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Tedizolid Activity against Gram-Positive Clinical Isolates Causing Bone and Joint Infections, Including Osteomyelitis in United States and European Hospitals (2014–2016)

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Introduction

- Bone and joint infections (BJI) comprises a series of disorders, including septic arthritis, osteomyelitis, and infections in prosthetic joints[1]
- *Staphylococcus aureus* remains the most common pathogen responsible for acute infections, while gram-negative organisms are usually associated with traumatic infections and chronic presentations[1, 2]
- Common therapies include antimicrobial agents with gram-positive coverage; however, combination therapy that includes gram-negative and anaerobe coverage is warranted for chronic, previously treated, or severe infections[2, 3]
- Tedizolid is currently in clinical development to treat nosocomial pneumonia with an ongoing Phase 3 clinical trial (NCT02019420), and it's being investigated for BJI (NCT03009045) and diabetic wound infections (NCT02620787)[4, 5]
- This study evaluated the activity of tedizolid against pathogens causing BJI, including osteomyelitis in United States (US) and European hospitals (2014–2016) to support its clinical development to treat BJI

Materials and Methods

- A total of 359 *S. aureus*, 98 coagulase-negative staphylococci (CoNS), 76 β-hemolytic streptococci (BHS), 59 *Enterococcus* spp., and 18 viridans group streptococci (VGS) causing BJI were included (2014–2016)
- Isolates were collected from 30 medical sites in the US and 11 European countries (21 sites), plus Russia (3 sites), Turkey (1 site) and Israel (1 site)
- Isolates were determined to be clinically significant based on local guidelines and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the Surveillance of Tedizolid Activity and Resistance (STAR) Program[4]
- Participating laboratories initially identified isolates and JMI confirmed the bacterial identifications through standard algorithms and supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Isolates were tested for susceptibility by broth microdilution following guidelines in the CLSI M07–A10 document[6]
- Susceptibility testing used reference 96-well panels manufactured by JMI Laboratories (North Liberty, Iowa, USA)
- Concurrently testing of CLSI-recommended quality-control (QC) reference strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619) provided quality assurance
- Breakpoint criteria for tedizolid and comparator agents were from CLSI (2016)[7] and EUCAST (2016)[8]
  - Tigecycline MIC interpretation used the FDA breakpoints[9]

Results

- *S. aureus* (58.9%) was the most common gram-positive pathogen followed by CoNS (16.1%; mostly *S. epidermidis*), BHS (12.5%; mostly *S. agalactiae*), enterococci (9.7%; mostly *E. faecalis*), and VGS (3.0%; Table 1)
- 45.9% of *S. aureus* and 69.4% of CoNS isolates were methicillin-resistant, while 15.3% of all *Enterococcus* spp. exhibited a vancomycin-resistance phenotype (Tables 1 and 2)

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

Organism / organism group[†]	No. of isolates inhibited at MIC in µg/mL (cumulative %)									MIC	
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>1	50%	90%
MSSA (246)			1 (0.4%)	47 (19.5%)	186 (95.1%)	12 (100.0%)				0.12	0.12
MRSA (113)			1 (0.9%)	33 (30.1%)	73 (94.7%)	6 (100.0%)				0.12	0.12
Coagulase-negative staphylococci (98)		1 (1.0%)	4 (5.1%)	40 (45.9%)	53 (100.0%)					0.12	0.12
Enterococcus spp. (59)				4 (6.8%)	32 (61.0%)	23 (100.0%)				0.12	0.25
β-haemolytic streptococci (76)				1 (1.3%)	66 (88.2%)	9 (100.0%)				0.12	0.25
Viridans group streptococci (18)				4 (22.2%)	14 (100.0%)					0.12	0.12

† MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; coagulase-negative staphylococci includes *S. capitis* (8), *S. caprae* (3), *S. cohnii* (1), *S. epidermidis* (57), *S. haemolyticus* (7), *S. hominis* (6), *S. lugdunensis* (12), *S. simulans* (1), *S. warneri* (3); *Enterococcus* spp. includes *E. faecalis* (44), *E. faecium* (14) and *E. gallinarum* (1); **β-h**aemolytic streptococci includes *S. agalactiae* (40), *S. dysgalactiae* (18) and *S. pyogenes* (18); viridans group streptococci includes *S. anginosus* (3), *S. constellatus* (2), *S. cristatus* (1), *S. gordonii* (2), *S. mitis* group (3), *S. mitis/oralis* (5), *S. parasanguinis* (1), *S. salivarius* (1)

