ASM Microbe 2017

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Activity of Tedizolid against Gram-Positive Clinical Isolates Causing Infections in United States Hospitals (2014–2016)

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Introduction

- Tedizolid is an oxazolidinone derivative that exhibits potency greater than linezolid when tested against a broad array of gram-positive cocci, including those exhibiting multidrug-resistance (MDR) phenotypes, such as methicillin-resistance *Staphylococcus aureus* (MRSA), vancomycin-resistance enterococci (VRE), and some linezolid-resistance phenotypes[1, 2]
- Tedizolid is currently approved to treat acute bacterial skin and skin structure infections (ABSSSI) in the United States, Europe[3,4], and other regions worldwide
  - Tedizolid is in a Phase 3 clinical trial (NCT02019420) to treat nosocomial pneumonia
  - This agent also is being investigated for bone and joint infections (NCT03009045) and diabetic wound infections (NCT02620787)[1,5]
- This study assessed the in vitro activities of tedizolid and comparator agents tested against gram-positive isolates responsible for SSSI, pneumonia, and bloodstream infections (BSI) in hospitalized patients in the United States (US)

Materials and Methods

- A total of 15,136 non-duplicate, single-patient gram-positive isolates were included
  - Isolates were recovered from patients hospitalized in 31 US sites during the Surveillance of Tedizolid Activity and Resistance (STAR) Program for 2014–2016
- Isolates were initially identified by the participating laboratory and submitted to a central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) where bacterial identifications were confirmed using standard algorithms and supported by matrix assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Isolates were susceptibility tested by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document[6]
- MIC reading for tedizolid and linezolid was performed according to the CLSI guidelines—i.e., the first well at which trailing begins without regard to pinpoint trailing in the wells[7]
- Quality assurance was performed by concurrently testing CLSI-recommended QC reference strains (*S. aureus* ATCC 29213 and *Enterococcus faecalis* 29212)[7]
  - All QC results were within published acceptable ranges
- Breakpoint criteria for tedizolid and comparator agents were those from CLSI (2016)[7] and EUCAST (2016)[8], and tigecycline MIC interpretation used the Food and Drug Administration (FDA) breakpoints[9]

Results

- *S. aureus* was the most common gram-positive pathogen responsible for BSI, pneumonia, and SSSI (Tables 1–3), and MRSA rates among *S. aureus* responsible for BSI (43.2%), pneumonia (43.3%), or SSSI (46.6%) were similar
- Rates of vancomycin-resistance phenotype in *E. faecium* varied from 68.2% among isolates causing BSI to 80.2% among those responsible for SSSI (Tables 1 and 3)
- Overall, tedizolid showed similar MIC_{50} results (0.12 µg/mL) regardless of pathogen/group or infection type, except for coagulase-negative staphylococci (CoNS) and viridans group streptococci (VGS) (SSSI), against which tedizolid had MIC_{50} values of 0.06 µg/mL (Tables 1–4)
- Tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL), daptomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL), ceftaroline ($MIC_{50/90}$, 0.5-1/1 µg/mL), linezolid ($MIC_{50/90}$, 1/1 µg/mL), and vancomycin ($MIC_{50/90}$, 0.5-1/1 µg/mL) had consistent MIC results against MRSA across infection types (Table 4)
- Against CoNS, tedizolid and tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL for both) exhibited MIC_{90} values 4- to 16-fold lower than daptomycin (MIC_{90}, 0.5 µg/mL), ceftaroline (MIC_{90}, 0.5 µg/mL), linezolid (MIC_{90}, 1 µg/mL), and vancomycin (MIC_{90}, 2 µg/mL; Table 4)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL) and tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL) were the most potent agents tested against *E. faecalis* (Table 4)
  - Although linezolid (MIC_{90}, 1 µg/mL), daptomycin (MIC_{90}, 1–2 µg/mL), ampicillin (MIC_{90}, 1 µg/mL), and vancomycin (MIC_{90}, 2 µg/mL) were consistently active against *E. faecalis*, these agents had MIC_{90} values 4- to 8-fold higher than tedizolid and tigecycline
- Tigecycline ($MIC_{50/90}$, 0.03/0.06 µg/mL) and ceftaroline ($MIC_{50/90}$, ≤0.015/0.06-012 µg/mL) displayed the lowest MIC values against *S. pneumoniae* (Table 4), followed by tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL) and vancomycin ($MIC_{50/90}$, 0.25/0.25 µg/mL)
- Tedizolid (MIC_{90}, 0.12 µg/mL), ceftaroline (MIC_{90}, 0.06–012 µg/mL), and tigecycline (MIC_{90}, 0.6-0.12 µg/mL) had the lowest MIC_{90} values against VGS (Table 4)
- *S. pyogenes* and *S. agalactiae* were very susceptible (≥93.8%) to the antimicrobial agents tested, except for erythromycin, clindamycin, and tetracycline (Table 4)

