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Activities of Tedizolid and Linezolid Determined by the Reference Broth Microdilution Method against 3,032 Gram-Positive Bacterial Isolates Collected in Asia-Pacific, Eastern Europe, and Latin American Countries in 2014

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Tedizolid and linezolid *in vitro* activities against 3,032 Gram-positive pathogens collected in Asia-Pacific, Eastern European, and Latin American medical centers during 2014 were assessed. The isolates were tested for susceptibility by the current reference broth microdilution methods. Due to concern over the effect of MIC endpoint criteria on the results of testing the oxazolidinones tedizolid and linezolid, MIC endpoint values were read by two methods: (i) reading the MIC at the first well where the trailing began without regard for pinpoint trailing, according to CLSI M07-A10 and M100-S26 document instructions for reading linezolid (i.e., 80% inhibition of growth; these reads were designated tedizolid 80 and linezolid 80), and (ii) at 100% inhibition of growth (designated tedizolid 100 and linezolid 100). All *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Enterococcus faecalis* isolates were inhibited at tedizolid 80 and 100 MIC values of 0.25 and 0.5, 0.25 and 0.25, 0.25 and 0.5, 0.12 and 0.25, and 0.5 and 1 μg/ml, respectively. Generally, MIC_{50} and MIC_{90} results for tedizolid 80 and linezolid 80 were one doubling dilution lower than those read at 100% inhibition. Tedizolid was 4- to 8-fold more potent than linezolid against all the isolates tested regardless of the MIC endpoint criterion used. Despite the differences in potency, >99.9% of isolates tested in this survey were susceptible to both linezolid and tedizolid using CLSI and EUCAST interpretive criteria. In conclusion, tedizolid demonstrated greater *in vitro* potency than linezolid against Gram-positive pathogens isolated from patients in medical centers across the Asia-Pacific region, Eastern Europe, and Latin America.

Tedizolid is an oxazolidinone derivative that exhibits greater potency and a broader spectrum than linezolid when tested against a broad array of Gram-positive cocci, including those with drug-resistant phenotypes, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), and linezolid-resistant phenotypes (1, 2). Tedizolid was approved by the U.S. Food and Drug Administration (FDA) in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and is undergoing phase III clinical trials for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilated nosocomial pneumonia (VNP) (2).

Numerous *in vitro* surveys have demonstrated that tedizolid is 4- to 8-fold more potent than linezolid against species of staphylococci, enterococci, and streptococci, including those with multidrug-resistant (MDR) phenotypes, such as MRSA, VRE, and linezolid-resistant *S. aureus* and enterococci (3–5). Structural modifications in the molecule result in enhanced binding to the 23S rRNA target and provide enhanced activity of tedizolid compared to that of linezolid; furthermore, tedizolid potency is not affected by strains harboring the transmissible *cfr* resistance gene (1, 2, 6).

Whereas the vast majority of *in vitro* studies of tedizolid confirm the activity and spectrum of the agent against pathogens associated with ABSSSI (2, 5, 7, 8), a recent study from Taiwan has raised concern about increased resistance to tedizolid among isolates of the *Streptococcus anginosus* group (including *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*) collected from January 2013 to October 2014 (9). Surprisingly, the Taiwanese isolates of the *S. anginosus* group were uniformly susceptible to linezolid despite only 38.7% susceptibility to tedizolid (9). Notably, a linezolid-susceptible and tedizolid-resistant phenotype had not been reported in previous *in vitro* surveillance surveys (1, 2, 5, 8, 10).

The study of Chen et al. (9) differed from previous studies of tedizolid in the use of an agar dilution method rather than the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution (BMD) method (11) to determine the susceptibility of tested isolates to tedizolid and linezolid. Furthermore, Chen et al. (9) did not provide methodological details concerning the inoculum concentration, the duration of incubation, or the criteria used for MIC endpoint determination. The last issue is especially important, as it is well known that this antimicrobial class tends to show pinpoint trailing growth in the microdilution test wells (read as 80% inhibition) rather than 100% inhibition, and it is the 80% inhibition endpoint criterion that has been used to set the interpretive breakpoints for both linezolid and tedizolid (12, 13). When either linezolid or tedizolid MICs are read at 100% inhibition rather than 80% inhibition, the resulting

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TABLE 1 Numbers of organisms included in this study stratified by site of infection

Organism or group	No. of organisms				
	BSI	PIHP	SSSI	Other	Total
S. aureus	263	208	484	1,427	2,382
MSSA	193	134	372	982	1,681
MRSA	70	74	112	445	701
S. pyogenes	16	5	62	175	258
S. agalactiae	25	2	8	110	145
S. anginosus group[a]	5	6	6	37	54
E. faecalis	60	0	52	81	193

[a] *S. constellatus* (23 isolates), *S. anginosus* group not otherwise specified (4 isolates), *S. anginosus* (26 isolates), *S. intermedius* (1 isolate).

