Tedizolid *In Vitro* Activity against a Collection of Multidrug-Resistant Gram-Positive Clinical Isolates from US Medical Centers (2017–2018)

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Introduction

- Surveillance of multidrug-resistant (MDR) organisms represents a cornerstone for recognizing the emergence of resistance and controlling its dissemination
- The Surveillance of Tedizolid Activity and Resistance (STAR) program has monitored tedizolid resistance worldwide since before its clinical approval by the Food and Drug Administration and European Medicines Agency
- Tedizolid is an oxazolidinone compound proven to be active *in vitro* and *in vivo* against gram-positive (GP) pathogens, including MDR strains
- Tedizolid was approved in the United States, Europe, and other regions to treat adults with acute bacterial skin and skin structure infections
- This study evaluates the activity of tedizolid and comparator agents against a large contemporary collection of MDR gram-positive clinical isolates from US medical centers

Materials and Methods

Bacterial isolates

- In 2017-2018, a total of 11,778 unique gram-positive isolates (1 per infection event) were collected from 32 US medical centers, including all 9 census divisions
- These isolates were submitted to the central monitoring laboratory (JMI Laboratories; North Liberty, Iowa, USA) as part of the STAR program
- Isolates were determined to be clinically significant based on local guidelines and were recovered from bloodstream infection (BSI; *n* = 3,256; 27.6% overall), skin and skin structure infection (SSSI; *n* = 4,099, 34.8%), pneumonia in hospitalized patients (PHP; *n* = 1,843; 15.6%), community-acquired respiratory tract infection (CARTI; *n* = 1,392; 11.8%), urinary tract infection (UTI; *n* = 460; 3.9%), and intra-abdominal infection (IAI; *n* = 557; 4.7%; Figure 1)
- Bacterial identifications were primarily performed by the participating laboratory and confirmed by the reference monitoring laboratory (JMI Laboratories) through standard algorithms and supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)

Antimicrobial susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following the Clinical and Laboratory Standards Institute (CLSI) M07 (2018) document
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth (2.5–5% lysed horse blood added for testing streptococci)
- MIC value validation was performed by concurrently testing CLSI-recommended quality control (QC) reference strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619) and interpreted using published ranges (M100, 2019)
- MIC interpretations were based on the CLSI breakpoint criteria (M100, 2019), as available
- MDR isolates were defined according to published criteria, which define MDR as nonsusceptible to 1 agent in ≥3 antimicrobial classes

Results

- The most common organisms varied by infection type (Figure 1)
- *S. aureus* (n=6,588, 55.5% overall) isolates were >99.9% susceptible to tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L)
  - All methicillin-resistant *S. aureus* (MRSA; 42.3% of *S. aureus*) and MDR-*S. aureus* isolates (28.5% of *S. aureus*) but 1 were susceptible to tedizolid (>99.9%; $MIC_{50/90}$, 0.12/0.25 mg/L), linezolid (>99.9%; $MIC_{50/90}$, 1/2 mg/L), and daptomycin (>99.9%; $MIC_{50/90}$, 0.25/0.25 mg/L); all were vancomycin susceptible ($MIC_{50/90}$, 1/1 mg/L; Tables 1 and 2)
- Among coagulase-negative staphylococcal isolates (CoNS; *n* = 777; 6.6% overall), 98.7% were inhibited by tedizolid at an MIC of ≤0.5 mg/L (*S. aureus* breakpoint)
  - Tedizolid was very active against MRCoNS (56.4% of CoNS; $MIC_{50/90}$, 0.12/0.25 mg/L) and MDR-CoNS isolates (41.7% of CoNS; $MIC_{50/90}$, 0.12/0.25 mg/L), inhibiting 97.7% and 96.9% of those isolates at an MIC ≤0.5 mg/L, respectively
  - Based on MIC_{50} values, tedizolid was 8- to 16-fold more active than linezolid ($MIC_{50/90}$, 1/1-2 mg/L) and vancomycin ($MIC_{50/90}$, 2/2 mg/L)
- Tedizolid was highly active against β-hemolytic streptococci (BHS; *n* = 1,208; 10.3% overall; $MIC_{50/90}$, 0.25/0.25 mg/L), viridans group streptococci (VGS; *n* = 283; 2.4% overall; $MIC_{50/90}$, 0.12/0.25 mg/L), and *S. pneumoniae* (*n* = 1,675; 14.2% overall; $MIC_{50/90}$, 0.25/0.25 mg/L), regardless the MDR phenotype (Tables 1 and 3)
  - MDR subsets of BHS and *S. pneumoniae* displayed similar $MIC_{50/90}$ values (0.25/0.25 mg/L)
  - Only 1 MDR-VGS isolate was included, against which the tedizolid MIC value was 0.12 mg/L
- All *E. faecalis* isolates (*n* = 824; 7.0% overall) were tedizolid susceptible ($MIC_{50/90}$, 0.25/0.5 mg/L), 99.9% were linezolid susceptible ($MIC_{50/90}$, 1/1 mg/L), 97.0% were vancomycin susceptible ($MIC_{50/90}$, 1/2 mg/L), 96.8% were daptomycin susceptible ($MIC_{50/90}$, 0.5/1 mg/L), and all were susceptible to ampicillin ($MIC_{50/90}$, 1/1 mg/L; Table 4)
  - Except for vancomycin, the VRE (3.0% of *E. faecalis*) subset displayed similar $MIC_{50/90}$ values for tedizolid and comparators (Table 4)
- Among *Enterococcus faecium* isolates (*n* = 371; 3.1% overall; $MIC_{50/90}$, 0.25/0.5 mg/L), 99.4% were inhibited at a tedizolid MIC of ≤0.5 mg/L (*E. faecalis* breakpoint; Table 1)
  - Tedizolid was very active against VRE isolates (67.1% of *E. faecium*, $MIC_{50/90}$, 0.25/0.5 mg/L), and inhibited all isolates at an MIC of ≤0.5 mg/L
  - Linezolid-nonsusceptible *E. faecium* isolates (*n* = 4) were inhibited by tedizolid at an MIC ≤1 mg/L (Table 1)
  - Based on MIC_{50}, tedizolid ($MIC_{50/90}$, 0.25/0.5 mg/L) was 4-fold more active than linezolid ($MIC_{50/90}$, 1/2 mg/L) and daptomycin ($MIC_{50/90}$, 1/2 mg/L) against *E. faecium* isolates and the VRE subset (Table 4)
  - Tedizolid inhibited all *E. faecium* isolates displaying a daptomycin-susceptible dose-dependent phenotype (SDD; 29.9% of *E. faecium* isolates) at an MIC of ≤1 mg/L