- Overall, tedizolid inhibited all tested isolates at ≤0.25 µg/mL and showed equivalent MIC_{50} results (0.12 µg/mL) regardless of pathogen or organism group (Tables 1 and 2)
- Most tested agents demonstrated in vitro activity against methicillin-susceptible *S. aureus* (MSSA) (≥93.1% susceptible), except for erythromycin (71.5–72.0%; Table 2)
- Tedizolid ($MIC_{50/90}$, 0.12/0.12 µg/mL) and tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL) showed the lowest MIC results against MRSA and CoNS (Table 2)
  - Against staphylococci, tedizolid and tigecycline had MIC_{90} values at least 4-fold lower than daptomycin (MIC_{90}, 0.5 µg/mL), ceftaroline (MIC_{90}, 1 µg/mL), and linezolid (MIC_{90}, 1 µg/mL)
- Tedizolid ($MIC_{50/90}$, 0.12/0.25 µg/mL) and tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL) were similarly potent against *Enterococcus* spp. (Table 2)
  - Tedizolid inhibited all *Enterococcus* spp. at ≤0.25 µg/mL, below the *E. faecalis* breakpoint (≤0.5 µg/mL)
- Daptomycin ($MIC_{50/90}$, 1/2 µg/mL; 100.0% susceptible) and linezolid ($MIC_{50/90}$, 1/1 µg/mL; 100.0% susceptible) were also active against *Enterococcus* spp., while other agents showed limited coverage (resistance rates ≥13.6%)
- BHS isolates were very susceptible (≥96.1%) to the antimicrobial agents tested, except for erythromycin, clindamycin, and tetracycline (Table 2), while tedizolid ($MIC_{50/90}$, 0.12/0.12 µg/mL) had an MIC_{90} value at least 8-fold lower than comparators against VGS

Conclusions

- Staphylococcal isolates remain the most frequent pathogens responsible for BJI
- High MRSA rates were observed, which precludes using commonly used empiric therapies (cefazolin and oxacillin)
- Tedizolid had potent in vitro activity against gram-positive isolates that cause BJI, including osteomyelitis from US and European countries/regions
- These in vitro data plus a favorable pharmacokinetics and side-effect profiles makes tedizolid an attractive alternative for treating BJI, pending further BJI clinical studies (NCT03009045)

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Table 2 Antimicrobial activity of tedizolid and comparator agents against main organisms and groups of isolates responsible for BJI

