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Current *In Vitro* Analysis of Tedizolid Activity against Gram-Positive Clinical Isolates Causing Bloodstream Infections in Europe and Surrounding Areas (2014–2017)

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INTRODUCTION

- Bloodstream infections (BSIs), including those associated with central-line catheters, are serious life-threatening infections in the nosocomial setting, particularly in the intensive care unit
  - The clinical consequences of BSIs include increased mortality (23%–30%), significant morbidity, and increased length of hospital stay and costs
  - BSIs are heterogenous clinical entities with a high risk of metastatic complications
- *Staphylococcus aureus* remains a common pathogen responsible for serious infections worldwide, including BSI, and the outcome can be improved by optimised diagnostic and therapeutic management
- Tedizolid is currently approved to treat acute bacterial skin and skin structure infections (ABSSSIs) and is in an ongoing Phase 3 clinical trial for nosocomial pneumonia (NCT02019420) and other indications
- This study evaluated tedizolid and comparator agent activities against gram-positive isolates causing BSIs in hospitalised patients in Europe and adjacent countries/regions

MATERIALS AND METHODS

Organism collection

- A total of 5,319 gram-positive nonduplicate single-patient isolates were collected from patients hospitalised with documented BSIs
  - Isolates originated from 20 European countries/regions (40 sites) and were submitted to a monitoring laboratory as part of the Surveillance of Tedizolid Activity and Resistance (STAR) program
- 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 technology mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Bremen, Germany)

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07 document (2018)
  - Broth microdilution used 96-well reference panels manufactured by JMI Laboratories (North Liberty, Iowa, USA) containing cation-adjusted Mueller-Hinton broth (CAMHB) as testing media
  - CAMHB supplemented with 2.5%-5% lysed horse blood was used for streptococci
- MIC readings for tedizolid and linezolid were performed according to the CLSI guidelines – i.e., MIC was read at the first well at which trailing begins without regard for pinpoint trailing in the wells
- Quality assurance was performed by concurrently testing CLSI-recommended quality control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* 29212, and *Streptococcus pneumoniae* ATCC 49619)
  - All QC results were within published acceptable ranges
- Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2018) and CLSI M100 (2018)

RESULTS

- Staphylococci comprised 61.2% of all gram-positive clinical isolates causing BSIs included in this study (Table 1)
  - *S. aureus* and coagulase-negative staphylococci (CoNS) comprised 44.3% and 16.8%, respectively
  - *S. epidermidis* (57.4%) constituted the majority of CoNS
  - A total of 25.6% of *S. aureus* were methicillin-resistant (MRSA), while an oxacillin resistance rate of 73.5% was observed in CoNS (Table 1)
  - Other gram-positive organisms were less prevalent (5.9%–11.2%)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) showed MIC_{90} values 2-, 4-, and 4-fold lower than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L), respectively, against MRSA (Table 2)
- Tedizolid ($MIC_{50/90}$, 0.12/0.12 mg/L) had the lowest MIC_{90} value against CoNS, which was 4- to 8-fold lower than daptomycin ($MIC_{50/90}$, 0.5/0.5 mg/L), linezolid ($MIC_{50/90}$, 0.5/1 mg/L), and ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L) and 16-fold lower than vancomycin ($MIC_{50/90}$, 1/2 mg/L) (Table 2)
- All *Enterococcus faecalis* were susceptible to ampicillin, and high susceptibility rates (≥99.0%) were observed for tedizolid, linezolid, daptomycin, teicoplanin, and vancomycin (Table 2)
- A total of 18.8% of *Enterococcus faecium* showed a VanA phenotype, and tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) inhibited 98.4% at ≤0.5 mg/L (Table 1)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and daptomycin ($MIC_{50/90}$, 2/2 mg/L) were active against the VanA population (Table 2)
- A total of 22.7% and 11.2% of *S. pneumoniae* were penicillin- and/or ceftriaxone-nonsusceptible, respectively, and tedizolid inhibited all isolates at ≤0.5 mg/L (Tables 1 and 2)
- Ceftaroline (MIC_{90}, ≤0.015 mg/L), ceftriaxone (MIC_{90}, ≤0.06 mg/L), and penicillin (MIC_{90}, ≤0.06 mg/L) showed the lowest MIC_{90} results against β-haemolytic streptococci, followed by tedizolid (MIC_{90}, 0.25 mg/L) and daptomycin (MIC_{90}, 0.25 mg/L) (Table 2)
- A total of 19.5% and 13.0% of viridans group streptococci were nonsusceptible to penicillin and/or ceftriaxone, respectively
  - Tedizolid (MIC_{90}, 0.25 mg/L), ceftaroline (MIC_{90}, 0.06 mg/L), and vancomycin (MIC_{90}, 0.5 mg/L) had the lowest MIC_{90} values against viridans group streptococci (Table 2)