Conclusions

- MRSA and VRE (*E. faecium*) rates remained high among isolates causing infections in patients in the US
- Overall, tedizolid displayed consistent in vitro potencies when tested against gram-positive pathogens or groups of pathogens in the US, regardless of infection type
- In general, the in vitro activity of tedizolid was similar or greater than comparator agents against gram-positive isolates causing infections in the US

Acknowledgements

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA. JMI Laboratories received compensation fees for services related to preparing this presentation.

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Table 1 Tedizolid activity against the main organisms and groups of isolates responsible for bloodstream infections

Organism/ organism group	No. of isolates at MIC (µg/mL; cumulative %)									MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>1	50%	90%
MSSA (1,188)			7 (0.6%)	243 (21.0%)	882 (95.3%)	56 (100.0%)				0.12	0.12
MRSA (902)			11 (1.2%)	263 (30.4%)	590 (95.8%)	38 (100.0%)				0.12	0.12
CoNS (725)	1 (0.1%)	0 (0.1%)	33 (4.7%)	352 (53.2%)	307 (95.6%)	18 (98.1%)	0 (98.1%)	3 (98.5%)	11 (100.0%)	0.06	0.12
Vancomycin-susceptible *E. faecalis* (366)			1 (0.3%)	11 (3.3%)	206 (59.6%)	146 (99.5%)	2 (100.0%)			0.12	0.25
Vancomycin-resistant *E. faecalis* (9)					6 (66.7%)	3 (100.0%)				0.12	—
Vancomycin-susceptible *E. faecium* (75)			2 (2.7%)	2 (5.3%)	40 (58.7%)	31 (100.0%)				0.12	0.25
Vancomycin-resistant *E. faecium* (161)			1 (0.6%)	21 (13.7%)	104 (78.3%)	33 (98.8%)	1 (99.4%)	0 (99.4%)	1 (100.0%)	0.12	0.25
S. pneumoniae (202)			1 (0.5%)	16 (8.4%)	142 (78.7%)	43 (100.0%)				0.12	0.25
S. pyogenes (152)				14 (9.2%)	133 (96.7%)	5 (100.0%)				0.12	0.12
S. agalactiae (257)				10 (3.9%)	187 (76.7%)	60 (100.0%)				0.12	0.25
VGS (228)	1 (0.4%)	1 (0.9%)	3 (2.2%)	58 (27.6%)	155 (95.6%)	10 (100.0%)				0.12	0.12

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci.

