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Original Article

Tedizolid *in vitro* activity against Gram-positive clinical isolates causing bone and joint infections in hospitals in the USA, Europe, Latin America, and the Asia-Pacific region (2015-2019)

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ABSTRACT

As bone and joint infections (BJIs) frequently require prolonged, systemic antibiotic use, tedizolid is an attractive candidate for BJI therapy in adults and children. Tedizolid activity was evaluated against 1,193 Gram-positive isolates causing BJI in American (USA), European (EUR), Latin American (LATAM), and Asian-Pacific (APAC) medical centers. Isolates consecutively collected from 2015 to 2019 were susceptibility tested by CLSI broth microdilution. *Staphylococcus aureus* (69.2%) was the most common pathogen with a 25.9% MRSA rate and tedizolid $MIC_{50/90}$ of 0.12/0.25 mg/L (100% susceptible). Tedizolid exhibited $MIC_{50/90}$ values of 0.12/0.12 mg/L (98.9% susceptible) for CoNS (7.5% of BJI), 0.12/0.25 mg/L for streptococci, and 0.25/0.25 mg/L for enterococci. Overall, high susceptibility rates (100.0%) for linezolid, daptomycin, and vancomycin were observed. In summary, tedizolid had potent *in vitro* activity against contemporary Gram-positive cocci causing BJI in adults and children in USA, EUR, LATAM, and APAC hospitals.

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1. Introduction

Bone and joint infections (BJIs) include septic arthritis, prosthetic joint infections (PJI), osteomyelitis (OM), spinal infections (discitis, vertebral OM, and epidural abscess), and diabetic foot OM [1,2]. Although relatively understudied, population-based data suggests that OM and other BJIs are common and increasing in incidence partially due to an increase in OM associated with diabetes mellitus [1–3]. These infections often require surgical intervention and prolonged, often suppressive, antimicrobial therapy targeted against the implicated pathogen [1,2,4–6]. Additionally, these infections carry a significant clinical and economic burden, especially in the elderly [6–8]. Recently, Premkumar et al. [9] reported that in the USA, projections for the year 2030 estimate that the annual number of PJIs (knee and hip) could rise to more than 66,000 cases per year with a total cost of more than $1.85 billion United States dollars [6].

Treatment of BJIs is often empirical and requires considering numerous parameters, including the antimicrobial susceptibility profile of the likely infecting pathogen(s), pharmacokinetics of the employed agents (especially penetration into bone and synovium), presence of prosthetic material, and tolerance for drugs to be employed [10–13]. Gram-positive cocci (GPC) are responsible for the majority of BJIs; *Staphylococcus aureus* is the most common bacteria followed by coagulase-negative staphylococci (CoNS), streptococci, and enterococci [3,7,8,14]. Community-associated (CA) methicillin-resistant *S. aureus* (CA-MRSA), health care-associated (HA) MRSA, and methicillin-resistant (MR)-CoNS, as well as, vancomycin-resistant enterococci (VRE), and macrolide resistance among β-hemolytic streptococci (BHS) complicate forms of therapy for OM and other BJI in children and adults [1,2].

Tedizolid, an oxazolidinone antibiotic, exhibits greater potency and spectrum than linezolid when tested against a broad array of GPC, including drug-resistant phenotypes such as MRSA, VRE, and linezolid-resistant (*cfr*-mediated) phenotypes [15,16]. Tedizolid may be administered parenterally or orally and has lower rates of myelotoxicity and drug-drug interactions than linezolid [17,18]. These features, coupled with once-daily dosing and documented safety in long-term therapy, makes tedizolid an attractive alternative for infections requiring long-term suppressive regimens, such as complex implant-associated BJI [5,18–20]. Tedizolid was approved by the United States (US) Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (in 2014) and in adolescents (>12 years of age; in 2020), and is undergoing Phase III clinical trials for the treatment of ABSSSI in neonates and children (≤12 years of age; ClinicalTrials.gov registration no. NCT02276482; [16]). Additionally, a Phase II clinical trial for the use of tedizolid as an oral prolonged treatment for BJIs in adults (ClinicalTrials.gov registration no. NCT3009045) is in enrollment.

