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In Vitro Activity of Tedizolid Against Gram-Positive Bacteria in Patients With Skin and Skin Structure Infections and Hospital-Acquired Pneumonia: A Korean Multicenter Study

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We compared the activities of tedizolid to those of linezolid and other commonly used antimicrobial agents against gram-positive cocci recovered from patients with skin and skin structure infections (SSSIs) and hospital-acquired pneumonia (HAP) in Korean hospitals. Gram-positive isolates were collected from 356 patients with SSSIs and 144 patients with HAP at eight hospitals in Korea from 2011 to 2014. SSSIs included impetigo, cellulitis, erysipelas, furuncles, abscesses, and infected burns. Antimicrobial susceptibility was tested by using the CLSI agar dilution method. All of the gram-positive isolates were inhibited by ≤1 μg/mL tedizolid. The minimum inhibitory concentration [MIC]$_{90}$ of tedizolid was 0.5 μg/mL for methicillin-resistant *Staphylococcus aureus*, which was 4-fold lower than that of linezolid. Tedizolid may become a useful option for the treatment of SSSIs and HAP caused by gram-positive bacteria.

Key Words: Tedizolid, Skin, Soft tissue, Infection, Pneumonia, Gram-positive bacteria

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Skin and skin structure infections (SSSIs) are common problems in both inpatients and outpatients. The vast majority of SSSIs are caused by gram-positive organisms that are normal flora on the skin of human beings. Staphylococci and streptococci cause majority of gram-positive infections [1]. A recent increase in staphylococcal infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has resulted in a significant increase of cases of MRSA pneumonia in the health care setting, especially in the chronically ill population [2]. Vancomycin has been the cornerstone of treatment for MRSA infections. However, recently, vancomycin-resistant *S. aureus* and linezolid-resistant *Staphylococcus* strains have emerged [3-5]. These strains pose significant challenges to the clinical treatment of infections caused by these organisms. Tedizolid offers broad *in vitro* activity against gram-positive pathogens, including MRSA and strains resistant to vancomycin or linezolid, and has greater potency than other drugs of its class [6, 7]. It was specifically designed to be active against linezolid-resistant *S. aureus*, including strains containing the multidrug-resistant *cfr* gene [8].

Tedizolid phosphate was recently approved by the U.S. Food and Drug Administration to treat patients with acute bacterial SSSI caused by *S. aureus*, various *Streptococcus* species, and

Enterococcus. In addition, planned studies will investigate the potential role of tedizolid in the treatment of community-acquired bacterial pneumonia and hospital-acquired pneumonia (HAP) [9]. We published a previous report focusing on the activity of tedizolid against collections of clinical isolates in a single institution, but it was not characterized by infection type [10]. Therefore, the present study aimed to compare the activities of tedizolid to those of linezolid and other commonly used antimicrobial agents against gram-positive cocci recovered from patients with SSSIs and HAP in Korean hospitals.

Non-duplicated aerobic and anaerobic gram-positive isolates were collected from clinical specimens of 356 patients with SSSIs and 144 patients with HAP at eight hospitals in Seoul and Gyeonggi province, Korea from 2011 to 2014. SSSIs included impetigo, cellulitis, erysipelas, furuncles, abscesses, and infected burns [1, 11]. HAP was defined as pneumonia that occurred 48 hr or more after admission.