Table 2 Tedizolid activity against the main organisms and groups of isolates responsible for pneumonia

Organisms/ organism group	No. of isolates at MIC (µg/mL; cumulative %)							MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%	90%
MSSA (1,454)			6 (0.4%)	277 (19.5%)	1,046 (91.4%)	125 (100.0%)		0.12	0.12
MRSA (1,112)		1 (0.1%)	6 (0.6%)	280 (25.8%)	745 (92.8%)	79 (99.9%)	1 (100.0%)	0.12	0.12
S. pneumoniae (1,996)			7 (0.4%)	117 (6.2%)	1,364 (74.5%)	508 (100.0%)		0.12	0.25

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*

Table 3 Tedizolid activity against the main organisms and groups of isolates responsible for skin and skin structure infections

Organism/ organism groups	No. of isolates at MIC (µg/mL; cumulative %)							MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	50%	90%
MSSA (2,445)		1 (<0.1%)	5 (0.2%)	423 (17.5%)	1833 (92.5%)	183 (100.0%)		0.12	0.12
MRSA (2,133)			3 (0.1%)	566 (26.7%)	1,468 (95.5%)	96 (100.0%)		0.12	0.12
CoNS (316)			19 (6.0%)	202 (69.9%)	95 (100.0%)			0.06	0.12
Vancomycin-susceptible *E. faecalis* (282)				7 (2.5%)	150 (55.7%)	122 (98.9%)	3 (100.0%)	0.12	0.25
Vancomycin-resistant *E. faecalis* (11)				1 (9.1%)	8 (81.8%)	2 (100.0%)		0.12	0.25
Vancomycin-susceptible *E. faecium* (16)					12 (75.0%)	4 (100.0%)		0.12	0.25
Vancomycin-resistant *E. faecium* (65)				6 (9.2%)	49 (84.6%)	8 (96.9%)	2 (100.0%)	0.12	0.25
S. pyogenes (466)				72 (15.5%)	367 (94.2%)	27 (100.0%)		0.12	0.12
S. agalactiae (302)			1 (0.3%)	19 (6.6%)	241 (86.4%)	41 (100.0%)		0.12	0.25
VGS (103)	3 (2.9%)	1 (3.9%)	7 (10.7%)	46 (55.3%)	44 (98.1%)	2 (100.0%)		0.06	0.12

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci

Table 4 Antimicrobial activity of tedizolid and comparator agents against main organisms and groups of isolates responsible for human infections in the US