Despite the lack of an approved indication for tedizolid in the treatment of BJI, the growing incidence of resistant pathogens

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involved in BJIs, such as multidrug-resistant (resistant to 3 or more classes of agents) staphylococci [1,2,21,22], plus the adverse effects of conventional therapies have led to the increasing use of off-label molecules for the treatment of BJIs [6]. A recent survey from France found that while the expense of using either daptomycin or linezolid for the treatment of BJIs has decreased significantly with the introduction of generic molecules, issues with adverse events, administration (parenteral versus oral), and concern over emerging resistance has led to an increased off-label use of newer, more expensive agents such as tedizolid [6]. Given the increasing use of tedizolid for indicated ABSSSI, ongoing BJI trials, and off-label treatment of BJI [18], continued monitoring of the spectrum and potency of this agent against target pathogens is warranted.

The present report describes tedizolid *in vitro* activity and potency when tested against a global contemporary (2015-2019) collection of GPC isolates responsible for BJI, including OM, recovered from adult and pediatric patients in American (USA), European (EUR), Latin American (LATAM), and Asian-Pacific (APAC) medical centers.

2. Materials and methods

2.1. Bacterial isolates

A total of 1,193 gram-positive pathogens were analyzed. The organisms were consecutively collected during 2015-2019 from 89 medical centers located in 31 countries: the USA (30 medical centers; 493 isolates; 41.3% overall), EUR (36 medical centers in 19 countries; 453 isolates; 38.0% overall), LATAM (10 medical centers in 6 countries; 139 isolates; 11.7% overall), and APAC (13 medical centers in 5 countries; 108 isolates; 9.1% overall; Table 1). All organisms were isolated from documented BJIs and only 1 organism per patient infection episode was included in the survey. APAC and LATAM only contributed isolates included in the FDA intended to treat list of pathogens [23]. Therefore, CoNS, *S. pneumoniae*, and *E. faecium* isolates from APAC and LATAM were not included. Isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for confirmation of species identification, if necessary, using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS; MBT Compass v.4.1.100.1; Bruker Daltonics, Bremen, Germany) or manual methods, such as hemolysis evaluation, bile solubility, and optochin susceptibility for *Streptococcus* spp.

2.2. Antimicrobial susceptibility testing

Susceptibility testing was performed by broth microdilution (BMD) following the guidelines of the CLSI M07 (2018). Quality control (QC) was performed by concurrently testing the following CLSI-recommended QC reference strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *Streptococcus pneumoniae* ATCC 49619. All QC results were within published acceptable ranges. MIC results for tested agents obtained against clinical isolates were interpreted using CLSI M100-31E (2021) and EUCAST breakpoint criteria, where published [24,25]. US FDA product package insert criteria were used as an alternative breakpoint source as necessary (e.g., tigecycline).

3. Results

3.1. Organisms

The most common isolate type from BJIs was *S. aureus* (69.2% overall; 25.9% of which were MRSA) followed by β-hemolytic streptococci (BHS; 14.1%), CoNS (7.5%; 57.8% of which were MRCoNS), *Enterococcus* sp. (6.5%), viridans group streptococci (1.9%), and *S. pneumoniae* (0.7%; Table 1). Among the key resistant phenotypes, MRSA was most common in the USA (35.8%) and least common in EUR (17.7%), while MRCoNS constituted 65.4% of CoNS from USA and 47.4% from EUR (Table 1).

3.2. Activity of tedizolid against key target BJI pathogens

The MIC distributions for each tested species or organism group are shown in Table 2. Importantly, all but one of the 1,193 isolates of GPC (99.9%) from BJIs in this survey were inhibited by ≤0.5 mg/L of tedizolid (Table 2). Tedizolid was very potent when tested against all 826 *S. aureus* isolates ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible), methicillin-susceptible *S. aureus* (MSSA; $MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible), and MRSA ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible; Table 2). Further analysis revealed that the same MIC_{90} values (0.25 mg/L) for tedizolid were observed for *S. aureus* isolates from all four regions (data not shown). MRSA isolates from LATAM displayed a higher MIC_{90} value (0.5 mg/L) than the other three regions (0.25 mg/L).

Out of 90 CoNS isolates, 98.9% were susceptible to tedizolid at the EUCAST breakpoint of 0.5 mg/L and this activity was unaffected by oxacillin resistance ($MIC_{50/90}$, 0.12/0.12 mg/L; 98.1% susceptible against MR-CoNS).

Table 1
Main organisms and organism groups stratified by geography.