Species were identified by using conventional methods or the Vitek 2 system (bioMérieux, Marcy l'Etolile, France). Antimicrobial susceptibility was tested by using the CLSI agar dilution method [12, 13]. Mueller-Hinton agar was used as a growth medium (Becton Dickinson, Cockeysville, MD, USA) for testing *Staphylococcus* spp. and *Enterococcus* spp.: Mueller-Hinton agar supplemented with 5% sheep blood for *Streptococcus* spp.; Brucella agar (Becton Dickinson) supplemented with 5 μg/mL hemin, 1 μg/mL vitamin K1; and 5% laked sheep blood for anaerobic bacteria. Tedizolid and linezolid (Dong-A ST, Seoul, Korea); erythromycin, tetracycline, oxacillin and penicillin G (Sigma Chemical, St. Louis, MO, USA); piperacillin and tazobactam (Yuhan, Seoul, Korea); clindamycin (Korea Upjohn, Seoul, Korea); levofloxacin (Daiichi Pharmaceutical, Tokyo, Japan); cefotetan (Daiichi Pharmaceutical); ampicillin and gentamicin (Chong Kun Dang, Seoul, Korea); cefoxitin and imipenem (Merck Sharp & Dohme, Rahway, NJ, USA); meropenem (Sumitomo, Tokyo, Japan); metronidazole (ChoongWae, Seoul, Korea); trimethoprim and sulfamethoxazole (Dong Wha, Seoul, Korea); vancomycin (Daewoong, Seoul, Korea); and teicoplanin (Sanofi Aventis, Bridgewater, NJ, USA) were used as antimicrobial powders. American type culture collection strains of *S. aureus* (ATCC29213), *E. faecalis* (ATCC 29212), *S. pneumoniae* (ATCC 49619), *Bacteroides fragilis* (ATCC 25285), and *B. thetaiotaomicron* (ATCC 29741) were used as reference strains. The non-meningeal breakpoints of penicillin G and cefotaxime were used for *S. pneumoniae*. This study used the breakpoints of tedizolid suggested by the US Food and Drug Administration [14].

All of the aerobic and anaerobic gram-positive isolates in patients with SSSIs were inhibited by ≤1 μg/mL tedizolid (Table 1). The most potent drugs against MRSA were tedizolid (minimum inhibitory concentration [MIC]$_{90}$=0.5 μg/mL), linezolid (MIC$_{90}$=2 μg/mL), and vancomycin (MIC$_{90}$=2 μg/mL). The MIC range of tedizolid was 0.125 to 0.5 μg/mL for MRSA, while that of linezolid was 0.25 to 4 μg/mL. The MIC$_{90}$s of tedizolid were 0.5 μg/mL for both MRSA and methicillin-susceptible *S. aureus* (MSSA) and ≤0.125 μg/mL for coagulase-negative staphylococci, which were 2- to 4-fold lower than those of linezolid. These MIC values were similar to those described in previous reports [10, 15]. The MICs of tedizolid were 0.25 μg/mL for all three vancomycin-intermediate *S. aureus* isolates.

The MIC ranges of tedizolid were 0.25 to 0.5 μg/mL for *Enterococcus*, while those of linezolid were 0.5 to 2 μg/mL. Tedizolid inhibited all vancomycin-resistant *Enterococcus* at 0.5 μg/mL. When the meningeal breakpoint was applied, most of the pneumococcal isolates tested were not susceptible to penicillin G or cefotaxime. However, the MIC range of tedizolid was 0.25 to 1 μg/mL, and the MIC$_{90}$ (0.5 μg/mL) was 4-fold lower than that of linezolid. Tedizolid inhibited all the isolates of viridans *Streptococcus* spp. and β-hemolytic streptococci such as *S. pyogenes* and *S. agalactiae* at 0.5 μg/mL.

Tedizolid had excellent activity against gram-positive anaerobes recovered from SSSIs (Table 1). The MIC ranges of tedizolid were 0.06 to 1 μg/mL for *Finegoldia magna* and ≤0.06 to 0.25 μg/mL for the other *Peptostreptococcus* spp. The MIC$_{90}$ values for these organisms were 0.5 and 0.25 μg/mL, respectively, which were 4-8 fold lower than those of linezolid. All the *Clostridium* spp. isolates were inhibited by tedizolid at 0.5 μg/mL.

All the gram-positive isolates in patients with HAP were inhibited by ≤0.5 μg/mL tedizolid (Table 2). The MIC ranges of tedizolid were 0.125 to 0.5 μg/mL for MRSA and 0.25 μg/mL for MSSA. The MIC$_{90}$ values of tedizolid were 0.25, 0.5, and 0.5 μg/mL for MSSA, MRSA, and pneumococci, respectively, which were 4- to 8-fold lower than those of linezolid.