Organism/group[†] (no.)	MIC (µg/mL):		CLSI[c]			EUCAST[§]		
antimicrobial agent[‡]	MIC_{50}	MIC_{90}	%S	%I	%R	%S	%I	%R
MSSA (246)								
Tedizolid	0.12	0.12	100.0	0.0	0.0	100.0	—	0.0
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Ceftaroline	0.25	0.25	100.0	0.0	0.0	100.0	—	0.0
Clindamycin	≤0.25	≤0.25	98.0	0.0	2.0	97.6	0.4	2.0
Daptomycin	0.25	0.5	100.0	—	—	100.0	—	0.0
Erythromycin	0.25	>8	71.5	7.7	20.7	72.0	3.7	24.4
Levofloxacin	≤0.12	0.5	93.1	0.0	6.9	93.1	0.0	6.9
Tetracycline	≤0.5	≤0.5	96.7	0.0	3.3	95.5	0.8	3.7
Tigecycline	0.06	0.12	100.0	—	—	100.0	—	0.0
TMP-SMX	≤0.5	≤0.5	100.0	—	0.0	100.0	0.0	0.0
Vancomycin	0.5	1	100.0	0.0	0.0	100.0	—	0.0
MRSA (113)								
Tedizolid	0.12	0.12	100.0	0.0	0.0	100.0	—	0.0
Linezolid	1	1	100.0	—	0.0	100.0	—	0.0
Ceftaroline	1	1	91.1	8.9	0.0	91.1	—	8.9
Clindamycin	≤0.25	>2	77.0	0.0	23.0	77.0	0.0	23.0
Daptomycin	0.25	0.5	99.1	—	—	99.1	—	0.9
Erythromycin	>8	>8	23.0	0.9	76.1	23.0	0.0	77.0
Levofloxacin	4	>4	31.9	1.8	66.4	31.9	1.8	66.4
Tetracycline	≤0.5	2	90.2	1.8	8.0	87.5	2.7	9.8
Tigecycline	0.06	0.12	100.0	—	—	100.0	—	0.0
TMP-SMX	≤0.5	≤0.5	97.3	—	2.7	97.3	0.9	1.8
Vancomycin	0.5	1	100.0	0.0	0.0	100.0	—	0.0
CoNS (98)								
Tedizolid	0.12	0.12	100.0[‖]	—	—	100.0	—	0.0
Linezolid	0.5	1	100.0	—	0.0	100.0	—	0.0
Ceftaroline	0.25	1	—	—	—	—	—	—
Clindamycin	≤0.25	>2	64.3	1.0	34.7	64.3	0.0	35.7
Daptomycin	0.25	0.5	100.0	—	—	100.0	—	0.0
Erythromycin	>8	>8	32.7	1.0	66.3	32.7	1.0	66.3
Levofloxacin	0.25	>4	54.1	3.1	42.9	54.1	3.1	42.9
Oxacillin	>2	>2	30.6	—	69.4	30.6	—	69.4
Tetracycline	≤0.5	>8	81.6	1.0	17.3	78.6	3.1	18.4
Tigecycline	0.06	0.12	—	—	—	100.0	—	0.0
TMP-SMX	≤0.5	>4	70.4	—	29.6	70.4	16.3	13.3
Vancomycin	1	2	100.0	0.0	0.0	100.0	—	0.0
Enterococcus spp. (59)								
Tedizolid	0.12	0.25	100.0[‖]	—	—	—	—	—
Linezolid	1	1	100.0	0.0	0.0	100.0	—	0.0
Ampicillin	1	>8	76.3	—	23.7	76.3	0.0	23.7
Daptomycin	1	2	100.0	—	—	—	—	—
Erythromycin	>16	>16	8.1	24.3	67.6	—	—	—
Levofloxacin	2	>4	54.2	0.0	45.8[¶]	54.2	—	45.8[¶]
Teicoplanin	≤2	>16	84.7	1.7	13.6	84.7	—	15.3
Tetracycline	>8	>8	23.7	1.7	74.6	—	—	—
Tigecycline	0.06	0.12	—	—	—	100.0	0.0	0.0
Vancomycin	1	>16	84.7	0.0	15.3	84.7	—	15.3
BHS								
Tedizolid	0.12	0.25	100.0[‖]	—	—	100.0	—	0.0
Linezolid	1	1	100.0	—	—	100.0	0.0	0.0
Amoxicillin-clavulanate	≤1	≤1	100.0	—	—	100.0	—	0.0
Ceftaroline	≤0.015	≤0.015	100.0	—	—	100.0	—	0.0
Ceftriaxone	≤0.06	0.12	100.0	—	—	100.0	—	0.0
Clindamycin	≤0.25	>2	78.9	0.0	21.1	78.9	—	21.1
Daptomycin	0.12	0.5	100.0	—	—	100.0	—	0.0
Erythromycin	≤0.12	>4	60.5	0.0	39.5	60.5	0.0	39.5
Levofloxacin	0.5	1	98.7	0.0	1.3	96.1	2.6	1.3
Penicillin	≤0.06	≤0.06	100.0	—	—	100.0	—	0.0
Tetracycline	>8	>8	46.1	2.6	51.3	44.7	1.3	53.9
Tigecycline	0.06	0.06	100.0	—	—	100.0	0.0	0.0
Vancomycin	0.25	0.5	100.0	—	—	100.0	—	0.0
VGS								
Tedizolid	0.12	0.12	100.0[‖]	—	—	—	—	—
Linezolid	0.5	1	100.0	—	—	—	—	—
Amoxicillin-clavulanate	≤1	>8	—	—	—	83.3	5.6	11.1
Ceftaroline	≤0.015	1	—	—	—	—	—	—
Ceftriaxone	0.12	8	88.9	0.0	11.1	77.8	—	22.2
Clindamycin	≤0.25	>2	72.2	0.0	27.8	72.2	—	27.8
Daptomycin	0.25	1	100.0	—	—	—	—	—
Erythromycin	1	>4	44.4	0.0	55.6	—	—	—
Levofloxacin	0.5	>4	83.3	0.0	16.7	—	—	—
Penicillin	≤0.06	8	72.2	16.7	11.1	83.3	5.6	11.1
Tetracycline	>8	>8	33.3	0.0	66.7	—	—	—
Vancomycin	0.5	1	100.0	—	—	100.0	—	0.0

† MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; CoNS = coagulase-negative staphylococci; BHS = β-hemolytic streptococci; VGS = viridans group streptococci.
‡ TMP-SMX = trimethoprim-sulfamethoxazole.
§ Breakpoint criteria for tedizolid and comparator agents were those from EUCAST (2016) and CLSI (2016), as available. Penicillin MIC interpretation against *S. pneumoniae* applied the parenteral CLSI (non-meningitis) breakpoint. MIC interpretation for tigecycline used the FDA breakpoints (results under the CLSI column). "—" breakpoint not available.
‖ Tedizolid breakpoint for *S. aureus* applied for CoNS; tedizolid breakpoint for *E. faecalis* applied for *Enterococcus* spp.; tedizolid breakpoints for *S. pyogenes* and *S. agalactiae* applied for BHS; tedizolid breakpoint for *S. anginosus* applied for VGS.
¶ For urinary tract infections only.