Conclusions

- Tedizolid displayed potent *in vitro* activity against MRSA, MRCoNS, enterococci, and streptococci in the United States, including isolates displaying decreased susceptibility (eg, MDR, VRE) to agents commonly used to treat serious infections
- Based on MIC_{50} values, tedizolid was generally 4- to 8-fold more active than linezolid and vancomycin against the overall gram-positive collection, 8-fold more active than linezolid and vancomycin against MDR *S. aureus*, and 4- to >32- fold more active than linezolid, daptomycin, and vancomycin against MDR *E. faecium*
- These results support the role of tedizolid as an option for treating infections caused by MDR gram-positive isolates

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Table 1 Antimicrobial activity of tedizolid tested against the main organisms and resistant phenotypes

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:										MIC_{50}	MIC_{90}
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>1			
Staphylococcus aureus (6,588)	0 0.0	1 <0.1	5 0.1	110 1.8	3,230 50.8	2,964 95.8	277 >99.9	0 >99.9	1 100.0		0.12	0.25
MRSA (2,784)	0 0.0	1 <0.1	2 0.1	71 2.7	1,630 61.2	599 97.1	80 >99.9	0 >99.9	1 100.0		0.12	0.25
MDR[b] (1,880)		0 0.0	1 0.1	54 2.9	1,046 58.6	713 96.5	65 99.9	0 99.9	1 100.0		0.12	0.25
Coagulase-negative staphylococci (777)	1 0.1	0 0.1	4 0.6	78 10.7	460 69.9	215 97.6	9 98.7	1 98.8	9 100.0		0.12	0.25
MRCoNS (438)			0 0.0	30 6.8	236 60.7	154 95.9	8 97.7	1 97.9	9 100.0		0.12	0.25
MDR (324)			0 0.0	18 5.6	174 59.3	118 95.7	4 96.9	1 97.2	9 100.0		0.12	0.25
Linezolid-nonsusceptible (10)							0 0.0	1 10.0	9 100.0		>1	>1
β-hemolytic streptococci (1,208)			0 0.0	1 0.1	293 24.3	878 97.0	36 100.0				0.25	0.25
MDR (179)				0 0.0	55 30.7	122 98.9	2 100.0				0.25	0.25
Viridans group streptococci (283)		2 0.7	7 3.2	27 12.7	161 69.6	83 98.9	3 100.0				0.12	0.25
MDR (1)				0 0.0	1 100.0							
Streptococcus pneumoniae (1,675)		0 0.0	1 0.1	15 1.0	267 16.9	1,230 90.3	162 100.0				0.25	0.25
Penicillin-resistant[a] (174)			0 0.0	1 0.6	26 15.5	130 90.2	17 100.0				0.25	0.25
MDR (240)			0 0.0	1 0.4	53 22.5	175 95.4	11 100.0				0.25	0.25
Enterococcus faecalis (824)			0 0.0	6 0.7	139 17.6	548 84.1	131 100.0				0.25	0.5
Vancomycin-nonsusceptible (VRE) (25)			0 0.0	1 4.0	8 36.0	13 88.0	3 100.0				0.25	0.5
Linezolid-nonsusceptible (1)						0 0.0	1 100.0					
Daptomycin-nonsusceptible[c] (26)				0 0.0	3 11.5	19 84.6	4 100.0				0.25	0.5
Enterococcus faecium (371)		0 0.0	3 0.8	8 3.0	111 32.9	190 84.1	57 99.5	2 100.0			0.25	0.5
Vancomycin-nonsusceptible (VRE) (249)		0 0.0	2 0.8	7 3.6	88 39.0	121 87.6	31 100.0				0.25	0.5
Linezolid-nonsusceptible (4)						0 0.0	2 50.0	2 100.0			0.5	
Daptomycin-nonsusceptible[c] (111)		0 0.0	1 0.9	0 0.9	28 26.1	56 76.6	25 99.1	1 100.0			0.25	0.5
MDR (112)				0 0.0	45 40.2	49 83.9	18 100.0				0.25	0.5