In summary, the MIC values of tedizolid in this study were not significantly different according to type of infection. All organisms tested were susceptible to tedizolid, nevertheless the breakpoint of tedizolid is 4- or 8-fold lower than that of linezolid. Tedizolid is a potent agent with high *in vitro* activity against common aerobic and anaerobic gram-positive pathogens in SSSIs and HAP. Tedizolid may become a useful option for the treatment of SSSIs and HAP.

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Table 1. Comparative *in vitro* activities of tedizolid and other antimicrobial agents against bacteria recovered from patients with skin and skin structure infections

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
Methicillin-resistant *Staphylococcus aureus* (90)									
Tedizolid*	≤0.5	1	≥2	0.125-0.5	0.5	0.5	100	0	0
Linezolid	≤4	-	≥8	0.25-4	2	2	100	NA	0
Erythromycin	≤0.5	1-4	≥8	0.5->128	>128	>128	28	0	72
Clindamycin	≤0.5	1-2	≥4	≤0.06->128	>128	>128	44	0	56
Cotrimoxazole	≤2	-	≥4	≤0.06-32	≤0.06	0.125	98	NA	2
Gentamicin	≤4	8	≥16	0.125->128	0.5	32	58	1	41
Levofloxacin	≤1	2	≥4	0.25->128	16	>128	37	0	63
Tetracycline	≤4	8	≥16	0.5->128	64	64	41	0	59
Oxacillin	≤2	-	≥4	8->128	>128	>128	0	NA	100
Vancomycin	≤2	4-8	≥16	1-4	1	2	94	6	0
Methicillin-susceptible *S. aureus* (90)									
Tedizolid	≤0.5	1	≥2	≤0.06-0.5	0.25	0.5	100	0	0
Linezolid	≤4	-	≥8	0.25-2	2	2	100	NA	0
Erythromycin	≤0.5	1-4	≥8	0.25->128	0.5	>128	74	1	24
Clindamycin	≤0.5	1-2	≥4	≤0.06->128	0.125	0.125	99	0	1
Cotrimoxazole	≤2	-	≥4	≤0.06-0.125	≤0.06	0.125	100	NA	0
Gentamicin	≤4	8	≥16	0.125-128	0.25	32	82	1	17
Levofloxacin	≤1	2	≥4	0.125-32	0.25	32	97	0	3
Tetracycline	≤4	8	≥16	0.25-128	0.5	0.5	91	0	9
Oxacillin	≤2	-	≥4	≤0.06-2	0.5	0.5	100	NA	0
Vancomycin	≤2	4-8	≥16	1-2	1	1	100	0	0
Coagulase-negative *Staphylococcus* (24)†									
Tedizolid	NA	NA	NA	≤0.06-0.25	0.125	0.125	NA	NA	NA
Linezolid	≤4	-	≥8	0.25-2	0.25	0.25	100	NA	0
Erythromycin	≤0.5	1-4	≥8	≤0.06->128	0.125	128	71	0	29
Clindamycin	≤0.5	1-2	≥4	≤0.06->128	≤0.06	0.125	96	0	4
Cotrimoxazole	≤2	-	≥4	≤0.06-4	≤0.06	4	79	NA	21
Gentamicin	≤4	8	≥16	≤0.06-128	0.125	16	50	21	29
Levofloxacin	≤1	2	≥4	≤0.06-128	0.25	8	75	4	21
Tetracycline	≤4	8	≥16	0.125-128	0.25	64	75	0	25
Oxacillin	≤0.25	-	≥0.5	0.125-128	0.5	2	38	NA	63
Vancomycin	≤4	8-16	≥32	1-2	2	2	100	0	0
Streptococcus pneumoniae (30)									
Tedizolid	NA	NA	NA	0.25-1	0.25	0.5	NA	NA	NA
Linezolid	≤2	-	-	1-2	1	2	100	NA	NA
Penicillin G	≤2	4	≥8	0.06-4	4	4	27	73	0
Cefotaxime	≤1	2	≥4	0.06-2	2	2	27	73	0

