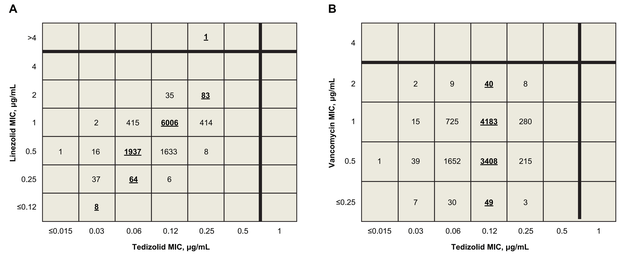
Table 2. Antimicrobial activity of tedizolid and comparator agents against contemporary *Staphylococcus aureus* and enterococcal clinical isolates causing infections in US and European hospitals

Organism/Group (n) Antimicrobial Agent	MIC, µg/mL			Susceptibility[†]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
MSSA (6678)						
Tedizolid	0.12	0.12	0.015 to 0.25	100.0	0.0	0.0
Linezolid	1	1	≤0.12 to 2	100.0	—	0.0
Ceftaroline	0.25	0.25	≤0.06 to 1	100.0	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25 to >2	96.2	0.1	3.7
Daptomycin	0.25	0.5	≤0.12 to 4	>99.9	—	—
Erythromycin	0.25	>8	≤0.12 to >8	73.3	5.5	21.2
Levofloxacin	0.25	0.5	≤0.12 to >4	91.9	0.3	7.8
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	96.0	0.5	3.5
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0	—	—
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	99.6	—	0.4
Vancomycin	0.5	1	≤0.12 to 2	100.0	0.0	0.0
MRSA (3988)						
Tedizolid	0.12	0.12	0.03 to 0.25	100.0	0.0	0.0
Linezolid	1	1	≤0.12 to >8	>99.9	—	<0.1
Ceftaroline	1	1	0.06 to 4	93.4	6.5	0.1
Clindamycin	≤0.25	>2	≤0.25 to >2	72.0	0.3	27.8
Daptomycin	0.25	0.5	≤0.12 to 2	99.9	—	—
Erythromycin	>8	>8	≤0.12 to >8	16.7	4.6	78.7
Levofloxacin	4	>4	≤0.12 to >4	26.6	1.1	72.3
Tetracycline	≤0.5	1	≤0.5 to >8	92.0	1.2	6.8
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0	—	—
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	97.2	—	2.8
Vancomycin	1	1	≤0.12 to 2	100.0	0.0	0.0
E. faecalis (1626)						
Tedizolid	0.12	0.25	≤0.03 to >1	99.9	—	—
Linezolid	1	1	≤0.25 to 8	99.7	0.2	0.1
Ampicillin	1	1	≤0.5 to 8	100.0	—	0.0
Daptomycin	1	2	≤0.25 to 4	100.0	—	—
Erythromycin	>16	>16	≤0.12 to >16	5.7	42.0	52.3
Levofloxacin	1	>4	≤0.5 to >4	72.8	0.5	26.7
Teicoplanin	≤2	≤2	≤2 to >16	98.2	0.1	1.7
Tetracycline	>8	>8	≤1 to >8	24.1	0.6	75.2
Vancomycin	1	2	≤0.5 to >16	97.9	0.1	2.0
E. faecium vancomycin–susceptible (462)						
Tedizolid	0.12	0.25	≤0.03 to 0.5	—	—	—
Linezolid	1	1	≤0.25 to 2	100.0	0.0	0.0
Ampicillin	>8	>8	≤0.5 to >8	17.5	—	82.5
Daptomycin	2	4	≤0.25 to 8	99.8	—	—
Erythromycin	>16	>16	≤0.12 to >16	2.4	17.9	79.7
Levofloxacin	>4	>4	≤0.5 to >4	15.4	6.3	78.3
Tetracycline	8	>8	≤1 to >8	48.4	1.7	49.9
Vancomycin	≤0.5	1	≤0.5 to 4	100.0	0.0	0.0
E. faecium vancomycin–resistant (359)						
Tedizolid	0.12	0.25	≤0.03 to >1	—	—	—
Linezolid	1	1	≤0.25 to 8	98.9	0.6	0.6
Ampicillin	>8	>8	≤0.5 to >8	0.8	—	99.2
Daptomycin	1	2	≤0.25 to >8	99.7	—	—
Erythromycin	>16	>16	≤0.12 to >16	4.0	5.6	90.4
Levofloxacin	>4	>4	4 to >4	0.0	0.3	99.7
Tetracycline	>8	>8	≤1 to >8	20.6	4.5	74.9
Vancomycin	>16	>16	>16	0.0	0.0	100.0

CLSI, Clinical and Laboratory Standards Institute; MIC_{50} = 50% minimum inhibitory concentration; MIC_{90} = 90% minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; TMP-SMX = trimethoprim-sulfamethoxazole; S = susceptible; I = intermediate; R = resistant.
— = breakpoint not available.
†Breakpoint criteria for tedizolid and comparator agents were those from the CLSI (2016), as available. Interpretation for tigecycline MIC results used breakpoints approved by the US Food and Drug Administration. Levofloxacin results against enterococci apply to patients with urinary tract infections only.