Organism/organism group	USA	EUR	LATAM	APAC	Total
Staphylococcus aureus	310	311	112	93	826
Methicillin-susceptible	199	256	85	72	612
Methicillin-resistant	111	55	27	21	214
Coagulase-negative staphylococci	52	38	0[a]	0[a]	90
Methicillin-susceptible	18	20	0[a]	0[a]	38
Methicillin-resistant	34	18	0[a]	0[a]	52
β-hemolytic streptococci	79	64	15	10	168
Viridans group streptococci	5	14	1	3	23
Streptococcus pneumoniae	4	4	0[a]	0[a]	8
Enterococcus spp.	43	22	11	2	78
Enterococcus faecalis	37	20	11	2	70
Enterococcus faecium	4	2	0[a]	0[a]	6
Total	493	453	139	108	1,193

USA = United States of America; EUR = Europe; LATAM = Latin America; APAC = Asia Pacific.
[a] Only intended to treat pathogens listed in the tedizolid FDA package insert (SINVEXTRO®) were included from APAC and LATAM regions, therefore, no coagulase-negative staphylococci, *S. pneumoniae* and *E. faecium* isolates were reported from these regions.

Table 2
Antimicrobial activity of tedizolid tested against the main organisms and organism groups.

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	>[a]		
Staphylococcus aureus (826)		0 0.0	1 0.1	98 12.0	434 64.5	277 98.1	16 100.0			0.12	0.25
Methicillin-susceptible (612)		0 0.0	1 0.2	71 11.8	316 63.4	215 98.5	9 100.0			0.12	0.25
Methicillin-resistant (214)			0 0.0	27 12.6	118 67.8	62 96.7	7 100.0			0.12	0.25
Coagulase-negative staphylococci (90)	0 0.0	1 1.1	2 3.3	30 36.7	51 93.3	5 98.9	0 98.9	0 98.9	1 100.0	0.12	0.12
Methicillin-susceptible (38)	0 0.0	1 2.6	1 5.3	13 39.5	21 94.7	2 100.0				0.12	0.12
Methicillin-resistant (52)		0 0.0	1 1.9	17 34.6	30 92.3	3 98.1	0 98.1	0 98.1	1 100.0	0.12	0.12
β-hemolytic streptococci (168)			0 0.0	3 1.8	79 48.8	85 99.4	1 100.0			0.25	0.25
Viridans group streptococci (23)		0 0.0	1 4.3	0 4.3	14 65.2	8 100.0				0.12	0.25
Streptococcus pneumoniae (8)				0 0.0	4 50.0	3 87.5	1 100.0			0.12	
Enterococcus spp. (78)			0 0.0	3 3.8	28 39.7	44 96.2	3 100.0			0.25	0.25
Enterococcus faecalis (70)			0 0.0	2 2.9	23 35.7	42 95.7	3 100.0			0.25	0.25
Enterococcus faecium (6)			0 0.0	1 16.7	3 66.7	2 100.0				0.12	

[a] Greater than the highest concentration tested.

Tedizolid was very potent against the β-hemolytic streptococci: all (100.0%) β-hemolytic streptococci (BHS; $MIC_{50/90}$, 0.25/0.25 mg/L) were inhibited by ≤0.5mg/L of tedizolid (Table 2). Likewise, all tested isolates of viridans group streptococci and *S. pneumoniae* were inhibited by ≤0.5 mg/L of tedizolid.

Tedizolid demonstrated potent activity against 78 isolates of enterococci ($MIC_{50/90}$, 0.25/0.25 mg/L; 100.0% inhibited at MIC ≤4 mg/L), including *Enterococcus faecium* isolates (MIC_{50}, 0.12 mg/L; Table 2).

3.3. Activities of tedizolid and comparators against BJI pathogens

The activities of tedizolid and comparator agents tested against *S. aureus* isolates are summarized in Table 3. Tedizolid MIC values ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible) were 4- to 8-fold lower than those of linezolid ($MIC_{50/90}$, 1/2 mg/L; 100.0% susceptible) and vancomycin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0% susceptible) against MSSA (Table 3). MSSA isolates were >94% susceptible to most of the tested agents, except erythromycin (74.2% susceptible). All (100.0%) MSSA isolates were susceptible to tedizolid, linezolid, ceftaroline, daptomycin, teicoplanin, tigecycline, and vancomycin at their respective breakpoints (Table 3).