MIC values are generally 2-fold higher (12). Thus, methodological differences, including agar dilution versus BMD and MIC endpoint criteria, could account for the unusual results reported by Chen and colleagues [9]) for the *S. anginosus* group isolates, as previously reported (14, 15).

In the present study, we employed the CLSI M07-A10 (11) reference BMD method to determine the activities of tedizolid and linezolid when tested against 3,032 Gram-positive pathogen isolates collected in Asia-Pacific, Eastern European, and Latin American medical centers from January through December 2014. In order to address the issue of trailing growth, the MIC values of both of the agents were determined using both 80 and 100% endpoint reading criteria. The results obtained for the *S. anginosus* group were compared to those published by Chen et al. (9).

MATERIALS AND METHODS

Bacterial isolates. A total of 3,032 Gram-positive pathogens were analyzed in this study. The organisms were collected consecutively between January and December 2014 from 34 medical centers located in 19 countries. Within this collection, there were a total of 13 isolates of the *S. anginosus* group recovered from Taiwan during the 2014 sampling. The isolates were identified locally and forwarded to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) for confirmation of species identification, if necessary (using Vitek2, matrix-assisted laser desorption ionization–time of flight mass spectrometry [MALDI-TOF MS], or manual methods), and reference antimicrobial susceptibility testing.

All organisms were isolated from documented infections, and only one organism per patient infection episode was included in the survey. The isolates were collected primarily from bloodstream infections (BSI), skin and skin structure infections (SSSI), pneumonia in hospitalized patients (PIHP), and other infection types according to a common surveillance design (16) (Table 1).

Antimicrobial susceptibility testing. Susceptibility testing was performed by BMD following the guidelines of the CLSI (11). Quality control and interpretation of results were performed in accordance with CLSI M100-S26 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2016 guidelines (12, 13). Tedizolid, linezolid, and all comparator categorized interpretations used CLSI M100-S26 (12) and EUCAST v6.0 (13) breakpoint criteria, where published. U.S. FDA product package insert criteria were used as an alternative breakpoint source as necessary (e.g., for tigecycline). Tedizolid and linezolid MIC values were read by two endpoint interpretive methods: (i) without regard for pinpoint trailing in the wells (80% read, according to CLSI M07-A10 [11] and CLSI M100-S26 [12] for reading linezolid and tedizolid; these reads have been designated tedizolid 80 and linezolid 80) and (ii) at 100% inhibition of growth (designated tedizolid 100 and linezolid 100).

Isolates were tested using frozen-form-validated BMD panels (ThermoFisher Scientific, Cleveland, OH, USA) of antibiotics appropriate for their genera. Staphylococcus, streptococcus, and enterococcus panels included the following agents: daptomycin, erythromycin, gentamicin, linezolid, moxifloxacin, oxacillin (staphylococci only), penicillin (streptococci only), ampicillin (enterococci only), tedizolid, teicoplanin, tigecycline, trimethoprim-sulfamethoxazole (TMP-SMX), and vancomycin.

RESULTS

Among the 3,032 isolates tested, there were 2,382 *S. aureus* isolates (1,681 methicillin-susceptible *S. aureus* [MSSA] and 701 MRSA), 258 *S. pyogenes* isolates, 145 *Streptococcus agalactiae* isolates, 54 isolates of the *S. anginosus* group (26 *S. anginosus*, 23 *S. constellatus*, 4 *S. anginosus* group isolates not otherwise specified, and 1 *S. intermedius* isolate), and 193 *Enterococcus faecalis* isolates (Table 1).