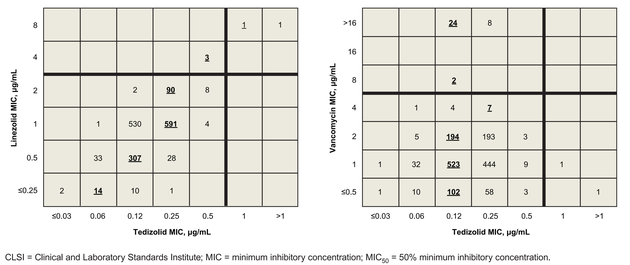
- MIC_{90} values obtained for tedizolid against *S. aureus* and the MRSA subset were 8-fold lower than those for linezolid (MIC_{90}, 1 µg/mL; >99.9% susceptible) and vancomycin (MIC_{90}, 1 µg/mL; 100.0% susceptible) (**Table 2**)
- Tedizolid had MIC_{50} and MIC_{90} values against *E. faecalis* of 0.12 and 0.25 µg/mL (99.9% susceptible), respectively (**Table 1**). Tedizolid MIC_{50} and MIC_{90} results ($MIC_{50/90}$, 0.12/0.25 µg/mL) against vancomycin-susceptible and -resistant *E. faecium* were equivalent (**Tables 1** and **2**)
- MIC results obtained for tedizolid against the *E. faecalis* population were 4- to 8-fold lower than those for linezolid ($MIC_{50/90}$, 1/1 µg/mL; 99.7% susceptible), ampicillin ($MIC_{50/90}$, 1/1 µg/mL; 100.0% susceptible), daptomycin ($MIC_{50/90}$, 1/2 µg/mL; 100.0% susceptible), and vancomycin ($MIC_{50/90}$, 1/2 µg/mL; 97.9% susceptible)
- When MIC results were analyzed against the vancomycin-resistant *E. faecium* subpopulation, those for tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL) were 4- to 8-fold lower than those for linezolid ($MIC_{50/90}$, 1/1 µg/mL; 98.9% susceptible) and daptomycin ($MIC_{50/90}$, 1/2 µg/mL; 99.7% susceptible) (**Table 2**)
- MIC correlation analysis revealed that the tedizolid modal MIC and MIC_{50} results obtained against *S. aureus*, *E. faecalis*, and *E. faecium* increased as the linezolid MIC values increased (**Figures 1-3**)
- Overall, no significant variations in the tedizolid modal MIC and MIC_{50} values were observed when analyzed against each vancomycin MIC result obtained against the 3 species of isolates investigated (**Figures 1-3**)

Figure 1. Scatter diagram of tedizolid MIC values plotted against the linezolid (A) and vancomycin (B) MIC values for 10,666 *Staphylococcus aureus* strains from US and European hospitals.



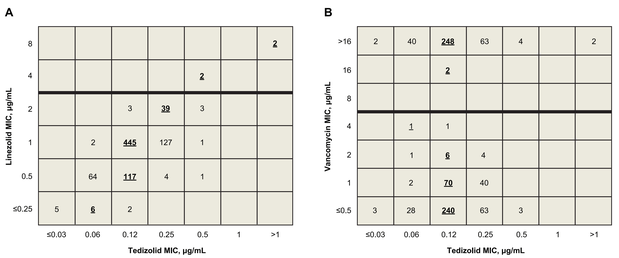
CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MIC_{50} = 50% minimum inhibitory concentration.
Thick vertical lines represent the tedizolid (≤0.5 µg/mL) breakpoint for susceptibility against *S. aureus* according to the CLSI, and thick horizontal lines represent the linezolid (≤2 µg/mL) and vancomycin (≤2 µg/mL) breakpoints for susceptibility, respectively. Tedizolid modal MIC and MIC_{50} values against groups of *S. aureus* at each linezolid or vancomycin MIC result are bold and underlined, respectively.

Figure 2. Scatter diagram of tedizolid MIC values plotted against the linezolid (A) and vancomycin (B) MIC values for 1626 *Enterococcus faecalis* strains from US and European hospitals.



CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MIC_{50} = 50% minimum inhibitory concentration.
Thick vertical lines represent the tedizolid (≤0.5 µg/mL) breakpoint for susceptibility against *E. faecalis* according to the CLSI, and thick horizontal lines represent the linezolid (≤2 µg/mL) and vancomycin (≤4 µg/mL) breakpoints for susceptibility, respectively. Tedizolid modal MIC and MIC_{50} values against groups of *E. faecalis* at each linezolid or vancomycin MIC result are bold and underlined, respectively.

Figure 3. Scatter diagram of tedizolid MIC values plotted against the linezolid (A) and vancomycin (B) MIC values for 823 *Enterococcus faecium* strains from US and European hospitals.



CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MIC_{50} = 50% minimum inhibitory concentration.
Thick horizontal lines represent the linezolid (≤2 µg/mL) and vancomycin (≤4 µg/mL) breakpoints for susceptibility, respectively, according to the CLSI. Tedizolid modal MIC and MIC_{50} values against groups of *E. faecium* at each linezolid or vancomycin MIC result are bolded and underlined, respectively.

CONCLUSIONS

- Tedizolid showed potent *in vitro* activity against this contemporary collection of clinical isolates causing infections in US and European hospitals. Other agents showed activity, but tedizolid potency was consistently higher (at least 4-fold) than that of comparators
- A monotonically increasing relationship between tedizolid and linezolid MIC results was observed against all three species included in the study. In contrast, no correlation was detected between tedizolid and vancomycin MIC values
- The lack of correlation between tedizolid and vancomycin MIC results was likely due to the presence of distinct mechanisms of action between the oxazolidinone and glycopeptide classes of antibacterials

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