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Table 1. Continued

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
Clindamycin	≤0.25	0.5	≥1	0.125->128	>128	>128	10	0	90
Erythromycin	≤0.25	0.5	≥1	8->128	>128	>128	0	0	100
Cotrimoxazole	≤0.5	1-2	≥4	0.5->128	32	64	13	0	87
Levofloxacin	≤2	4	≥8	2-8	2	4	87	10	3
Tetracycline	≤1	2	≥4	0.25-64	32	32	3	3	93
S. agalactiae (22)									
Tedizolid	≤0.5	-	-	0.25-0.5	0.5	0.5	100	NA	NA
Linezolid	≤2	-	-	2-4	2	2	96	NA	NA
Penicillin G	≤0.12	-	-	0.015-0.06	0.06	0.06	100	NA	NA
Cefotaxime	≤0.5	-	-	0.015-0.06	0.06	0.06	100	NA	NA
Clindamycin	≤0.25	0.5	≥1	0.125->128	0.125	>128	82	0	18
Erythromycin	≤0.25	0.5	≥1	0.125–>128	0.25	>128	77	0	23
Levofloxacin	≤2	4	≥8	1-64	2	64	59	9	32
Tetracycline	≤2	4	≥8	0.25-32	1	32	59	0	41
S. pyogenes (8)									
Tedizolid	≤0.5	-	-	0.125-0.5	NA	NA	NA	NA	NA
Linezolid	≤2	-	-	1-2	NA	NA	NA	NA	NA
Penicillin G	≤0.12	-	-	0.015	NA	NA	NA	NA	NA
Cefotaxime	≤0.5	-	-	0.015-0.06	NA	NA	NA	NA	NA
Clindamycin	≤0.25	0.5	≥1	0.125->128	NA	NA	NA	NA	NA
Erythromycin	≤0.25	0.5	≥1	0.25-32	NA	NA	NA	NA	NA
Levofloxacin	≤2	4	≥8	0.5-8	NA	NA	NA	NA	NA
Tetracycline	≤2	4	≥8	0.25-8	NA	NA	NA	NA	NA
Enterococcus faecalis (14)									
Tedizolid	≤0.5	-	-	0.25-0.5	0.5	0.5	100	NA	NA
Linezolid	≤2	4	≥8	1-2	2	2	100	0	0
Ampicillin	≤8	-	≥16	0.5-4	1	4	100	NA	0
Erythromycin	≤0.5	1-4	≥8	0.5->128	>128	>128	0	36	64
Levofloxacin	≤2	4	≥8	1->128	1	128	64	0	36
Tetracycline	≤4	8	≥16	0.5->128	64	128	14	0	86
Teicoplanin	≤8	16	≥32	≤0.06-1	0.5	1	100	0	0
Vancomycin	≤4	8-16	≥32	0.5-4	1	2	100	0	0
E. faecium (16)									
Tedizolid	NA	NA	NA	0.25-0.5	0.25	0.25	NA	NA	NA
Linezolid	≤2	4	≥8	0.5-2	2	2	100	0	0
Ampicillin	≤8	-	≥16	16->128	64	128	0	NA	100
Erythromycin	≤0.5	1-4	≥8	≤0.06->128	>128	>128	6	0	94
Levofloxacin	≤2	4	≥8	32-128	128	128	0	0	100