Overall activity of tedizolid and linezolid according to MIC endpoint criteria. During the year 2014, both tedizolid and linezolid maintained a consistent and potent level of activity against the five target pathogens from the Asia-Pacific, Eastern European, and Latin American study sites (Table 2). As expected, MIC results for each agent determined using the 100% inhibition criterion were generally 2-fold higher than those determined using the 80% inhibition criterion for each tested species. Likewise, tedizolid was 4- to 8-fold more active than linezolid against all the isolates tested irrespective of the MIC endpoint criterion used. Tedizolid 80 MIC values ranged from ≤0.008 to 0.5 μg/ml, and >99.9% of the tested isolates were inhibited at a MIC value of ≤0.25 μg/ml (100% at ≤0.5 μg/ml). Tedizolid 100 MIC values ranged from ≤0.008 to 1 μg/ml, and 99.8% of the tested isolates were inhibited at a MIC value of ≤0.5 μg/ml (data not shown). Notably, 100% of *S. anginosus* group isolates were inhibited at a tedizolid MIC value of ≤0.25 μg/ml (susceptible by both CLSI and EUCAST interpretive breakpoints) irrespective of the MIC endpoint criterion employed (Table 2). The linezolid MIC_{90} values ranged from 1 to 2 μg/ml using either method of MIC determination, and >99.9% of the tested strains were susceptible at ≤2 μg/ml when read using the CLSI-recommended 80% inhibition criterion. Thus, despite the difference in potency, >99.9% of all Gram-positive isolates tested were susceptible to both oxazolidinones.

Activities of tedizolid and comparators against *S. aureus*. A total of 2,382 *S. aureus* strains were evaluated: 100% of the strains were inhibited at tedizolid 80 and 100 MIC values of 0.25 and 0.5 μg/ml, respectively (Tables 2 and 3). The MIC_{50}/MIC_{90} values for tedizolid 80 (0.12 and 0.12 μg/ml) were one doubling dilution lower than for tedizolid 100 (0.25 and 0.25 μg/ml). Tedizolid 80 was 8-fold more potent than linezolid 80 (MIC_{50}/MIC_{90}, 1 and 1 μg/ml) (Table 3). Using CLSI and EUCAST breakpoints (MIC, ≤0.5 μg/ml), 100.0% of the isolates tested were susceptible to tedizolid. All the isolates were also susceptible to linezolid. The rates of susceptibility (CLSI and EUCAST interpretations) to erythromycin and moxifloxacin were 69.2 and 69.5% and 82.0 and 82.0%, respectively. Susceptibility rates were much higher for TMP-SMX (97.9%), daptomycin (>99.9%), tigecycline (100.0%), and vancomycin (100.0%).

Overall, 1,681 (70.6%) *S. aureus* isolates were oxacillin MSSA, and 701 (29.4%) were MRSA. Tedizolid 80 and linezolid 80 MIC_{50}/MIC_{90} values (0.12 and 0.12 μg/ml and 1 and 1 μg/ml, respectively) were identical for MSSA and MRSA and overall (Table 3). Erythromycin and moxifloxacin CLSI and EUCAST

TABLE 2 Summary of tedizolid and linezolid activity tested against five pathogen groups (3,032 isolates) included in this study