MRSA isolates comprised 17.9% of all BJIs in this survey, ranging from 12.1% in EUR to 22.5% in the USA. Among all 214 MRSA isolates, tedizolid MICs ($MIC_{50/90}$, 0.12/0.25 mg/L; 100.0% susceptible) were 4- to 8-fold lower than those of linezolid ($MIC_{50/90}$, 1/2 mg/L; 100.0% susceptible) and vancomycin ($MIC_{50/90}$, 1/1 mg/L; 100.0% susceptible) (Table 3). Teicoplanin (100.0% susceptible), daptomycin (100.0% susceptible), ceftaroline (93.8% susceptible), tigecycline (100.0% susceptible), and trimethoprim/sulfamethoxazole (96.3% susceptible) were also active against MRSA (Table 3). Tetracycline showed somewhat greater coverage against MRSA from the USA (90.1% susceptible) than MRSA from EUR (82.4% susceptible; data not shown). Tedizolid was active against the single isolate with reduced susceptibility to vancomycin (vancomycin MIC value of 2 mg/L and tedizolid MIC value of 0.12 mg/L) and the two MRSA isolates showing elevated linezolid MIC values (linezolid MIC values of 4 mg/L and tedizolid MIC values of 0.5 mg/L; data not shown).

CoNS accounted for 10.5% of BJIs in the USA and 8.4% of BJIs in EUR. No CoNS were contributed by medical centers in LATAM or APAC. Susceptibility results for CoNS, including methicillin-resistant (MR) isolates, are presented in Table 3. A total of 57.8% of the CoNS isolates tested were resistant to oxacillin (Table 1). Tedizolid (MIC_{90}, 0.12 mg/L) and tigecycline (MIC_{90}, 0.12 mg/L) were the most potent agents tested against CoNS (Table 3). Tedizolid was 8- to 16-fold more potent than linezolid (MIC_{90}, 1 mg/L) and vancomycin (MIC_{90}, 2 mg/L) by MIC_{90} value (Table 3): 98.9% of CoNS were susceptible to tedizolid at the *S. aureus* EUCAST susceptible breakpoint of ≤0.5 mg/L (Tables 2 and 3). The antibiogram results for comparators against CoNS isolates showed high resistance rates for all tested drugs except daptomycin (100.0% susceptible), linezolid (98.9% susceptible), teicoplanin (100.0% susceptible), tigecycline (100.0% susceptible [EUCAST]), and vancomycin (100.0% susceptible).

Enterococci accounted for 6.5% of all BJIs in this survey, all but 6 of which were *Enterococcus faecalis* (89.7%). Tedizolid demonstrated potent activity against *E. faecalis*, with MIC_{50} and MIC_{90} values of 0.25 and 0.25 mg/L, respectively (100.0% susceptible at the CLSI breakpoint of 0.5 mg/L; Tables 2 and 3). All *E. faecalis* isolates were susceptible to tedizolid, ampicillin, daptomycin, linezolid, and tigecycline (Table 3). A total of 2.9% of *E. faecalis* strains were resistant to vancomycin (tedizolid MIC values, 0.12 mg/L for both isolates). The 6 *E. faecium* isolates were all inhibited by ≤0.25 mg/L of tedizolid and either were susceptible or susceptible-dose dependent to linezolid and daptomycin, respectively. The remaining 2 isolates were identified as *Enterococcus avium* and were susceptible to all antimicrobials tested but tetracycline.

All (100.0%) BHS isolates were susceptible to tedizolid (EUCAST breakpoint), linezolid, amoxacillin-clavulanic acid, ceftaroline, ceftriaxone, daptomycin, penicillin, tigecycline, and vancomycin (Table 3). Macrolide resistance was common in BHS from the USA (46.8%) and EUR (28.1%). Tedizolid ($MIC_{50/90}$, 0.12/0.25 mg/L) was the most active agent against Viridans group streptococci (VGS), inhibiting all isolates at 0.25 mg/L (Tables 2 and 3). Daptomycin, linezolid, tigecycline, and vancomycin were also active (100.0% susceptible) against VGS (Table 3).