Organism (no. tested) anti-microbial agent	MIC_{50}, MIC_{90}, and %susceptible (CLSI/EUCAST)† by infection type											
	BSI				Pneumonia				SSSI			
MRSA												
Tedizolid	0.12	0.12	100.0	100.0	0.12	0.12	100.0	100.0	0.12	0.12	100.0	100.0
Linezolid	1	1	100.0	100.0	1	1	99.9	99.9	1	1	100.0	100.0
Ceftaroline	1	1	93.1	93.1	1	1	94.3	94.3	0.5	1	98.3	98.3
Clindamycin	≤0.25	>2	68.1	68.0	≤0.25	>2	60.6	60.4	≤0.25	>2	79.8	79.8
Daptomycin	0.25	0.5	99.8	99.8	0.25	0.5	100.0	100.0	0.25	0.5	>99.9	>99.9
Erythromycin	>8	>8	11.2	12.0	>8	>8	8.7	9.4	>8	>8	12.9	13.2
Levofloxacin	4	>4	25.2	25.2	>4	>4	18.9	18.9	4	>4	37.5	37.5
Tetracycline	≤0.5	1	95.6	92.7	≤0.5	1	92.9	90.3	≤0.5	1	93.8	91.4
Tigecycline	0.06	0.12	100.0	100.0	0.06	0.12	100.0	100.0	0.06	0.12	100.0	100.0
TMP-SMX	≤0.5	≤0.5	95.2	95.2	≤0.5	≤0.5	96.4	96.4	≤0.5	≤0.5	97.0	97.0
Vancomycin	0.5	1	100.0	100.0	1	1	100.0	100.0	0.5	1	100.0	100.0
S. pneumoniae												
Tedizolid	0.12	0.25	-	-	0.12	0.25	-	-				
Linezolid	1	1	100.0	100.0	1	1	100.0	100.0				
Ceftaroline	≤0.015	0.06	100.0	100.0	≤0.015	0.12	99.9	99.6				
Ceftriaxone	≤0.06	0.5	98.0	90.6	≤0.06	1	96.2	84.9				
Clindamycin	≤0.25	≤0.25	90.1	90.6	≤0.25	>1	84.5	85.2				
Erythromycin	≤0.12	>2	61.4	61.4	≤0.12	>2	53.5	53.5				
Levofloxacin	1	1	100.0	100.0	1	1	98.6	98.6				
Penicillin	≤0.06	1	98.0	74.3	≤0.06	2	95.1	60.2				
Tetracycline	≤0.5	>4	85.6	85.6	≤0.5	>4	78.0	78.0				
Tigecycline	0.03	0.06	100.0	-	0.03	0.06	99.1	-				
TMP-SMX	≤0.5	4	77.7	83.7	≤0.5	>4	71.3	78.3				
Vancomycin	0.25	0.25	100.0	100.0	0.25	0.25	100.0	100.0				
CoNS												
Tedizolid	0.06	0.12	-	98.1					0.06	0.12	-	100.0
Linezolid	0.5	1	98.1	98.1					0.5	1	100.0	100.0
Ceftaroline	0.25	0.5	-	-					0.25	0.5	-	-
Clindamycin	≤0.25	>2	66.3	65.9					≤0.25	>2	74.4	71.5
Daptomycin	0.5	0.5	100.0	100.0					0.25	0.5	100.0	100.0
Erythromycin	>8	>8	34.1	35.3					0.25	>8	52.8	52.8
Levofloxacin	2	>4	47.9	47.9					0.25	>4	73.7	73.7
Oxacillin	>2	>2	33.0	33.0					1	>2	55.4	55.4
Tetracycline	≤0.5	>8	83.2	81.1					≤0.5	>8	87.0	84.4
Tigecycline	0.06	0.12	-	100.0					0.06	0.12	-	100.0
TMP-SMX	≤0.5	>4	67.7	67.7					≤0.5	4	81.3	81.3
Vancomycin	1	2	100.0	100.0					1	2	100.0	100.0
E. faecalis												
Tedizolid	0.12	0.25	100.0	-					0.12	0.25	100.0	-
Linezolid	1	1	100.0	100.0					1	1	100.0	100.0
Ampicillin	1	1	100.0	100.0					1	1	100.0	100.0
Daptomycin	1	2	100.0	-					1	1	100.0	-
Erythromycin	>16	>16	8.7	-					16	>16	12.4	-
Levofloxacin	1	>4	74.5	74.5					1	>4	74.1	74.1
Tetracycline	>8	>8	25.6	-					>8	>8	25.3	-
Tigecycline	0.06	0.12	100.0	100.0					0.06	0.12	100.0	100.0
Teicoplanin	≤2	≤2	98.1	98.1					≤2	≤2	96.2	95.9
Vancomycin	1	2	97.3	97.3					1	2	96.2	96.2
E. faecium												
Tedizolid	0.12	0.25	-	-					0.12	0.25	-	-
Linezolid	1	1	99.2	99.6					1	1	98.8	100.0
Ampicillin	>8	>8	15.7	14.4					>8	>8	11.1	11.1
Daptomycin	1	4	98.7	-					1	2	100.0	-
Erythromycin	>16	>16	4.6	-					>16	>16	0.0	-
Levofloxacin	>4	>4	10.6	16.1					>4	>4	7.4	11.1
