In Vitro Activity of Tedizolid and Comparator Agents against Gram-Positive Isolates Causing Bloodstream Infections in US and European Hospitals (2018)

Cecilia Carvalhaes, Helio S. Sader, Jennifer M. Streit, Robert K. Flamm, Rodrigo E. Mendes

JMI Laboratories, North Liberty, IA, USA

Introduction

- Tedizolid, an oxazolidinone active against gram-positive pathogens, was approved in the United States, Europe, and other regions to treat adults with acute bacterial skin and skin structure infections
- Clinical trials are ongoing to assess the safety and efficacy of tedizolid for additional indications
- Bloodstream infections (BSIs) are associated with morbidity, mortality, prolonged hospital stay, and increased healthcare costs
- Aerobic gram-positive cocci, most notably *Staphylococcus aureus,* coagulase-negative staphylococci (CoNS), and enterococci are important causes of BSIs
  - In addition, enterococci are among the most common pathogens to cause infective endocarditis
  - The epidemiology and antimicrobial susceptibilities of these pathogen populations are constantly evolving, challenging the empiric treatment of such infections
- This study evaluated tedizolid *in vitro* activity and potency when tested against a large collection of gram-positive isolates collected from patients with BSIs

Materials and Methods

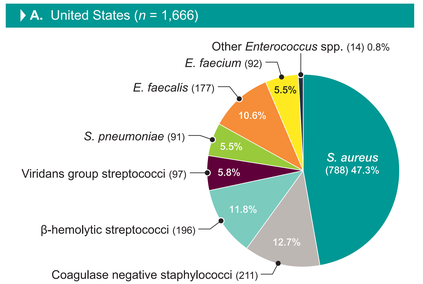
Bacterial isolates

- In 2018, 2,963 unique gram-positive isolates were collected from patients with BSIs in US (1,666 isolates, 31 sites) and European (1,297 isolates, 33 sites) medical centers
  - Bacterial distribution is shown in Figure 1
  - Only 1 isolate per patient infection episode was included
- Isolates were determined to be clinically significant based on local guidelines and were submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) as part of the Surveillance of Tedizolid Activity and Resistance (STAR) program
- Participating laboratories initially identified isolates and JMI confirmed bacterial identifications by standard algorithms 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 Clinical and Laboratory Standards Institute (CLSI M07, 2018) guidelines
- Frozen-form broth microdilution panels were manufactured by JMI Laboratories and contained cation-adjusted Mueller-Hinton broth (2.5–5% lysed horse blood was added for testing streptococci)
- Quality assurance was performed by concurrently testing CLSI-recommended quality control reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619)
- Breakpoint criteria for comparator agents were from the CLSI M100 (2019) document

