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In Vitro Activity of Tedizolid against Gram-Positive Cocci Isolates from Patients Hospitalized with Pneumonia in the United States and Europe, 2014-2016

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Abstract

Objectives: Tedizolid and comparator agent *in vitro* activities were assessed against clinically relevant gram-positive pathogens causing pneumonia in patients in European and US hospitals. Tedizolid was approved in the United States, Europe, and other regions to treat adults with acute bacterial skin and skin structure infections (ABSSSIs) and is being evaluated for treating nosocomial pneumonia.

Methods: A total of 6,019 unique clinical isolates deemed to be responsible for community-acquired (CAP) and healthcare-associated pneumonia (HCAP), including hospital-acquired (HAP) in hospitalized patients, were included. A separate analysis included the HAP subset. Isolates originated from 33 and 30 institutions in Europe and the United States, respectively, between 2014 and 2016.

Results: No substantive differences in tedizolid MIC values were found for the different species/organism groups over time or by geographic region. Isolates causing HAP showed slightly decreased activity to comparator agents compared to CAP/HCAP isolates. Tedizolid (100.0% susceptible) showed $MIC_{50/90}$ results of 0.12/0.12 mg/L (US) and 0.12/0.25 mg/L (Europe) when tested against *S. aureus* HAP isolates, regardless of methicillin susceptibility or year of isolation. Coagulase-negative staphylococci from the United States and Europe (MIC_{50}, 0.12 mg/L) demonstrated identical MIC_{50} values for tedizolid. Tedizolid exhibited MIC50 results of 0.25 mg/L and 0.12 mg/L when tested against β-hemolytic streptococci and viridans group streptococci isolates, respectively, regardless of geographic region.

Conclusions: Tedizolid had potent activity *in vitro* against this contemporary collection of European and US gram-positive pneumonia isolates that was sustained over a period of 3 years (2014–2016).

Keywords: Oxazolidinone; Pneumonia; Gram-positive

Introduction

Bacterial pneumonia is a leading cause of morbidity and mortality in the United States (US) and Europe and results in substantial antibiotic usage [1-8]. It is now apparent that delaying pathogen-appropriate antimicrobial therapy to patients with either community-acquired (CAP) or hospital-acquired (HAP; nosocomial including ventilator-associated pneumonia [VAP]) pneumonia results in excess mortality [2,3,6,7,9,10].

Given the lack of timely, sensitive, and specific means of diagnosing bacterial pneumonia [2,6,11,12], initial antibiotic selection remains empiric for most patients while considering the suspected etiology, pathogen-directed therapy changes, and antibiotic resistance [1-3,6,10,11]. Although the causes of bacterial pneumonia may vary according to the onset of infection [2,6,12,13], *Streptococcus pneumoniae* and *Staphylococcus aureus* are predominant pathogens in CAP and HAP, respectively [1,2,4,6,8,10-13].

A HAP subset that includes patients with substantial exposure to the healthcare setting, so-called healthcare-associated pneumonia (HCAP), was designed to identify patients with pneumonia who may be at greater risk to be infected with resistant organisms [6,9,12,13]. Patients with HCAP generally have greater co-morbidities than other patients with CAP and, in some settings, may be more likely to become infected with organisms such as methicillin-resistant *S. aureus* (MRSA) in addition to CAP-associated organisms, such as *S. pneumoniae* [1,9-13]. As such, empiric treatments must adequately cover these key target pathogens, including multidrug-resistant organisms, resulting in the use of 2 or 3-

drug regimens to cover >90% of the contemporary pathogens [3,5,7,12].

Tedizolid is an oxazolidinone derivative that exhibits greater potency and spectrum than linezolid when tested against a broad array of gram-positive cocci (GPC) that includes multidrug-resistant phenotypes, such as MRSA, vancomycin-resistant enterococci (VRE), and linezolid-resistant phenotypes [14,15]. Importantly, tedizolid demonstrates activity against linezolid-resistant bacterial strains harboring the horizontally transmissible cfr gene in the absence of certain ribosomal mutations conferring reduced oxazolidinone susceptibility [15]. Tedizolid was approved in the US, Europe, and other regions to treat acute bacterial skin and skin structure infections (ABSSSI) and is undergoing Phase 3 clinical trials for treating HAP and VAP [15].