Organism (no.)	Agent and read[a]	No. (cumulative percentage) of isolates inhibited at MIC (μg/ml):										MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
		≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4		
S. aureus (2,382)	Linezolid 80					2 (0.1)	17 (0.8)	668 (28.8)	1661 (98.6)	34 (100.0)		1	1
	Linezolid 100						3 (0.1)	51 (2.3)	1128 (49.6)	1166 (98.6)	34 (100.0)	2	2
	Tedizolid 80			8 (0.3)	445 (19.0)	1807 (94.9)	122 (100.0)					0.12	0.12
	Tedizolid 100			2 (0.1)	24 (1.1)	875 (37.8)	1427 (97.7)	54 (100.0)				0.25	0.25
MSSA (1,681)	Linezolid 80						5 (0.3)	429 (25.8)	1218 (98.3)	29 (100.0)		1	1
	Linezolid 100							24 (1.4)	760 (46.6)	869 (98.3)	28 (100.0)	2	2
	Tedizolid 80			3 (0.2)	300 (18.0)	1294 (95.0)	84 (100.0)					0.12	0.12
	Tedizolid 100				15 (0.9)	605 (36.9)	1023 (97.7)	38 (100.0)				0.25	0.25
MRSA (701)	Linezolid 80					2 (0.3)	12 (2.0)	239 (36.1)	443 (99.3)	5 (100.0)		1	1
	Linezolid 100						3 (0.4)	27 (4.3)	368 (56.8)	297 (99.1)	6 (100.0)	1	2
	Tedizolid 80			5 (0.7)	145 (21.4)	513 (94.6)	38 (100.0)					0.12	0.12
	Tedizolid 100			2 (0.3)	9 (1.6)	270 (40.1)	404 (97.7)	16 (100.0)				0.25	0.25
S. pyogenes (258)	Linezolid 80							103 (39.9)	155 (100.0)			1	1
	Linezolid 100							3 (1.2)	233 (91.5)	22 (100.0)		1	1
	Tedizolid 80				52 (20.2)	203 (98.8)	3 (100.0)					0.12	0.12
	Tedizolid 100				7 (2.7)	150 (60.9)	101 (100.0)					0.12	0.25
S. agalactiae (145)	Linezolid 80							36 (24.8)	109 (100.0)			1	1
	Linezolid 100							2 (1.4)	136 (95.2)	7 (100.0)		1	1
	Tedizolid 80				9 (6.2)	126 (93.1)	10 (100.0)					0.12	0.12
	Tedizolid 100				1 (0.7)	69 (48.3)	74 (99.3)	1 (100.0)				0.25	0.25
S. anginosus group (54)	Linezolid 80					1 (1.9)	7 (14.8)	29 (68.5)	16 (98.1)	1 (100.0)		0.5	1
	Linezolid 100					1 (1.9)	4 (9.3)	10 (27.8)	35 (92.6)	4 (100.0)		1	1
	Tedizolid 80	1 (1.9)	0 (1.9)	5 (11.1)	26 (59.3)	22 (100.0)						0.06	0.12
	Tedizolid 100	1 (1.9)	0 (1.9)	2 (5.6)	12 (27.8)	30 (83.3)	9 (100.0)					0.12	0.25
E. faecalis (193)	Linezolid 80						1 (0.5)	31 (16.6)	140 (89.1)	20 (99.5)	1 (100.0)	1	2
	Linezolid 100						1 (0.5)	0 (0.5)	71 (37.3)	112 (95.3)	9 (100.0)	2	2
	Tedizolid 80			1 (0.5)	3 (2.1)	80 (43.5)	108 (99.5)	1 (100.0)				0.25	0.25
	Tedizolid 100				1 (0.5)	14 (17.8)	130 (75.1)	42 (96.9)	6 (100.0)			0.25	0. 5

[a] 100, MIC read at first well that showed no growth; 80, MIC read at first well where trailing began, with tiny buttons ignored (per CLSI document M07-A10 [2015]). For purposes of comparison with tedizolid, the linezolid data are presented as MIC values determined at 80% read to exclude a known trailing effect for bacteriostatic agents and at 100% read, i.e., with no consideration of the trailing endpoint.

TABLE 3 Activities of tedizolid and comparator antimicrobial agents against 3,032 Gram-positive bacterial isolates collected in Asia-Pacific, Eastern European, and Latin American countries in 2014