Figure 1 Gram-positive cocci causing BSI in US and Europe



Results

- The most common gram-positive organisms were *S. aureus* (47.3% in the USA, 39.9% in EUR), followed by CoNS (12.7% in the USA, 15.7% in EUR)
- β-hemolytic streptococci (BHS; 11.8%) was the third most common organism in the USA while in Europe, *E. faecalis* (13.6%) was more frequently recovered than BHS (9.4%; Figure 1)
- All *S. aureus* isolates were susceptible to tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L), linezolid ($MIC_{50/90}$, 1/2 mg/L), vancomycin ($MIC_{50/90}$, 1/1 mg/L), and daptomycin ($MIC_{50/90}$, 0.25/0.25 mg/L; Tables 1 and 2)
- Based on MIC_{50} values, tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) was 8-fold more active than linezolid ($MIC_{50/90}$, 1/2 mg/L) against *S. aureus,* and tedizolid activity was not adversely affected by oxacillin resistance (*n* = 465, 35.6% of *S. aureus;* $MIC_{50/90}$, 0.12/0.25 mg/L; Tables 1 and 2)
- Among CoNS isolates, 98.6% were inhibited at a tedizolid MIC of ≤1 mg/L ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 1); susceptibility rates among US and European CoNS isolates to linezolid ($MIC_{50/90}$, 1/1 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), and vancomycin ($MIC_{50/90}$, 1/2 mg/L) were 98.6-100.0%, 99.5-100.0%, and 100.0%, respectively (Table 2)
- Tedizolid activity was equivalent against CoNS isolates and methicillin-resistant (MR) CoNS isolates ($MIC_{50/90}$, 0.12/0.25 mg/L; *n* = 262, 63.1% of CoNS; Table 1)
- All but 1 *E. faecalis* isolates were tedizolid susceptible (100.0% in the USA, 99.4% in EUR; $MIC_{50/90}$, 0.25/0.5 mg/L), 99.7% were linezolid susceptible (100.0% in the USA, 99.4% in EUR; $MIC_{50/90}$, 1/2 mg/L), 96.9% were vancomycin susceptible (96.6% in the USA, 97.2% in EUR; $MIC_{50/90}$, 1/2 mg/L), 96.6% were daptomycin susceptible (96.6% in both regions; $MIC_{50/90}$, 0.5/1 mg/L), and all isolates were susceptible to ampicillin ($MIC_{50/90}$, 1/1 mg/L; Table 2)
- Among *E. faecium* isolates (*n* = 205; 6.9% overall), 99.5% were inhibited at ≤0.5 mg/L (*E. faecalis* breakpoint) of tedizolid (98.9% in USA, 100.0% in EUR), 99.0% were linezolid susceptible (97.8% in the USA, 100.0% in EUR), and only 57.6% were vancomycin susceptible (32.6% in the USA, 77.9% in EUR; Tables 1 and 2)
- Tedizolid was very active ($MIC_{50/90}$, 0.25/0.5 mg/L) against vancomycin-resistant *E. faecium* (*n* = 87, 42.4% of *E. faecium*)
- Tedizolid was highly active against BHS (*n* = 318 [10.7% overall]; $MIC_{50/90}$, 0.25/0.25 mg/L), viridans group streptococci (VGS; *n* = 178 [6.0% overall]; $MIC_{50/90}$, 0.12/0.25 mg/L), and *S. pneumoniae* (*n* = 163 [5.5% overall]; $MIC_{50/90}$, 0.25/0.5 mg/L; Tables 1 and 2)

Table 1 Antimicrobial activity of tedizolid tested against the main organisms and resistant phenotypes causing bloodstream infection in the United States and Europe

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:								MIC		%S
	0.015	0.03	0.06	0.12	0.25	0.5	1	>1	50%	90%	
Staphylococcus aureus (1,306)		3 (0.2)	14 (1.3)	676 (53.1)	579 (97.4)	34 (100.0)			0.12	0.25	100.0
MSSA (841)		2 (0.2)	9 (1.3)	368 (45.1)	437 (97.0)	25 (100.0)			0.25	0.25	100.0
MRSA (465)		1 (0.2)	5 (1.3)	308 (67.5)	142 (98.1)	9 (100.0)			0.12	0.25	100.0
Coagulase-negative staphylococci (415)		1 (0.2)	14 (3.6)	264 (67.2)	128 (98.1)	1 (98.3)	1 (98.6)	6 100.0	0.12	0.25	
MSCoNS (153)		1 (0.7)	7 (5.2)	106 (74.5)	39 (100.0)				0.12	0.25	
MRCoNS (262)			7 (2.7)	158 (63.0)	89 (96.9)	1 (97.3)	1 (97.7)	6 100.0	0.12	0.25	
Enterococcus faecalis (354)			49 (13.8)	245 (83.1)	59 (99.7)			1 100.0	0.25	0.5	99.7
VRE (10)			3 (30.0)	5 (80.0)	2 (100.0)				0.25	0.5	100.0
Enterococcus faecium (205)			3 (1.5)	56 (28.8)	110 (82.4)	35 (99.5)	1 (100.0)		0.25	0.5	
VRE (87)			2 (2.3)	32 (39.1)	41 (86.2)	12 (100.0)			0.25	0.5	
Other enterococci [a] (24)				5 (20.8)	12 (70.8)	7 (100.0)			0.25	0.5	
β-hemolytic streptococci [b] (318)			2 (0.6)	92 (29.6)	213 (96.5)	11 (100.0)			0.25	0.25	100.0
Viridans group streptococci [c] (178)		4 (2.2)	17 (11.8)	105 (70.8)	50 (98.9)	2 (100.0)			0.12	0.25	98.9
Streptococcus pneumoniae (163)			1 (0.6)	31 (19.6)	114 (89.6)	17 (100.0)			0.25	0.5	

MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSCoNS, methicillin-susceptible coagulase-negative staphylococci; MRCoNS, methicillin-resistant coagulase-negative staphylococci; VRE, vancomycin-resistant enterococci.
[a] Includes *Enterococcus avium* (4), *E. casseliflavus* (10) , *E. durans* (1) , *E. gallinarum* (5) , *E. hirae* (2) , *E. raffinosus* (2)
[b] Includes *Streptococcus agalactiae* (127) , *S. canis* (2) , *S. dysgalactiae* (66) , *S. equi* (1) , *S. pyogenes* (132)
[c] Includes *Streptococcus anginosus* (14) , *S. anginosus* group (6) , *S. australis* (2) , *S. bovis* group (5) , *S. constellatus* (3) , *S. cristatus* (4) , *S. equinus* (1) , *S. gallolyticus* (13) , *S. gordonii* (4) , *S. infantis* (4) , *S. intermedius* (4) , *S. salivarius* (3) , *S. mitis* group (53) , *S. mitis/oralis* (1) , *S. mutans* (5) , *S. oralis* (30) , *S. parasanguinis* (9) , *S. salivarius* (2) , *S. salivarius* group (5) , *S. salivarius/vestibularis* (1) , *S. sanguinis* (9) , *S. vestibularis* (2)

Table 2 Antimicrobial activity of tedizolid and comparator agents tested against the main organisms and resistant phenotypes causing BSI in the United States (USA, *n* = 1,666) and Europe (EUR; *n* = 1,297)

Organism (no. tested in USA/EUR) Antimicrobial agent	USA				EUR			
	MIC_{50} [a]	MIC_{90} [a]	%S [a]	%R [a]	MIC_{50}	MIC_{90}	%S [a]	%R [a]
S. aureus (788/518)								
Tedizolid	0.12	0.25	100.0	0.0	0.25	0.25	100.0	0.0
Linezolid	1	2	100.0	0.0	1	2	100.0	0.0
Vancomycin	1	1	100.0	0.0	1	1	100.0	0.0
Daptomycin	0.25	0.25	100.0		0.25	0.25	100.0	
Oxacillin	1	>2	57.0	43.0	0.5	>2	75.7	24.3
Clindamycin	0.06	>2	84.4	15.5	0.06	0.12	94.6	5.4
Levofloxacin	0.25	>4	66.0	33.8	0.25	>4	77.8	21.8
Coagulase-negative staphylococci (211/204)								
Tedizolid	0.12	0.25			0.12	0.25		
Linezolid	1	1	98.6	1.4	1	1	100.0	0.0
Vancomycin	1	2	100.0	0.0	1	2	100.0	0.0
Daptomycin	0.25	0.5	99.5	0.5	0.25	0.5	100.0	
Oxacillin	>2	>2	33.2	66.8	>2	>2	35.3	64.7
Clindamycin	0.12	>2	60.7	36.5	0.06	>2	75.5	22.1
Levofloxacin	0.5	>4	52.1	46.4	0.25	>4	51.5	44.1
E. faecalis (177/177)								
Tedizolid	0.25	0.5	100.0	0.0	0.25	0.5	99.4	0.6
Linezolid	1	2	100.0	0.0	1	2	99.4	0.6
Vancomycin	1	2	96.6	3.4	1	2	97.2	2.3
Daptomycin	0.5	1	96.6	0.0	0.5	1	96.6	0.0
Ampicillin	1	1	100.0	0.0	1	1	100.0	0.0
Levofloxacin	1	>4	77.4	21.5	1	>4	68.4	31.6
E. faecium (92/113)								
Tedizolid	0.25	0.5			0.25	0.5		
Linezolid	1	2	97.8	0.0	1	2	100.0	0.0
Vancomycin	>16	>16	32.6	67.4	0.5	>16	77.9	22.1
Daptomycin	1	2	65.2	0.0	1	2	70.5	0.0
Ampicillin	>16	>16	18.5	81.5	>16	>16	9.7	90.3
Levofloxacin	>4	>4	12.0	81.5	>4	>4	7.1	92.9
β-hemolytic streptococci (196/122)								
Tedizolid	0.25	0.25	100.0		0.25	0.25	100.0	
Linezolid	1	2	100.0		1	2	100.0	
Vancomycin	0.5	0.5	100.0		0.5	0.5	100.0	
Daptomycin	≤0.06	0.25	100.0		≤0.06	0.25	100.0	
Ceftriaxone	0.03	0.06	100.0		0.03	0.06	99.2	
Penicillin	0.015	0.06	100.0		0.015	0.06	100.0	
Clindamycin	≤0.25	>2	77.0	22.4	≤0.25	2	86.0	12.4
Levofloxacin	0.5	1	99.5	0.5	0.5	1	100.0	0.0