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Table 1. Continued

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
Tetracycline	≤4	8	≥16	0.25-128	0.5	128	56	0	44
Vancomycin	≤4	8-16	≥32	1->128	1	>128	56	0	44
Teicoplanin	≤8	16	≥32	0.25-128	1	32	56	19	25
Viridans group *Streptococcus* spp. (10)‡									
Tedizolid	NA	NA	NA	0.25-0.5	0.25	0.25	NA	NA	NA
Linezolid	≤2	-	-	1-2	1	2	100	NA	NA
Penicillin G	≤0.12	0.25-2	≥4	0.03-2	0.06	0.5	70	10	0
Cefotaxime	≤1	2	≥4	0.06-2	0.25	1	90	10	0
Clindamycin	≤0.25	0.5	≥1	≤0.06->128	0.125	>128	60	0	40
Erythromycin	≤0.25	0.5	≥1	≤0.06->128	0.125	128	50	10	40
Levofloxacin	≤2	4	≥8	0.5-2	1	2	100	0	0
Tetracycline	≤2	4	≥8	0.25-64	16	64	40	0	60
Finegoldia magna (21)									
Tedizolid	NA	NA	NA	0.06-1	0.25	0.5	NA	NA	NA
Linezolid	NA	NA	NA	0.5-2	2	2	NA	NA	NA
Piperacillin	≤32	64	≥128	≤0.06-0.25	0.125	0.25	100	0	0
Pip/tazobactam	≤32	64	≥128	≤0.06-0.25	≤0.06	0.125	100	0	0
Cefoxitin	≤16	32	≥64	0.125-2	1	1	100	0	0
Cefotetan	≤16	32	≥64	0.25-2	1	2	100	0	0
Imipenem	≤4	8	≥16	≤0.06-0.125	≤0.06	0.125	100	0	0
Clindamycin	≤2	4	≥8	≤0.06->128	2	>128	55	9	36
Metronidazole	≤8	16	≥32	0.25-4	1	2	100	0	0
Vancomycin	NA	NA	NA	0.25-1	0.25	0.5	NA	NA	NA
Peptostreptococcus spp. (27)§									
Tedizolid	NA	NA	NA	≤0.06-0.25	0.125	0.25	NA	NA	NA
Linezolid	NA	NA	NA	0.5-2	1	2	NA	NA	NA
Piperacillin	≤32	64	≥128	≤0.06-1	≤0.06	1	100	0	0
Pip/tazobactam	≤32	64	≥128	≤0.06-1	≤0.06	0.25	100	0	0
Cefoxitin	≤16	32	≥64	≤0.06-8	0.5	4	100	0	0
Cefotetan	≤16	32	≥64	0.125-8	0.5	2	100	0	0
Imipenem	≤4	8	≥16	≤0.06-0.5	≤0.06	0.125	100	0	0
Clindamycin	≤2	4	≥8	≤0.06-128	0.25	128	74	4	22
Metronidazole	≤8	16	≥32	0.5-2	1	2	100	0	0
Vancomycin	NA	NA	NA	0.125-1	0.25	1	NA	NA	NA
Clostridium spp. (4)‖									
Tedizolid	NA	NA	NA	0.25-0.5	NA	NA	NA	NA	NA
Linezolid	NA	NA	NA	2-4	NA	NA	NA	NA	NA
Piperacillin	≤32	64	≥128	0.25-2	NA	NA	NA	NA	NA

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Table 1. Continued

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
Pip/tazobactam	≤32	64	≥128	0.125-2	NA	NA	NA	NA	NA
Cefoxitin	≤16	32	≥64	4-32	NA	NA	NA	NA	NA
Cefotetan	≤16	32	≥64	0.25-2	NA	NA	NA	NA	NA
Imipenem	≤4	8	≥16	0.25-2	NA	NA	NA	NA	NA
Clindamycin	≤2	4	≥8	0.125->128	NA	NA	NA	NA	NA
Metronidazole	≤8	16	≥32	0.5-8	NA	NA	NA	NA	NA
Vancomycin	NA	NA	NA	0.5-4	NA	NA	NA	NA	NA

*FDA breakpoints were used for tedizolid; †*Staphylococcus epidermidis* (N=22), *S. caprae* (N=1), *S. warneri* (N=1); ‡*Streptococcus mitis* (N=6), *S. anginosus* (N=2), *S. constellatus* (N=2); §*P. asaccharolyticus* (N=11), *P. micros* (N=7), *Anaerococcus prevotii* (N=8), *P. anaerobius* (N=1); ‖*C. perfringens* (N=2), *C. ramosum* (N=2).
Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; NA, not available/applicable; Pip/tazobactam, piperacillin/tazobactam.