[a] MIC ≥4 mg/L.
[b] MDR as nonsusceptible to 1 agent in ≥3 antimicrobial classes.
[c] MIC ≥2 mg/L.
MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant; MRCoNS, methicillin-resistant coagulase-negative staphylococci; VRE, vancomycin-resistant enterococci.

Table 2 Antimicrobial activity of tedizolid and comparator agents tested against resistant subsets of *S. aureus* and coagulase-negative *Staphylococcus* isolates

Subset Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %R
MRSA (2,784)				
Tedizolid	0.12	0.25	>99.9	<0.1
Linezolid	1	2	>99.9	<0.1
Clindamycin	0.06	>2	73.4	26.2
Daptomycin	0.25	0.25	>99.9	
Levofloxacin	4.0	>4	34.4	65.3
TMP-SMX	≤0.5	≤0.5	96.8	3.2
Vancomycin	1	1	100.0	0.0
MDR *S. aureus* (1,880)				
Tedizolid	0.12	0.25	99.9	0.1
Linezolid	1	2	99.9	0.1
Clindamycin	0.06	>2	55.3	44.0
Daptomycin	0.25	0.25	99.9	
Levofloxacin	>4	>4	7.7	91.9
Oxacillin	>2	>2	5.8	94.2
TMP-SMX	≤0.5	≤0.5	94.9	5.1
Vancomycin	1	1	100.0	0.0
MRCoNS (438)				
Tedizolid	0.12	0.25		
Linezolid	1	2	97.7	2.3
Clindamycin	0.25	>2	52.5	44.5
Daptomycin	0.25	0.5	100.0	
Levofloxacin	>4	>4	40.2	58.7
TMP-SMX	2	8	51.8	48.2
Vancomycin	2	2	100.0	0.0
MDR CoNS (324)				
Tedizolid	0.12	0.25		
Linezolid	1	1	96.9	3.1
Clindamycin	>2	>2	32.4	63.3
Daptomycin	0.25	0.5	100.0	
Levofloxacin	>4	>4	24.1	73.8
Oxacillin	>2	>2	7.4	92.6
TMP-SMX	4	8	39.2	60.8
Vancomycin	2	2	100.0	0.0

[a] Criteria as published by CLSI (2019).
MRSA, methicillin-resistant *S. aureus*; MDR, multidrug-resistant; MRCoNS, methicillin-resistant coagulase-negative staphylococci; VRE, vancomycin-resistant enterococci; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 3 Antimicrobial activity of tedizolid and comparator agents tested against 3,166 *Streptococcus* spp. and resistant subsets