4. Discussion

Tedizolid is an attractive option for empirical and targeted therapy of BJI due to its (1) broad spectrum of activity against aerobic GPC; (2) activity against key resistant pathogens, including MRSA, MR-CoNS, *cfr*-mediated linezolid-resistant strains, VRE, and macrolide-resistant BHS; (3) penetration into bone and activity against biofilms and biofilm-producing organisms; (4) high bioavailability with oral administration; (5) long half-life, allowing once-daily administration; (6) lower risk of drug-drug interactions and better safety profile than linezolid; and (7) efficacy and safety of long-term use in the treatment of osteoarticular infections [16,18,26,27]. Tedizolid was highly active against clinical BJI isolates from the major Gram-positive pathogen groups collected from USA, EUR, LATAM, and APAC medical centers during 2015-2019. Overall, 1192/1193 (99.9%) isolates were susceptible to tedizolid at ≤0.5 mg/L. *S. aureus* comprised the majority (69.2%) of the Gram-positive BJI pathogens. The *S. aureus* BJI isolate set, including MRSA, was 100.0% susceptible to tedizolid. Tedizolid activity against the BJI isolate set was nearly identical to previously reported activity against GPC isolates globally obtained

Table 3
Activity of tedizolid and comparator antimicrobial agents against gram-positive cocci.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
S. aureus (826)									
Tedizolid	0.12	0.25	0.03-0.5	100.0	0.0	0.0	100.0		0.0
Linezolid	1	2	≤0.12-4	100.0		0.0	100.0		0.0
Ceftaroline	0.25	1	≤0.06-2	98.3	1.7	0.0	98.3	1.7	0.0
Clindamycin	≤0.25	≤0.25	≤0.25->2	92.3	0.0	7.7	92.0	0.3	7.7
Daptomycin	≤0.25	0.5	≤0.12-1	100.0			100.0		0.0
Erythromycin	0.25	>8	≤0.06->8	63.3	5.3	31.4	63.8	2.4	33.8
Vancomycin	0.5	1	≤0.12-2	100.0	0.0	0.0	100.0		0.0
Levofloxacin	0.25	>4	0.06->4	77.2	0.3	22.4	[b]	77.2	22.8
Oxacillin	0.5	>2	≤0.25->2	74.1		25.9	74.1		25.9
Teicoplanin	≤0.5	≤0.5	≤0.5-2	100.0	0.0	0.0	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5->8	94.4	1.0	4.6	93.7	0.5	5.8
Tigecycline	0.06	0.12	0.03-0.5	100.0[c]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	98.4		1.6	98.4	0.4	1.2
MSSA (612)									
Tedizolid	0.12	0.25	0.03-0.5	100.0	0.0	0.0	100.0		0.0
Linezolid	1	2	≤0.12-4	100.0		0.0	100.0		0.0
Ceftaroline	0.25	0.25	≤0.06-0.5	100.0	0.0	0.0	100.0	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25->2	98.4	0.0	5.1	97.9	0.5	1.6
Daptomycin	0.25	0.5	≤0.12-1	100.0			100.0		0.0
Erythromycin	0.25	>8	≤0.06->8	74.2	6.2	19.6	74.7	2.8	22.5
Vancomycin	0.5	1	≤0.12-2	100.0	0.0	0.0	100.0		0.0
Levofloxacin	0.25	0.25	0.06->4	94.1	0.0	5.9	[b]	94.1	5.9
Oxacillin	0.5	0.5	≤0.25-2	100.0		0.0	100.0		0.0
Teicoplanin	≤0.5	≤0.5	≤0.5-2	100.0	0.0	0.0	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5->8	96.9	0.5	2.6	96.5	0.2	3.3
Tigecycline	0.06	0.12	0.03-0.25	100.0[c]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5-8	99.2		0.8	99.2	0.5	0.3
MRSA (214)									
Tedizolid	0.12	0.25	0.06-0.5	100.0	0.0	0.0	100.0		0.0
Linezolid	1	2	≤0.12-4	100.0		0.0	100.0		0.0
Ceftaroline	0.5	1	0.25-2	93.8	6.2	0.0	93.8	6.2	0.0
Clindamycin	≤0.25	>2	≤0.25->2	76.5	0.0	23.5	76.5	0.0	23.5
Daptomycin	0.25	0.5	≤0.12-1	100.0			100.0		0.0
Erythromycin	>8	>8	0.12->8	32.2	2.8	65.0	32.7	1.4	65.9
Vancomycin	1	1	≤0.12-2	100.0	0.0	0.0	100.0		0.0
Levofloxacin	4	>4	0.06->4	32.7	1.2	66.0	[b]	32.7	67.3
Oxacillin	>2	>2	>2->2	0.0		100.0	0.0		100.0
Teicoplanin	≤0.5	≤0.5	≤0.5-2	100.0	0.0	0.0	100.0		0.0
Tetracycline	≤0.5	8	≤0.5->8	87.7	2.5	9.9	86.4	1.2	12.3
Tigecycline	0.06	0.12	0.03-0.5	100.0[c]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	96.3		3.7	96.3	0.0	3.7
CoNS (90)[d]									
Tedizolid	0.12	0.12	0.015->1				98.9		1.1
Linezolid	0.5	1	0.25-8	98.9		1.1	98.9		1.1
Ceftaroline	0.25	0.5	≤0.06-2						
Clindamycin	≤0.25	>2	≤0.25->2	74.4	2.2	23.3	74.4	0.0	25.6
Daptomycin	0.25	0.5	≤0.12-1	100.0			100.0		0.0
Erythromycin	>8	>8	≤0.06->8	41.1	1.1	57.8	41.1	1.1	57.8
Vancomycin	1	2	≤0.12-2	100.0	0.0	0.0	100.0		0.0
Levofloxacin	0.25	>4	0.06->4	60.0	3.3	36.7	[b]	60.0	40.0
Oxacillin	>2	>2	≤0.25->2	42.2		57.8	36.7		63.3
Teicoplanin	1	4	≤0.5-8	100.0	0.0	0.0	91.1		8.9
Tetracycline	≤0.5	>8	≤0.5->8	86.7	1.1	12.2	85.6	1.1	13.3
Tigecycline	0.06	0.12	≤0.015-0.5				100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5->4	73.3		26.7	73.3	14.4	12.2
Enterococcus sp. (78)[e]									
Tedizolid	0.25	0.25	0.06-0.5						
Linezolid	1	2	≤0.25-2	100.0	0.0	0.0	100.0		0.0
Ampicillin	1	2	≤0.5->8	92.3		7.7	92.3	0.0	7.7
Ceftaroline	2	8	≤0.25->8						
Daptomycin	1	1	≤0.25-2						
Levofloxacin	1	>4	≤0.5->4	70.3	0.0	29.7	70.3		29.7
Teicoplanin	≤2	≤2	≤2->16	91.0	1.3	7.7	91.0		9.0
Tetracycline	>8	>8	≤1->8	21.9	0.0	78.1			
Tigecycline	0.06	0.12	0.03-0.12	100.0			100.0		0.0
Vancomycin	1	4	≤0.5->16	91.0	0.0	9.0	91.0		9.0
BHS (168)[f]									
Tedizolid	0.25	0.25	0.06-0.5				100.0		0.0
Linezolid	1	2	0.5-2	100.0			100.0		0.0
Amoxacillin-clavulanic acid	≤0.03	0.06	≤0.03-0.12	100.0					
Ceftaroline	≤0.008	0.015	≤0.008-0.03	100.0			100.0		0.0