Table 2. Comparative *in vitro* activities of tedizolid and other antimicrobial agents against bacteria recovered from patients with hospital-acquired pneumonia

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
Methicillin-resistant *Staphylococcus aureus* (61)									
Tedizolid*	≤0.5	1	≥2	0.125-0.5	0.25	0.5	100	0	0
Linezolid	≤4	-	≥8	1-2	2	2	100	NA	0
Erythromycin	≤0.5	1-4	≥8	0.25->128	>128	>128	10	0	90
Clindamycin	≤0.5	1-2	≥4	≤0.06->128	>128	>128	23	0	77
Cotrimoxazole	≤2	-	≥4	≤0.06-4	≤0.06	0.125	98	NA	2
Gentamicin	≤4	8	≥16	0.125-128	32	64	38	0	62
Levofloxacin	≤1	2	≥4	0.25->128	32	32	16	0	84
Tetracycline	≤4	8	≥16	0.25-128	128	128	18	0	82
Oxacillin	≤2	-	≥4	32->128	>128	>128	0	NA	100
Vancomycin	≤2	4-8	≥16	0.5-2	1	2	100	0	0
Methicillin-susceptible *S. aureus* (28)									
Tedizolid	≤0.5	1	≥2	0.25-0.25	0.25	0.25	100	0	0
Linezolid	≤4	-	≥8	1-2	2	2	100	NA	0
Erythromycin	≤0.5	1-4	≥8	0.25->128	0.25	0.25	93	4	4
Clindamycin	≤0.5	1-2	≥4	≤0.06-64	≤0.06	≤0.06	93	4	4
Cotrimoxazole	≤2	-	≥4	≤0.06-0.25	≤0.06	≤0.06	100	NA	0
Gentamicin	≤4	8	≥16	0.125-16	0.25	0.25	96	0	4
Levofloxacin	≤1	2	≥4	0.125-8	0.25	1	93	0	7
Tetracycline	≤4	8	≥16	0.25-0.25	0.25	0.25	100	0	0
Oxacillin	≤2	-	≥4	0.125-0.5	0.25	0.5	100	NA	0
Vancomycin	≤2	4-8	≥16	1-2	1	1	100	0	0

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Table 2. Continued

Organism (N of isolates) and antimicrobial agents	Breakpoint (μg/mL)			MIC (μg/mL)			Susceptibility (%)		
	S	I	R	Range	50%	90%	S	I	R
S. epidermidis (8)									
Tedizolid	NA	NA	NA	≤0.06	NA	NA	NA	NA	NA
Linezolid	≤4	-	≥8	0.25	NA	NA	NA	NA	NA
Erythromycin	≤0.5	1-4	≥8	≤0.06-128	NA	NA	NA	NA	NA
Clindamycin	≤0.5	1-2	≥4	≤0.06->128	NA	NA	NA	NA	NA
Cotrimoxazole	≤2	-	≥4	≤0.06-4	NA	NA	NA	NA	NA
Gentamicin	≤4	8	≥16	≤0.06-128	NA	NA	NA	NA	NA
Levofloxacin	≤1	2	≥4	4-128	NA	NA	NA	NA	NA
Tetracycline	≤4	8	≥16	0.125-32	NA	NA	NA	NA	NA
Oxacillin	≤0.25	-	≥0.5	0.5-32	NA	NA	NA	NA	NA
Vancomycin	≤4	8-16	≥32	1-2	NA	NA	NA	NA	NA
Streptococcus pneumoniae (47)									
Tedizolid	NA	NA	NA	0.25-0.5	0.25	0.5	NA	NA	NA
Linezolid	≤2	-	-	1-2	1	2	100	NA	NA
Penicillin G	≤2	4	≥8	0.015-8	2	8	49	28	23
Cefotaxime	≤1	2	≥4	0.015-32	1	32	55	26	19
Clindamycin	≤0.25	0.5	≥1	0.125->128	>128	>128	15	0	85
Erythromycin	≤0.25	0.5	≥1	0.25->128	>128	>128	6	0	94
Cotrimoxazole	≤0.5	1-2	≥4	1-32	8	32	23	15	62
Levofloxacin	≤2	4	≥8	2-128	2	32	72	2	26
Tetracycline	≤1	2	≥4	0.25-128	32	64	13	0	87

*FDA breakpoints were used for tedizolid.
Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant; NA, not available/applicable; Pip/tazobactam, piperacillin/tazobactam.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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