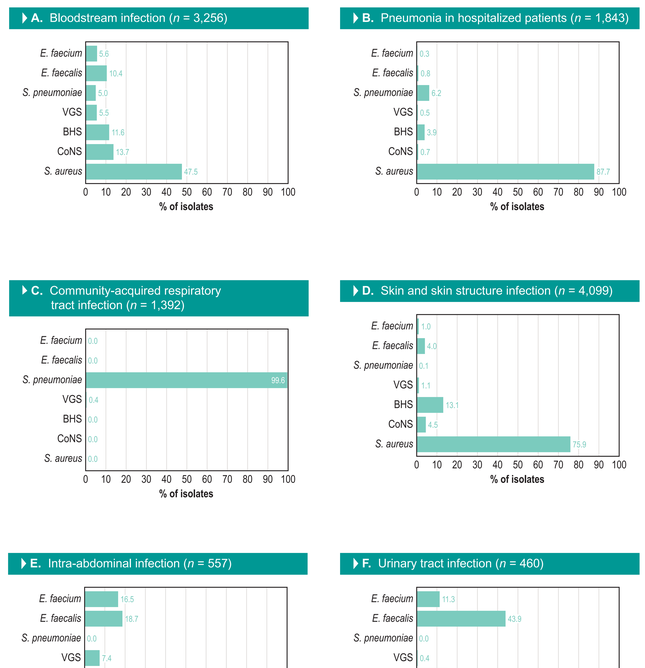
Subset Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %R
BHS (1,208)				
Tedizolid	0.25	0.25		
Linezolid	1	2	100.0	
Amoxicillin-clavulanic acid	≤0.03	0.06	100.0	
Ceftriaxone	0.03	0.06	100.0	
Clindamycin	≤0.25	>2	81.6	17.1
Daptomycin	≤0.06	0.25	100.0	
Levofloxacin	0.5	1	99.3	0.6
Penicillin	0.015	0.06	100.0	
Vancomycin	0.5	0.5	100.0	
MDR BHS (179)				
Tedizolid	0.25	0.25	100.0	
Linezolid	1	1	100.0	
Amoxicillin-clavulanic acid	0.06	0.06	100.0	
Ceftriaxone	0.06	0.06	100.0	
Clindamycin	>2	>2	1.7	98.3
Daptomycin	0.12	0.25	100.0	
Levofloxacin	1	1	98.3	1.7
Penicillin	0.03	0.06	100.0	
Vancomycin	0.5	0.5	100.0	
VGS (283)				
Tedizolid	0.12	0.25		
Linezolid	1	1	100.0	
Amoxicillin-clavulanic acid	0.06	1		
Ceftriaxone	0.12	0.5	96.5	2.5
Clindamycin	≤0.25	>2	86.6	13.1
Daptomycin	0.25	0.5	100.0	
Levofloxacin	1	>4	88.0	11.7
Penicillin	0.06	0.5	74.6	3.9
Vancomycin	0.5	1	100.0	

Table 4 Antimicrobial activity of tedizolid and comparator agents tested against 824 *E. faecalis* and 371 *E. faecium* and resistant subsets

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	CLSI[a] %R
***E. faecalis* (824)**				
Tedizolid	0.25	0.25	100.0	0.0
Linezolid	1	1	99.9	0.0
Ampicillin	1	1	100.0	0.0
Daptomycin	0.5	1	96.8 [b]	0.0
Vancomycin	1	2	97.0	3.0
VR *E. faecalis* (25)				
Tedizolid	0.25	0.5	100.0	
Linezolid	1	2	100.0	0.0
Ampicillin	1	1	100.0	0.0
Daptomycin	0.5	1	100.0 [b]	0.0
Vancomycin	>16	>16	0.0	100.0
***E. faecium* (371)**				
Tedizolid	0.25	0.5		
Linezolid	1	2	98.9	0.3
Ampicillin	>16	>16	18.6	81.4
Daptomycin	1	2	70.1 [b]	0.0
Vancomycin	>16	>16	32.9	66.6
VR *E. faecium* (249)				
Tedizolid	0.25	0.5		
Linezolid	1	2	99.6	0.0
Ampicillin	>16	>16	2.0	98.0
Daptomycin	1	2	73.1 [b]	0.0
Vancomycin	>16	>16	0.0	99.2
MDR *E. faecium* (112)				
Tedizolid	0.25	0.5		
Linezolid	1	2	100.0	0.0
Ampicillin	>16	>16	0.0	100.0
Daptomycin	1	2	58.0 [b]	0.0
Vancomycin	>16	>16	0.0	100.0

[a] Criteria as published by CLSI (2019).
[b] MIC of ≤1 mg/L interpreted as susceptible; MIC of 2–4 mg/L intermediate interpreted as susceptible dose-dependent; and MIC of ≥4 interpreted as resistant.
VR, vancomycin-resistant; MDR, multidrug-resistant.

Figure 1. Distribution of gram-positive cocci by infection type



VGS, viridans group streptococci; BHS, β-hemolytic streptococci; CoNS, coagulase-negative staphylococci.

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