Organism (no. tested) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
S. aureus (2,382)									
Tedizolid 80	0.12	0.12	0.03 to 0.25	100.0	–	0.0	100.0	–	0.0
Tedizolid 100	0.25	0.25	0.03 to 0.5						
Linezolid 80	1	1	≤0.12 to 2	100.0	–	0.0	100.0	–	0.0
Linezolid 100	2	2	0.25 to 4						
Daptomycin	0.25	0.5	≤0.06 to 2	>99.9	–	–	>99.9	–	<0.1
Erythromycin	0.25	>16	≤0.12 to >16	69.2	3.5	27.2	69.5	1.3	29.2
Gentamicin	≤1	>8	≤1 to >8	86.6	0.4	13.1	86.1	–	13.9
Moxifloxacin	≤0.12	2	≤0.12 to >4	82.0	4.7	13.3	82.0	4.7	13.3
Oxacillin	0.5	>2	≤0.25 to >2	70.6	–	29.4	70.6	–	29.4
Teicoplanin	≤2	≤2	≤2 to 16	>99.9	<0.1	0.0	98.5	–	1.5
Tigecycline[b]	0.06	0.06	≤0.015 to 0.5	100.0	–	–	100.0	–	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	97.9	–	2.1	97.9	0.5	1.6
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0	100.0	–	0.0
MSSA (1,681)									
Tedizolid 80	0.12	0.12	0.03 to 0.25	100.0	–	0.0	100.0	–	0.0
Tedizolid 100	0.25	0.25	0.06 to 0.5						
Linezolid 80	1	1	0.25 to 2	100.0	–	0.0	100.0	–	0.0
Linezolid 100	2	2	0.5 to 4	–	–	–	–	–	–
Daptomycin	0.25	0.5	≤0.06 to 2	99.9	–	–	99.9	–	0.1
Erythromycin	0.25	>16	≤0.12 to >16	84.5	3.3	12.2	84.6	1.1	14.3
Gentamicin	≤1	≤1	≤1 to >8	95.7	0.3	4.0	95.3	–	4.7
Moxifloxacin	≤0.12	≤0.12	≤0.12 to 4	97.5	1.1	1.5	97.5	1.1	1.5
Teicoplanin	≤2	≤2	≤2 to 4	100.0	0.0	0.0	99.9	–	0.1
Tigecycline	0.06	0.06	≤0.015 to 0.25	100.0	–	–	100.0	–	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	99.7	–	0.3	99.7	0.1	0.2
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0	100.0	–	0.0
MRSA (701)									
Tedizolid 80	0.12	0.12	0.03 to 0.25	100.0	–	0.0	100.0	–	0.0
Tedizolid 100	0.25	0.25	0.03 to 0.5						
Linezolid 80	1	1	≤0.12 to 2	100.0	–	0.0	100.0	–	0.0
Linezolid 100	1	2	0.25 to 4	–	–	–	–	–	–
Daptomycin	0.25	0.5	≤0.06 to 1	100.0	–	–	100.0	–	0.0
Erythromycin	>16	>16	≤0.12 to >16	32.7	4.0	63.3	33.3	1.7	65.0
Gentamicin	≤1	>8	≤1 to >8	64.6	0.6	34.8	64.1	–	35.9
Moxifloxacin	2	>4	≤0.12 to >4	18.8	19.7	61.5	18.8	19.7	61.5
Teicoplanin	≤2	≤2	≤2 to 16	99.9	0.1	0.0	95.1	–	4.9
Tigecycline	0.06	0.12	≤0.015 to 0.5	100.0	–	–	100.0	–	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	93.4	–	6.6	93.4	1.6	5.0
Vancomycin	1	1	0.25 to 2	100.0	0.0	0.0	100.0	–	0.0
S. pyogenes (258)									
Tedizolid 80	0.12	0.12	0.06 to 0.25	100.0	–	–	100.0	–	0.0
Tedizolid 100	0.12	0.25	0.06 to 0.25						
Linezolid 80	1	1	0.5 to 1	100.0	–	–	100.0	0.0	0.0
Linezolid 100	1	1	0.5 to 2	–	–	–	–	–	–
Daptomycin	≤0.06	≤0.06	≤0.06 to 0.25	100.0	–	–	100.0	–	0.0
Erythromycin	≤0.12	0.25	≤0.12 to >16	90.3	0.0	9.7	90.3	0.0	9.7
Moxifloxacin	≤0.12	0.25	≤0.12 to 0.5	–	–	–	100.0	0.0	0.0
Penicillin	≤0.06	≤0.06	≤0.06 to 0.12	100.0	–	–	100.0	–	0.0
Teicoplanin	≤2	≤2	≤2 to ≤2	–	–	–	100.0	–	0.0
Tigecycline	0.03	0.03	≤0.015 to 0.12	100.0	–	–	100.0	0.0	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	–	–	–	98.4	0.4	1.2
Vancomycin	0.25	0.25	≤0.12 to 0.5	100.0	–	–	100.0	–	0.0

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TABLE 3 (Continued)