Table 1 Antimicrobial activity of tedizolid tested against the main gram-positive organisms and organism groups of isolates causing BSIs in 2014–2017

Organism / organism group (no. of isolates)	Number of isolates and cumulative % inhibited at MIC (mg/L) of:								MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	>1		
Staphylococcus aureus (2,358)	1 <0.1	10 0.5	419 18.2	1,462 80.2	446 99.2	18 99.9	2 100.0		0.12	0.25
MRSA (604)		4 0.7	130 22.2	375 84.3	86 98.5	8 99.8	1 100.0		0.12	0.25
MSSA (1,754)	1 0.1	6 0.4	289 16.9	1,087 78.8	360 99.4	10 99.9	1 100.0		0.12	0.25
CoNS[a] (895)		20 2.2	357 42.1	448 92.2	66 99.6	0 99.6	0 99.6	4 100.0	0.12	0.12
Enterococcus faecalis (598)			21 3.5	299 53.5	269 98.5	9 100.0			0.12	0.25
Enterococcus faecium (409)		1 0.2	27 6.8	245 66.7	122 96.6	11 99.3	2 99.8	1 100.0	0.12	0.25
Vancomycin-susceptible (332)		1 0.3	20 6.3	198 66.0	101 96.4	10 99.4	2 100.0		0.12	0.25
VanA (61)			4 6.6	38 68.9	17 96.7	1 98.4	0 98.4	1 100.0	0.12	0.25
VanB (16)			3 18.8	9 75.0	4 100.0				0.12	0.25
Streptococcus pneumoniae (313)		2 0.6	14 5.1	179 62.3	113 98.4	5 100.0			0.12	0.25
β-haemolytic streptococci[b] (384)			18 4.7	248 69.3	112 98.4	6 100.0			0.12	0.25
Viridans group streptococci[c] (333)		6 1.8	61 20.1	224 87.4	41 99.7	1 100.0			0.12	0.25

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.
[a] CoNS, coagulase-negative staphylococci, includes: *Staphylococcus capitis* (60), *S. caprae* (2), *S. carnosus* (1), *S. cohnii* (2), *S. epidermidis* (514), *S. haemolyticus* (129), *S. hominis* (143), *S. lentus* (1), *S. lugdunensis* (13), *S. pasteuri* (3), *S. pettenkoferi* (4), *S. saprophyticus* (8), *S. schleiferi* (1), *S. simulans* (2), *S. warneri* (12)
[b] Includes: *Streptococcus agalactiae* (158), *S. dysgalactiae* (84), *S. pyogenes* (142)
[c] Includes: *Streptococcus anginosus* (38), *S. anginosus* group (11), *S. australis* (3), *S. bovis* group (3), *S. constellatus* (5), *S. equinus* (1), *S. gallolyticus* (36), *S. gordonii* (8), *S. infantis* (2), *S. lutetiensis* (5), *S. massiliensis* (1), *S. mitis* (6), *S. mitis* group (64), *S. mitis/oralis* (26), *S. mutans* (5), *S. oralis* (29), *S. parasanguinis* (25), *S. salivarius* (18), *S. salivarius* group (17), *S. salivarius/vestibularis* (5), *S. sanguinis* (22), *S. vestibularis* (3)