Tetracycline	>8	>8	22.9	-					>8	>8	19.8	-
Tigecycline	0.03	0.06	-	100.0					0.06	0.06	-	100.0
Teicoplanin	>16	>16	33.9	32.2					>16	>16	19.8	19.8
Vancomycin	>16	>16	31.8	31.8					>16	>16	19.8	19.8
VGS												
Tedizolid	0.12	0.12	-	-					0.06	0.12	-	-
Linezolid	0.5	1	100.0	-					0.5	1	100.0	-
Amoxicillin-clavulanate	≤1	2	-	76.8					≤1	≤1	-	93.2
Ceftaroline	≤0.015	0.12	-	-					≤0.015	0.06	-	-
Ceftriaxone	0.12	1	92.5	86.8					0.12	0.5	97.1	95.1
Clindamycin	≤0.25	>2	85.1	87.7					≤0.25	>2	78.6	79.6
Daptomycin	0.5	0.5	100.0	-					0.25	0.5	100.0	-
Erythromycin	1	>4	43.0	-					0.25	>4	52.4	-
Levofloxacin	1	>4	88.6	-					0.5	1	99.0	-
Penicillin	≤0.06	1	69.3	76.8					≤0.06	0.25	88.3	93.2
Tetracycline	≤0.5	>8	64.0	-					4	>8	49.5	-
Tigecycline	0.03	0.12	100.0	-					0.015	0.06	100.0	-
Vancomycin	0.5	0.5	100.0	100.0					0.5	0.5	100.0	100.0
S. pyogenes												
Tedizolid	0.12	0.12	100.0	100.0					0.12	0.12	100.0	100.0
Linezolid	1	1	100.0	100.0					1	1	100.0	100.0
Amoxicillin-clavulanate	≤1	≤1	100.0	100.0					≤1	≤1	100.0	100.0
Ceftaroline	≤0.015	≤0.015	100.0	100.0					≤0.015	≤0.015	100.0	100.0
Ceftriaxone	≤0.06	≤0.06	100.0	100.0					≤0.06	≤0.06	100.0	100.0
Clindamycin	≤0.25	≤0.25	96.1	97.4					≤0.25	≤0.25	96.6	96.6
Daptomycin	≤0.06	0.12	100.0	100.0					≤0.06	0.12	100.0	100.0
Erythromycin	≤0.12	>4	82.1	82.1					≤0.12	2	87.8	87.8
Levofloxacin	0.5	1	100.0	95.4					0.5	1	99.6	93.8
Penicillin	≤0.06	≤0.06	100.0	100.0					≤0.06	≤0.06	100.0	100.0
Tetracycline	≤0.5	8	86.8	86.2					≤0.5	>8	85.6	84.5
Tigecycline	0.03	0.06	100.0	100.0					0.03	0.06	100.0	100.0
Vancomycin	0.25	0.5	100.0	100.0					0.25	0.5	100.0	100.0
S. agalactiae												
Tedizolid	0.12	0.25	100.0	100.0					0.12	0.25	100.0	100.0
Linezolid	1	1	100.0	100.0					1	1	100.0	100.0
Amoxicillin-clavulanate	≤1	≤1	100.0	100.0					≤1	≤1	100.0	100.0
Ceftaroline	≤0.015	≤0.015	100.0	100.0					≤0.015	≤0.015	100.0	100.0
Ceftriaxone	≤0.06	0.12	100.0	100.0					≤0.06	0.12	100.0	100.0
Clindamycin	≤0.25	>2	62.6	63.4					≤0.25	>2	61.1	62.1
Daptomycin	0.25	0.5	100.0	100.0					0.25	0.5	100.0	100.0
Erythromycin	2	>4	42.4	42.4					1	>4	45.5	45.5
Levofloxacin	0.5	1	100.0	98.4					0.5	1	99.0	98.3
Penicillin	≤0.06	≤0.06	100.0	100.0					≤0.06	≤0.06	100.0	100.0
Tetracycline	>8	>8	17.9	17.9					>8	>8	17.2	17.2
Tigecycline	0.06	0.06	100.0	100.0					0.06	0.06	100.0	100.0
Vancomycin	0.5	0.5	100.0	100.0					0.5	0.5	100.0	100.0

MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; VGS = viridans group streptococci; TMP-SMX = trimethoprim-sulfamethoxazole; BSI = bloodstream infection; SSSI = skin and skin structure infection

†Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2016) and CLSI (2016), as available. Penicillin and ceftriaxone MIC interpretation against *S. pneumoniae* applied the parenteral CLSI (non-meningitis) breakpoint. MIC interpretation for tigecycline used FDA breakpoints (results under the CLSI column). "-" breakpoint not available.