(*continued*)

Table 3 (*Continued*)

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
Clindamycin	≤0.25	>2	≤0.25->2	72.0	1.4	26.6	73.4		26.6
Daptomycin	0.12	0.25	≤0.06-1	100.0			100.0		0.0
Erythromycin	0.06	>4	≤0.03->4	64.3	0.6	35.1	64.3	0.6	35.1
Levofloxacin	0.5	1	0.12->4	97.4	1.3	1.3	0.0	97.4	2.6
Teicoplanin	0.25	8	≤0.06-0.25				100.0		0.0
Tigecycline	0.06	0.06	0.03-0.12	100.0[c]			100.0		0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5-≤0.5				100.0	0.0	0.0
VGS (23)[g]									
Tedizolid	0.12	0.25	0.03-0.25						
Linezolid	1	2	0.5-2	100.0					
Ceftriaxone	0.12	0.5	≤0.03-2	94.7	5.3	0.0	94.7		5.3
Clindamycin	≤0.25	>2	≤0.25->2	73.7	0.0	26.3	73.7		26.3
Daptomycin	0.25	0.5	≤0.06-1	100.0					
Erythromycin	≤0.03	>4	≤0.03->4	60.9	0.0	39.1			
Levofloxacin	1	2	0.25-4	95.7	4.3	0.0			
Penicillin	≤0.03	0.25	≤0.03-2	87.0	13.0	0.0	95.7	4.3	0.0

CLSI = Clinical and Laboratory Standards Institute; EUCAST = European Committee on Antimicrobial Susceptibility Testing; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus;* CoNS = coagulase-negative staphylococci; BHS = β-haemolytic streptococci; VGS = viridans group streptococci; S = susceptible; I = intermediate; R = resistant.