The vast majority of tedizolid *in vitro* studies confirm the activity and spectrum of this agent against pathogens associated with ABSSSI, but similar data is lacking for the GPC isolated from patients hospitalized with pneumonia [15-18]. In the present study, we employed the CLSI M07-A10 reference broth microdilution (BMD) method to determine the activity of tedizolid and comparator agents when tested against 6,095 GPC collected in US and European medical centers from January 2014 through December 2016 [19]. Antimicrobial susceptibilities of isolates from CAP/HCAP patients were compared to those from HAP patients.

Materials and Methods

Bacterial isolates

A total of 6,019 gram-positive pathogens were analyzed. The organisms were consecutively collected between January 2014 and December 2016 from 63 medical centers located in the US (3,723 isolates, 30 medical centers) and Europe (2,296 isolates, 33 medical centers in 14 countries). Within this collection, a total of 4,198 isolates were from patients hospitalized with pneumonia (CAP/HCAP), and a subset of 1,821 isolates were from patients with documented HAP. All organisms were isolated from documented infections and only 1 organism per patient infection episode was included in the survey. The isolates were all collected from respiratory tract specimens obtained from patients who were hospitalized with pneumonia. Those isolates cultured from clinical specimens obtained within 48 hours of hospital admission were classified as CAP/HCAP and those recovered from specimens obtained after 48 hours of admission were classified as HAP [2,6].

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 Vitek2, matrix-assisted laser desorption ionization-time of flight mass spectrometry or manual methods).

Antimicrobial susceptibility testing

Susceptibility testing was performed by BMD following the guidelines of the CLSI [20]. Quality control (QC) and interpretation of MIC results obtained against QC strains were performed according to CLSI M100-S26 [20]. MIC results for tested agents obtained against clinical isolates were interpreted using CLSI M100-S26 and EUCAST v6.0 breakpoint criteria, where published [20,21]. US FDA product package insert criteria were used as an alternative breakpoint source as necessary (e.g., tigecycline).

Results

The frequency of the different organisms isolated from patients with CAP/HCAP and HAP in US and European medical centers is shown in **Table 1**. The most common organisms from both regions were *S. pneumoniae* and *S. aureus*. MRSA accounted for 44.5% of *S. aureus* isolates from the US and 27.6% from Europe. *S. pneumoniae* was the predominant organism isolated from patients with CAP/HCAP in both the US (52.0% of all CAP/HCAP isolates) and Europe (90.4%), whereas *S. aureus* was the predominant organism isolated from HAP patients, accounting for 84.2% of isolates in the US (40.5% MRSA) and 68.2% (20.2% MRSA) in Europe.

The *in vitro* activity of tedizolid against GPC isolated from patients hospitalized with pneumonia showed consistent potency over the 3-year study period: the majority of isolates were inhibited at MIC values of ≤ 0.25 mg/L and all isolates of staphylococci, streptococci, and enterococci were inhibited at ≤ 0.5 mg/L (**Tables 2 and 3**).

Activity of tedizolid and comparators against HAP isolates

Overall, tedizolid showed $MIC_{50/90}$ results of 0.12/0.12 mg/L when tested against *S. aureus*, regardless of the geographic origin, year of isolation, or methicillin susceptibility phenotype (100.0% of isolates inhibited at ≤ 0.5 mg/L) (**Table 2**). Tedizolid (100.0/100.0% susceptible [US/Europe]) and comparator agents such as linezolid (100.0/100.0% susceptible), vancomycin (100.0/100.0% susceptible), teicoplanin (100.0/100.0% susceptible [US/EU] using CLSI criteria and 99.5/98.9% susceptible using EUCAST criteria), trimethoprim/sulfamethoxazole (93.6/98.9% susceptible [US/EU]), tetracycline (92.3/91.1% susceptible [US/EU] using CLSI criteria and 88.9/90.6% susceptible using EUCAST criteria), tigecycline (100.0/100.0% susceptible [US/EU]), and ceftaroline (91.8/74.4% susceptible [US/EU]) demonstrated good antimicrobial coverage when tested against MRSA isolates from both regions (**Table 2**). Comparative analyses showed that tedizolid MIC results (MIC_{50}/MIC_{90}, 0.12/0.12 mg/L [US and EU]) were at least 8-fold lower than these agents, with the exception of tigecycline and trimethoprim/sulfamethoxazole, against US or EU isolates (**Table 2**).