Table 2 Activity of tedizolid and comparator antimicrobial agents against clinical isolates causing BSIs in hospitalised patients (2014–2017)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	EUCAST[a]			CLSI[a]		
				%S	%I	%R	%S	%I	%R
MRSA (604)									
Tedizolid	0.12	0.25	0.03 to 1	99.8		0.2	99.8	0.2	0.0
Linezolid	1	1	≤0.12 to 4	100.0		0.0	100.0		0.0
Ceftaroline	1	2	0.12 to 4	81.9	17.9	0.2	81.9	17.9	0.2
Clindamycin	≤0.25	>2	≤0.25 to >2	78.2	0.2	21.6	78.4	0.2	21.5
Daptomycin	0.25	0.5	≤0.12 to 2	99.8		0.2	99.8		
Erythromycin	>8	>8	≤0.12 to >8	36.1	2.8	61.1	35.3	7.0	57.8
Gentamicin	≤1	>8	≤1 to >8	53.3		46.7	53.3	4.4	42.2
Levofloxacin	>4	>4	≤0.12 to >4	20.4		79.6	20.4	0.4	79.2
Teicoplanin	≤2	≤2	≤2 to 8	99.7		0.3	100.0	0.0	0.0
Tetracycline	≤0.5	>8	≤0.5 to >8	86.8	0.4	12.9	87.3	1.3	11.4
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	98.3	0.2	1.5	98.3		1.7
Vancomycin	0.5	1	0.25 to 2	100.0		0.0	100.0	0.0	0.0
CoNS[b] (895)									
Tedizolid	0.12	0.12	≤0.008 to >1	99.6		0.4			
Linezolid	0.5	1	≤0.12 to >8	99.6		0.4	99.6		0.4
Ceftaroline	0.25	1	≤0.06 to 4						
Clindamycin	≤0.25	>2	≤0.25 to >2	72.1	1.6	26.4	73.6	0.8	25.6
Daptomycin	0.5	0.5	≤0.12 to 2	99.8		0.2	99.8		
Erythromycin	>8	>8	≤0.12 to >8	36.0	0.9	63.1	36.0	1.6	62.4
Levofloxacin	4	>4	≤0.12 to >4	42.1		57.9	42.1	5.7	52.2
Oxacillin	>2	>2	≤0.25 to >2	27.2		72.8	26.5		73.5
Teicoplanin	≤2	8	≤2 to 16	88.7		11.3	99.3	0.7	0.0
Tetracycline	≤0.5	>8	≤0.5 to >8	79.1	5.5	15.4	86.6	2.0	11.4
TMP-SMX	≤0.5	>4	≤0.5 to >4	65.5	17.4	17.1	65.5		34.5
Vancomycin	1	2	≤0.12 to 4	100.0		0.0	100.0	0.0	0.0
E. faecalis (598)									
Tedizolid	0.12	0.25	0.06 to 0.5				100.0		
Linezolid	1	2	≤0.25 to 4	100.0		0.0	99.8	0.2	0.0
Ampicillin	1	2	≤0.5 to 4	100.0	0.0	0.0	100.0		0.0
Daptomycin	1	1	≤0.25 to 4				100.0		
Teicoplanin	≤2	≤2	≤2 to >16	99.0		1.0	99.0	0.0	1.0
Vancomycin	1	2	≤0.5 to >16	99.0		1.0	99.0	0.0	1.0
E. faecium (409)									
Tedizolid	0.12	0.25	0.03 to >1						
Linezolid	1	2	0.25 to 8	99.3		0.7	99.3	0.0	0.7
Ampicillin	>8	>8	≤0.5 to >8	6.1	0.5	93.4	6.6		93.4
Daptomycin	2	2	≤0.25 to 4				100.0		
Teicoplanin	≤2	>16	≤2 to >16	84.4		15.6	85.1	2.2	12.7
Vancomycin	≤0.5	>16	≤0.5 to >16	81.2		18.8	81.2	1.5	17.4
VanA (61)									
Tedizolid	0.12	0.25	0.06 to >1						
Linezolid	1	1	0.5 to 8	98.4		1.6	98.4	0.0	1.6
Ampicillin	>8	>8	>8	0.0	0.0	100.0	0.0		100.0
Daptomycin	2	2	≤0.25 to 4				100.0		
Teicoplanin	>16	>16	16 to >16	0.0		100.0	0.0	14.8	85.2
Vancomycin	>16	>16	>16	0.0		100.0	0.0	0.0	100.0
S. pneumoniae (313)									
Tedizolid	0.12	0.25	0.03 to 0.5						
Linezolid	1	2	0.25 to 2	100.0	0.0	0.0	100.0		
Ceftaroline	≤0.015	0.06	≤0.015 to 0.5	99.7		0.3	100.0		[b]
Ceftriaxone	≤0.06	1	≤0.06 to >2	88.8	10.2	1.0	95.8	3.2	1.0
Clindamycin	≤0.25	>1	≤0.25 to >1	86.3		13.7	85.9	0.3	13.7
Erythromycin	≤0.12	>2	≤0.12 to >2	80.2	0.6	19.2	80.2	0.6	19.2
Levofloxacin	1	1	0.5 to >4	98.7		1.3	98.7	0.0	1.3
Penicillin[c]	≤0.06	1	≤0.06 to 4	77.3	17.6	5.1	94.9	5.1	0.0
Tetracycline	≤0.5	>4	≤0.5 to >4	80.8	0.6	18.5	80.8	0.6	18.5
TMP-SMX	≤0.5	>4	≤0.5 to >4	79.2	2.6	18.2	74.1	7.7	18.2
Vancomycin	0.25	0.25	≤0.12 to 0.5	100.0		0.0	100.0		
BHS[d] (384)									
Tedizolid	0.12	0.25	0.06 to 0.5	100.0		0.0			
Linezolid	1	1	0.5 to 2	100.0	0.0	0.0	100.0		
Ceftaroline	≤0.015	≤0.015	≤0.015 to 0.03				100.0		
Ceftriaxone	≤0.06	≤0.06	≤0.06 to 0.25				100.0		
Clindamycin	≤0.25	1	≤0.25 to >2	89.7		10.3	88.8	0.8	10.3
Daptomycin	0.12	0.25	≤0.06 to 0.5	100.0		0.0	100.0		
Erythromycin	≤0.12	>4	≤0.12 to >4	81.7	1.0	17.3	81.7	1.0	17.3
Levofloxacin	0.5	1	0.25 to >4	99.2		0.8	99.2	0.0	0.8
Penicillin	≤0.06	≤0.06	≤0.06	100.0		0.0	100.0		
Teicoplanin	≤2	≤2	≤2	100.0		0.0			
Tetracycline	≤0.5	>4	≤0.5 to >4	51.3	0.0	48.7	51.3	1.4	47.3
Vancomycin	0.25	0.5	0.25 to 1	100.0		0.0	100.0		
VGS[e] (333)									
Tedizolid	0.12	0.25	0.03 to 0.5						
Linezolid	1	1	0.12 to 2				100.0		
Ceftaroline	≤0.015	0.06	≤0.015 to >1						
Ceftriaxone	0.12	1	≤0.06 to >2	87.0		13.0	91.5	3.0	5.5
Clindamycin	≤0.25	>2	≤0.25 to >2	87.9		12.1	87.6	0.3	12.1
Daptomycin	0.25	1	≤0.06 to >1				99.3		
Erythromycin	≤0.12	>4	≤0.12 to >4				54.1	1.2	44.7
Levofloxacin	1	2	≤0.03 to >4				94.8	1.2	3.9
Penicillin	≤0.06	2	≤0.06 to >4	80.5	12.6	6.9	71.2	21.9	6.9
Tetracycline	≤0.5	>4	≤0.5 to >4				65.8	1.8	32.4
Vancomycin	0.5	0.5	0.12 to 1	100.0		0.0	100.0		

MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative streptococci; BHS, β-haemolytic streptococci; VGS, viridans group streptococci; TMP-SMX, trimethoprim-sulfamethoxazole
[a] Criteria as published by EUCAST (2018) and CLSI M100 (2018).
[b] CoNS, coagulase-negative staphylococci, includes: *Staphylococcus capitis* (60), *S. caprae* (2), *S. carnosus* (1), *S. cohnii* (2), *S. epidermidis* (514), *S. haemolyticus* (129), *S. hominis* (143), *S. lentus* (1), *S. lugdunensis* (13), *S. pasteuri* (3), *S. pettenkoferi* (4), *S. saprophyticus* (8), *S. schleiferi* (1), *S. simulans* (2), *S. warneri* (12).
[c] Using parenteral (nonmeningitis) breakpoints.
[d] Includes: *Streptococcus agalactiae* (158), *S. dysgalactiae* (84), *S. pyogenes* (142)
[e] Includes: *Streptococcus anginosus* (38), *S. anginosus* group (11), *S. australis* (3), *S. bovis* group (3), *S. constellatus* (5), *S. equinus* (1), *S. gallolyticus* (36), *S. gordonii* (8), *S. infantis* (2), *S. lutetiensis* (5), *S. massiliensis* (1), *S. mitis* (6), *S. mitis* group (64), *S. mitis/oralis* (26), *S. mutans* (5), *S. oralis* (29), *S. parasanguinis* (25), *S. salivarius* (18), *S. salivarius* group (17), *S. salivarius/vestibularis* (5), *S. sanguinis* (22), *S. vestibularis* (3)

CONCLUSIONS

- *S. aureus* remains a highly frequent gram-positive pathogen responsible for BSIs in patients hospitalised in European countries and adjacent regions
- Tedizolid showed potent activity against staphylococcal, enterococcal, and streptococcal isolates causing BSIs
  - Tedizolid may be an additional option for treating infections caused by VRE, where options are limited
- These data warrant the clinical development of tedizolid for treating BSIs

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