Organism (no. tested) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	Range (μg/ml)	CLSI[a]			EUCAST[a]		
				%S	%I	%R	%S	%I	%R
S. agalactiae (145)									
Tedizolid 80	0.12	0.12	0.06 to 0.25	100.0	–	–	100.0	–	0.0
Tedizolid 100	0.25	0.25	0.06 to 0.5						
Linezolid 80	1	1	0.5 to 1	100.0	–	–	100.0	0.0	0.0
Linezolid 100	1	1	0.5 to 2	–	–	–	–	–	–
Daptomycin	0.25	0.25	≤0.06 to 0.5	100.0	–	–	100.0	–	0.0
Erythromycin	≤0.12	>16	≤0.12 to >16	70.8	2.8	26.4	70.8	2.8	26.4
Moxifloxacin	≤0.12	0.25	≤0.12 to 0.25	–	–	–	100.0	0.0	0.0
Penicillin	≤0.06	≤0.06	≤0.06 to 0.12	100.0	–	–	100.0	–	0.0
Teicoplanin	≤2	≤2	≤2 to ≤2	–	–	–	100.0	–	0.0
Tigecycline	0.03	0.06	≤0.015 to 0.06	100.0	–	–	100.0	0.0	0.0
TMX-SMX	≤0.5	≤0.5	≤0.5 to ≤0.5	–	–	–	100.0	0.0	0.0
Vancomycin	0.5	0.5	≤0.12 to 1	100.0	–	–	100.0	–	0.0
S. anginosus group[c] (54)									
Tedizolid 80	0.06	0.12	≤0.008 to 0.12	100.0	–	–	100.0	–	0.0
Tedizolid 100	0.12	0.25	≤0.008 to 0.25						
Linezolid 80	0.5	1	≤0.12 to 2	100.0	–	–	–	–	–
Linezolid 100	1	1	≤0.12 to 2	–	–	–	–	–	–
Daptomycin	0.25	0.5	≤0.06 to 1	100.0	–	–	–	–	–
Erythromycin	≤0.12	0.5	≤0.12 to >16	88.9	1.9	9.3	–	–	–
Penicillin	≤0.06	≤0.06	≤0.06 to 0.12	100.0	0.0	0.0	100.0	0.0	0.0
Teicoplanin	≤2	≤2	≤2 to ≤2	–	–	–	100.0	–	0.0
Tigecycline	0.03	0.03	≤0.015 to 0.06	100.0	–	–	–	–	–
Vancomycin	0.5	0.5	0.25 to 1	100.0	–	–	100.0	–	0.0
E. faecalis (193)									
Tedizolid 80	0.25	0.25	0.03 to 0.5	100.0	–	–	–	–	–
Tedizolid 100	0.25	0.5	0.06 to 1						
Linezolid 80	1	2	0.25 to 4	99.5	0.5	0.0	100.0	–	0.0
Linezolid 100	2	2	0.25 to 4	–	–	–	–	–	–
Ampicillin	1	2	0.5 to 8	100.0	–	0.0	98.4	1.6	0.0
Daptomycin	1	2	0.12 to 4	100.0	–	–	–	–	–
Erythromycin	>16	>16	≤0.12 to >16	7.8	37.5	54.7	–	–	–
Teicoplanin	≤2	≤2	≤2 to >16	98.4	0.0	1.6	98.4	–	1.6
Tigecycline	0.03	0.06	≤0.015 to 0.25	100.0	–	–	100.0	0.0	0.0
TMP-SMX	≤0.5	≤0.5	≤0.5 to >4	–	–	–	0.0	25.0	75.0
Vancomycin	1	2	0.5 to >16	97.9	0.5	1.6	97.9	–	2.1

[a] Criteria as published by CLSI (12) and EUCAST (13). –, breakpoint not available. S, susceptible; R, resistant; I, intermediate.
[b] For tigecycline, U.S. FDA breakpoints were applied when available (Tygacil package insert [2012]; Wyeth Pharmaceuticals Company).
[c] *S. constellatus* (23 isolates), *S. anginosus* group (4 isolates), *S. anginosus* (26 isolates), *S. intermedius* (1 isolate).

resistance rates for MRSA were 63.3 and 65.0% and 61.5 and 61.5%, respectively (Table 3). Daptomycin (100.0%), teicoplanin (99.9%), tigecycline (100.0%), and vancomycin (100.0%) were all very active against MRSA.

Activities of tedizolid and comparators against *S. pyogenes*. A total of 258 *S. pyogenes* strains were evaluated: all the strains tested were inhibited at tedizolid 80/100 MIC values of 0.25 and 0.25 μg/ml (Table 3). The MIC_{50}/MIC_{90} values for tedizolid 80 (0.12 and 0.12 μg/ml) were up to one doubling dilution lower than for tedizolid 100 (0.12 and 0.25 μg/ml). Tedizolid 80 (MIC_{50}/MIC_{90}, 0.12 and 0.12 μg/ml) was 8-fold more potent than linezolid 80 (MIC_{50}/MIC_{90}, 1 and 1 μg/ml). Using CLSI and EUCAST breakpoints (MIC, ≤0.5 μg/ml), all the isolates were susceptible to tedizolid. Also, all the isolates were susceptible to linezolid, daptomycin, penicillin, tigecycline, moxifloxacin, teicoplanin, and vancomycin. The rates of susceptibility (CLSI and EUCAST interpretations) to erythromycin were 90.3 and 90.3%, respectively, and 98.4% of the isolates were susceptible to TMP-SMX using EUCAST breakpoint criteria.