Although an infrequent cause of HAP, coagulase-negative staphylococcal (CoNS) isolates from the US demonstrated MIC_{50} values for tedizolid (MIC_{50}, 0.12 mg/L) that were identical to the MIC_{50} values for isolates from European countries (**Table 2**). A total of 62.5% and 87.2% of CoNS from the US and Europe, respectively, were methicillin-resistant (MR-CoNS) (**Table 1**). Overall, tedizolid, vancomycin,

tigecycline, teicoplanin, and linezolid demonstrated activity *in vitro* against CoNS, while other comparators had limited coverage (12.9–80.6% susceptible).

Table 1 Frequency of gram-positive cocci causing pneumonia in US and European hospitals (2014–2016). Note: US, United States; CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; HAP, hospital-acquired pneumonia; CoNS, coagulase-negative staphylococci; BHS, β-hemolytic streptococci; VGS, viridans group streptococci.

	US (no. tested, %)		Europe (no. tested, %)	
Organism	**CAP/HCAP**	**HAP**	**CAP/HCAP**	**HAP**
S. aureus	1,234 (44.2)	785 (84.2)	520 (37.0)	606 (68.2)
Methicillin-susceptible	712 (25.5)	408 (43.8)	389 (27.6)	426 (47.9)
Methicillin-resistant	522 (18.7)	377 (40.5)	131 (9.3)	180 (20.2)
CoNS	13 (0.5)	3 (0.3)	8 (0.6)	31 (3.5)
Methicillin-susceptible	4 (0.1)	2 (0.2)	1 (<0.1)	4 (0.4)
Methicillin-resistant	9 (0.3)	1 (0.1)	7 (0.5)	27 (3.0)
S. pneumoniae	1,452 (52.0)	129 (13.8)	1,272 (90.4)	233 (26.2)
BHS	79 (2.8)	11 (1.2)	41 (2.9)	6 (0.7)
VGS	13 (0.5)	4 (0.4)	34 (2.4)	13 (1.5)
Total	2,791 (100.0)	932 (100.0)	1,407 (100.0)	889 (100.0)

Tedizolid showed comparable activity against *S. pneumoniae* causing HAP ($MIC_{50/90}$, 0.12/0.25 mg/L) from both regions, and 100.0% of all isolates were inhibited by ≤ 0.5 mg/L (**Table 2**). A total of 6.2% and 10.3% of *S. pneumoniae* from the US and Europe, respectively, were nonsusceptible (MIC, ≥ 2 mg/L) to ceftriaxone and 55.0/51.9% (US/Europe) were nonsusceptible to penicillin (MIC, ≥ 0.12 mg/L). Overall, more than 90% of *S. pneumoniae* isolates were susceptible to linezolid, amoxicillin-clavulanic acid (Europe only), ceftaroline, levofloxacin, and vancomycin. Erythromycin (41.9/61.4% susceptible [US/Europe]), tetracycline (72.1/63.5% susceptible [US/Europe]), and trimethoprim-sulfamethoxazole (62.8/63.9% susceptible [US/Europe] using CLSI criteria and 64.3/75.5% susceptible using EUCAST criteria) were not active against this *S. pneumoniae* collection.

Tedizolid exhibited MIC_{50} results of 0.12 mg/L when tested against β-hemolytic streptococci (BHS) and VGS isolates, respectively, regardless of geographical region (**Table 2**). Other agents, such as penicillin, vancomycin, teicoplanin, amoxicillin-clavulanic acid, ceftaroline, ceftriaxone, linezolid, and levofloxacin demonstrated antimicrobial coverage (100.0% susceptible) against BHS (**Table 2**). When tested against VGS, tedizolid, linezolid, ceftaroline, ceftriaxone, vancomycin, and levofloxacin were all highly active (**Table 2**). VGS isolates from Europe were less susceptible to most comparators than US isolates.