Organism (no. tested in USA/EUR) Antimicrobial agent	USA				EUR			
	MIC_{50} [a]	MIC_{90} [a]	%S [a]	%R [a]	MIC_{50}	MIC_{90}	%S [a]	%R [a]
Viridans group streptococci (97/81)								
Tedizolid	0.12	0.25	100.0		0.12	0.25	100.0	
Linezolid	1	1	100.0		1	1	100.0	
Vancomycin	0.5	0.5	100.0		0.5	0.5	100.0	
Daptomycin	0.25	0.5	100.0		0.5	0.5	100.0	
Ceftriaxone	0.12	0.5	94.8	3.1	0.12	1	93.8	2.5
Penicillin	0.06	1	66.0	3.1	0.06	1	77.8	3.7
Clindamycin	≤0.25	>2	87.6	11.3	≤0.25	>2	82.5	17.5
Levofloxacin	1	>4	78.4	21.6	1	2	95.1	2.5
S. pneumoniae (91/72)								
Tedizolid	0.25	0.25			0.25	0.25		
Linezolid	1	2	100.0		1	2	100.0	
Vancomycin	0.25	0.5	100.0		0.25	0.25	100.0	
Ceftriaxone	0.03	0.5	90.1 [b] 97.8 [c]	2.2 [b] 1.1 [c]	0.03	0.25	95.8 [b] 100.0 [c]	0.0 [b] 0.0 [c]
Penicillin	0.015	1	70.3 [d] 96.7 [e]	6.6 [d] 1.1 [e]	0.015	0.12	88.9 [d] 100.0 [e]	4.2 [d] 0.0 3
Clindamycin	≤0.25	≤0.25	91.2	8.8	≤0.25	>2	87.5	12.5
Erythromycin	0.12	16	51.6	47.3	0.03	>16	84.7	15.3
Levofloxacin	1	1	100.0	0.0	1	1	98.6	1.4

[a] Criteria as published by CLSI (2019).
[b] Using meningitis breakpoints.
[c] Using non-meningitis breakpoints.
[d] Using oral breakpoints.
[e] Using parenteral, non-meningitis breakpoints.

Conclusions

- Tedizolid was very active against *S. aureus*, CoNS, enterococci, BHS, VGS and *S. pneumoniae* responsible for BSIs in patients hospitalized in US and EUR medical centers
- Tedizolid retained *in vitro* activity against resistant phenotypes, such as MRSA, MRCoNS, and VRE
- Based on MIC_{50} values, tedizolid was generally 4- to 8-fold more active than linezolid and at least 64-fold more active than vancomycin against *E. faecium* isolates causing BSI
- These results support further investigations to determine the role of tedizolid in the treatment of BSI

Acknowledgements

Funding for this research was provided by Funding for the STAR program and this presentation was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

References

Clinical and Laboratory Standards Institute (2019). *M100Ed29E. Performance standards for antimicrobial susceptibility testing: 29th Informational Supplement.* Wayne, PA, USA.

Clinical and Laboratory Standards Institute (2018). *M07Ed11E. Methods for dilution antimicrobial susceptibilty tests for bacteria that grow aerobically; Approved Standard - Eleventh edition.* Wayne, PA, USA.

EUCAST (2019). Breakpoint tables for interpretation of MIC's and zone diameters. Version 9.0, January 2019. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf. Accessed January 2019.

Sivextro® (tedizolid phosphate) for injection, for intravenous and oral use. Package Insert (2017). Merck & Co, Inc. Available at: https://www.merck.com/product/usa/pi_circulars/s/sivextro/sivextro_pi.pdf. Accessed April 2019.

Zhanel GG, Love R, Adam H, et al. (2015). Tedizolid: a novel oxazolidinone with potent activity against multidrug-resistant gram-positive pathogens. *Drugs* 75: 253-270.

Contact Information
Cecilia Carvalhaes, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: cecilia-carvalhaes@jmilabs.com

https://bit.ly/2PVIVag