Activities of tedizolid and comparators against *S. agalactiae*. Among 145 strains of *S. agalactiae* evaluated, 100% were inhibited at tedizolid 80 and 100 MIC values of 0.25 and 0.5 μg/ml (Table 3). The MIC_{50}/MIC_{90} values for tedizolid 80 (0.12 and 0.12 μg/ml) were one doubling dilution lower than for tedizolid 100 (0.25 and 0.25 μg/ml). Tedizolid 80 (MIC_{50}/MIC_{90}, 0.12 and 0.12 μg/ml) was 8-fold more potent than linezolid 80 (MIC_{50}/MIC_{90}, 1 and 1 μg/ml). Using CLSI and EUCAST breakpoints (MIC, ≤0.5 μg/ml), all the isolates were susceptible to tedizolid. Furthermore, all the isolates were susceptible to linezolid, daptomycin, penicillin, tigecycline, moxifloxacin, TMP-SMX, vancomycin, and teicoplanin at their respective CLSI and EUCAST breakpoints. Erythromycin susceptibility was only 70.8% (Table 3).

Activities of tedizolid and comparators against the *S. anginosus* group. A total of 54 *S. anginosus* group isolates (*S. angino-*

TABLE 4 MIC distribution of *S. anginosus* group isolates as determined by agar dilution (9) and CLSI broth microdilution methods using 80% and 100% MIC endpoint criteria

Agent and read[a]	No. (cumulative percentage) of isolates inhibited at MIC (μg/ml)[d]:								
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2
Tedizolid[b]			1 (1.3)	5 (8.0)	5 (14.7)	18 (38.7)	**41 (93.3)**	5 (100.0)	
Tedizolid 80[c]	1 (1.9)	0 (1.9)	5 (11.1)	**26 (59.3)**	22 (100.0)				
Tedizolid 100[c]	1 (1.9)	0 (1.9)	2 (5.6)	12 (27.8)	**30 (83.3)**	9 (100.0)			
Linezolid[b]						1 (1.3)	4 (6.7)	14 (25.3)	**66 (100.0)**
Linezolid 80[c]					1 (1.9)	7 (14.8)	**29 (68.5)**	16 (98.1)	1 (100.0)
Linezolid 100[c]					1 (1.9)	4 (9.3)	10 (27.8)	**35 (92.6)**	4 (100.0)

[a] 100, MIC read at first well that showed no growth; 80, MIC read at first well where trailing began, with tiny buttons ignored (per CLSI documents M07-A10 [2015] and M100-S26 [2016]). For purposes of comparison with tedizolid, the linezolid data are presented as MIC values determined at 80% read to exclude a known trailing effect for bacteriostatic agents and at 100% read, i.e., with no consideration of the trailing endpoint.
[b] Data from Chen et al. (9). MIC values were determined by agar dilution. MIC endpoint criteria are unknown.
[c] Data from the present study. A total of 13 isolates of the *S. anginosus* group from Taiwan were included in the data set. Tedizolid had MIC ranges of 0.03 to 0.12 μg/ml (modal MIC, 0.06 μg/ml) and 0.06 to 0.12 μg/ml (modal MIC, 0.12 μg/ml) when read at 80 and 100% growth inhibition, respectively, against these 13 isolates. Linezolid showed MIC ranges of 0.25 to 1 μg/ml for both readings, with modal MIC values of 0.5 and 1 μg/ml, when read at 80 and 100% growth inhibition, respectively, against the isolates.
[d] Modal MIC results are in boldface.

sus, 26 isolates; *S. constellatus*, 23 isolates; *S. anginosus* group, 4 isolates; and *S. intermedius*, 1 isolate) were evaluated, and all the strains were inhibited at tedizolid 80 and 100 MIC values of 0.12 and 0.25 μg/ml (Table 3). The MIC_{50}/MIC_{90} values for tedizolid 80 (0.06 and 0.12 μg/ml) were one doubling dilution lower than for tedizolid 100 (0.12 and 0.25 μg/ml), and tedizolid 80 (MIC_{50}/MIC_{90}, 0.06 and 0.12 μg/ml) was 8-fold more potent than linezolid 80 (MIC_{50}/MIC_{90}, 0.5 and 1 μg/ml). Using CLSI and EUCAST breakpoints (MIC, ≤0.25 μg/ml), 100.0% of the isolates were susceptible to tedizolid (Table 3). All the isolates were also susceptible to linezolid, daptomycin, penicillin, tigecycline, and vancomycin. Erythromycin susceptibility was lower at 88.9%. Thirteen of the isolates were from Taiwan in the Asia-Pacific sample.