[a] Criteria as published by CLSI (2021) and EUCAST (2020).

[b] An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as susceptible increased exposure.

[c] Breakpoints from FDA Package Insert were revised 12/2014.

[d] Organisms include *Staphylococcus capitis* (7), *S. caprae* (3), *S. cohnii* (1), *S. epidermidis* (46), *S. haemolyticus* (9), *S. hominis* (3), *S. lugdunensis* (16), *S. simulans* (2), and *S. warneri* (3).

[e] Organisms include *Enterococcus avium* (2), *E. faecalis* (70), and *E. faecium* (6).

[f] Organisms include *Streptococcus agalactiae* (86), *S. dysgalactiae* (35), and *S. pyogenes* (47).

[g] Organisms include *Streptococcus anginosus* (8), *S. anginosus* group (1), *S. constellatus* (2), *S. gallolyticus* (3), *S. intermedius* (1), *S. mitis* group (4), *S. mitis/oralis* (1), *S. oralis* (2), and *S. sanguinis* (1).

from various infection types [28–31]. Consistent with previous studies, we found no evidence of a linezolid-susceptible/tedizolid-resistant phenotype and resistance to other antimicrobial classes had no effect on the activity of tedizolid [1,23,28,29]. The potent antibacterial activity of tedizolid, including against MRSA, supports its further evaluation for the potential treatment of BJIs caused by Gram-positive pathogens.

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Transparency Declarations

JMI Laboratories was contracted to perform services in 2015-2019 for Achaogen, Inc., Albany College of Pharmacy and Health Sciences, Allecra Therapeutics, Allergan, AmpliPhi Biosciences Corp., Amicrobe Advanced Biomaterials, Amplyx, Antabio, American Proficiency Institute, Arietis Corp., Arixa Pharmaceuticals, Inc., Astellas Pharma Inc., Athelas, Basilea Pharmaceutica Ltd., Bayer AG, Becton, Dickinson and Company, bioMerieux SA, Boston Pharmaceuticals, Bugworks Research Inc., CEM-102 Pharmaceuticals, Cepheid, Cidara Therapeutics, Inc., CorMedix Inc., DePuy Synthes, Destiny Pharma, Discuva Ltd., Dr. Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, Eurofarma Laboratorios SA, US Food and Drug Administration, Fox Chase Chemical Diversity Center, Inc., Gateway Pharmaceutical LLC, GenePOC Inc., Geom Therapeutics, Inc., GlaxoSmithKline plc, Harvard University, Helperby, HiMedia Laboratories, F. Hoffmann-La Roche Ltd., ICON plc, Idorsia Pharmaceuticals Ltd., Iterum Therapeutics plc, Laboratory Specialists, Inc., Melinta Therapeutics, Inc., Merck & Co., Inc., Microchem Laboratory, Micromyx, MicuRx Pharmaceuticals, Inc., Mutabilis Co., Nabriva Therapeutics plc, NAEJA-RGM, Novartis AG, Oxoid Ltd., Paratek Pharmaceuticals, Inc., Pfizer, Inc., Polyphor Ltd., Pharmaceutical Product Development, LLC, Prokaryotics Inc., Qpex Biopharma, Inc., Roivant Sciences, Ltd., Safeguard Biosystems, Scynexis, Inc.,SeLux Diagnostics, Inc., Shionogi and Co., Ltd., SinSa Labs, Spero Therapeutics, Summit Pharmaceuticals International Corp., Synlogic, T2 Biosystems, Inc., Taisho Pharmaceutical Co., Ltd., TenNor Therapeutics Ltd., Tetraphase Pharmaceuticals, Theravance Biopharma, University of Colorado, University of Southern California-San Diego, University of North Texas Health Science Center, VenatoRx Pharmaceuticals, Inc., Viosera Therapeutics, Vyome Therapeutics Inc., Wockhardt, Yukon Pharmaceuticals, Inc., Zai Lab, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

Authors' Contributions

Michael Pfaller: Conceptualization, Methodology, Data Curation, Writing – Original Draft Jennifer M. Streit: Methodology, Data Curation, Visualization, Supervision Rodrigo E. Mendes: Conceptualization, Methodology, Investigation, Writing – Review & Edit Cecilia Carvalhaes: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Supervision, Project Administration, Funding Acquisition; Writing – Review & Edit, Supervision.

Declaration of Competing Interest

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