Activities of tedizolid and comparators against *E. faecalis*. Among the 193 strains of *E. faecalis* tested, 100.0% were inhibited at tedizolid 80 and 100 MIC values of 0.5 and 1 μg/ml (Table 3). The MIC_{50}/MIC_{90} values for tedizolid 80 (0.25 and 0.25 μg/ml) were up to one doubling dilution lower than for tedizolid 100 (0.25 and 0.5 μg/ml). Tedizolid 80 (MIC_{50}/MIC_{90}, 0.25 and 0.25 μg/ml) was 4- to 8-fold more potent than linezolid 80 (MIC_{50}/MIC_{90}, 1 and 2 μg/ml). Using CLSI breakpoints, 100.0 and 99.5% were susceptible to tedizolid (≤0.5 μg/ml) and linezolid (≤2 μg and ml), respectively. All the isolates were susceptible (CLSI) to ampicillin, daptomycin, and tigecycline, while vancomycin susceptibility was 97.9%.

DISCUSSION

The results of this survey confirm the excellent activities and spectra of both tedizolid and linezolid against wild-type (WT) strains of the target Gram-positive pathogens (5, 8, 10). Our findings agree with those of Zurenko et al. (5), who observed no evidence of a linezolid-susceptible and tedizolid-resistant phenotype among 7,187 isolates of *S. aureus*, 1,600 isolates of *Streptococcus* spp., and 91 isolates of the *S. anginosus* group. We also found that tedizolid demonstrated greater *in vitro* potencies (4- to 8-fold, depending on the 80% or 100% endpoint read-matched comparisons and species) than linezolid when tested against recent Gram-positive target pathogens isolated from patients in medical centers across the Asia-Pacific region, Eastern Europe, and Latin America. Generally, MIC endpoint values (including MIC distributions and MIC_{50}/MIC_{90}) for tedizolid and linezolid used without regard for pinpoint trailing colonies (80% read) were one doubling dilution lower than those read at 100% inhibition. Despite the differences in potency, >99.9% of the isolates tested in this survey were susceptible to both linezolid and tedizolid using CLSI and EUCAST interpretive criteria.

Applying CLSI and EUCAST breakpoints (MIC, ≤0.5 μg/ml), all 2,382 tested *S. aureus* isolates (29.4% MRSA) were susceptible to tedizolid. There were no linezolid-nonsusceptible strains identified in this surveillance sample, except for one *E. faecalis* strain (CLSI criteria). Using CLSI breakpoints and the 80% read criterion, 100% of *S. pyogenes*, *S. agalactiae*, *S. anginosus* group, and *E. faecalis* isolates were categorized as susceptible to tedizolid.

These finding are very similar to those published earlier by Sahm et al. (8) and Zurenko et al. (5). In contrast, the tedizolid MIC values obtained in the present survey by BMD against all *S. anginosus* group isolates, as well as those from Taiwan, were 4- to 8-fold lower than those recently reported by Chen et al. (9), who employed an agar dilution method. These differences were maintained regardless of the MIC endpoint criteria employed with the BMD and were most striking for the *S. anginosus* group (Table 4). Whereas all the isolates of the *S. anginosus* group were susceptible (MIC, ≤2 μg/ml) to linezolid when tested by agar dilution (9) or by BMD using either the 80% or 100% criterion (Table 4), the MIC values for tedizolid determined by agar dilution (modal MIC, 0.5 μg/ml) were significantly higher than those for tedizolid 80 (modal MIC, 0.06 μg/ml) or tedizolid 100 (modal MIC, 0.12 μg/ml) (Table 4). Indeed, all of the *S. anginosus* group isolates in the present survey, as well as those reported by Zurenko et al. (5), were susceptible to tedizolid by the CLSI BMD method. In contrast, only 38.7% of the Taiwanese isolates were susceptible by the agar dilution method (9). These extreme disparities in tedizolid MIC values for WT strains of the *S. anginosus* group, coupled with the fact that 61.3% of the isolates reported by Chen et al. (9) were susceptible to linezolid but nonsusceptible to tedizolid, suggest that methodological issues may be responsible for such confusing results. Similar methodological issues were observed during the initial *in vitro* activity studies for linezolid (14, 15).

In order to avoid such discrepant or inconsistent results due to methodological issues, we encourage future investigators to employ the CLSI BMD method using the recommended 80% inhibi-

tion MIC endpoint criterion for testing both tedizolid and linezolid. By applying a standard method for susceptibility testing and MIC reading, the number of testing variables would be kept at a minimum. In this study, we found no evidence of emerging resistance to tedizolid among Gram-positive cocci, including the *S. anginosus* group isolates from Taiwan found in our surveillance sample (MIC_{50}, 0.06 μg/ml), when applying the recommended reference CLSI BMD method and MIC reading (80% growth).

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