Tedizolid (MIC_{50}, 0.12/0.25 mg/L[US/Europe]) was equally active when tested against Enterococcus faecalis from Europe and the US, inhibiting 100.0% of strains at the CLSI breakpoint for susceptibility (≤ 0.5 mg/L) (**Table 2**). *E. faecalis* isolates from both regions were all (100.0%) susceptible to ampicillin, vancomycin, teicoplanin, and linezolid (**Table 2**). These comparator agents had MIC_{50} results (all MIC_{50} of ≤ 2 mg/L) that were 4 to 8-fold higher than those obtained for tedizolid, regardless of geographic region. All *Enterococcus faecium* isolates (90.0/12.5% VRE [US/Europe]) were inhibited by tedizolid at ≤ 0.25 mg/L. Only linezolid showed clinically useful activity against *E. faecium* among comparators, including VRE isolates (100.0/100.0% susceptible [US/Europe]; **Table 2**).

Table 2 Activity of tedizolid and comparator antimicrobial agents when tested against isolates causing HAP in US and European hospitals (2014–2016). Note: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; TMP-SMX, trimethoprim-sulfamethoxazole [a]Criteria as published by CLSI and EUCAST. [b]Breakpoints from FDA Package Insert revised 12/2014. [c]Using non-meningitis breakpoints. [d]Using meningitis breakpoints. [e]Using oral breakpoints. [f]Using parenteral, meningitis breakpoints. [g]Using parenteral, non-meningitis breakpoints.

Organism group (no. tested) antimicrobial agent	**United States**				**Europe**			
	CLSI[a]	**EUCAST[a]**	**$MIC_{50/90}$**	**MIC Range**	**CLSI[a]**	**EUCAST[a]**	**$MIC_{50/90}$**	**MIC Range**

	%S	%S			%S	%S		
Staphylococcus aureus	(785)				(606)			
Tedizolid	100.0	100.0	0.12/0.12	0.03–0.25	100.0	100.0	0.12/0.25	0.03–0.25
Linezolid	100.0	100.0	1/1	0.25–2	100.0	100.0	1/1	≤ 0.12–2
Ceftaroline	96.1	96.1	0.25/1	0.03–2	92.4	92.4	0.25/1	0.06–4
Clindamycin	77.2	77.1	≤ 0.25/>2	≤ 0.25–>2	93.1	93.1	≤ 0.25/ ≤ 0.25	≤ 0.25–>2
Erythromycin	39.4	39.9	8/>8	≤ 0.12–>8	69.5	70.3	0.25/>8	≤ 0.12–>8
Levofloxacin	56.2	56.2	0.25/>4	≤ 0.12–>4	71.9	71.9	0.25/>4	≤ 0.12–>4
Oxacillin	52.0	52.0	1/>2	≤ 0.25–>2	70.3	70.3	0.5/>2	≤ 0.25–>2
Teicoplanin	100.0	99.7	≤ 2/ ≤ 2	≤ 2–8	100.0	99.7	≤ 2/ ≤ 2	≤ 2–4
Tetracycline	95.3	92.9	≤ 0.5/1	≤ 0.5–>8	93.7	93.4	≤ 0.5/ ≤ 0.5	≤ 0.5–>8
Tigecycline	100.0[b]	100.0	0.06/0.12	≤ 0.015–0.5	100.0b	100.0	0.06/0.12	≤ 0.015–0.25
TMP-SMX	96.3	96.3	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	99.7	99.7	≤ 0.5/ ≤ 0.5	≤ 0.5–>4
Vancomycin	100.0	100.0	0.5/1	0.25–2	100.0	100.0	0.5/1	0.25–2
MSSA	(408)				(426)			
Tedizolid	100.0	100.0	0.12/0.12	0.03–0.25	100.0	100.0	0.12/0.25	0.06–0.25
Linezolid	100.0	100.0	1/1	0.25–2	100.0	100.0	1/1	0.25–2
Ceftaroline	100.0	100.0	0.25/0.25	0.03–0.5	100.0	100.0	0.25/0.25	0.06–0.5
Clindamycin	95.8	95.6	≤ 0.25/ ≤ 0.25	≤ 0.25–>2	99.3	99.3	≤ 0.25/ ≤ 0.25	≤ 0.25–>2
Erythromycin	67.2	67.4	0.25/>8	≤ 0.12–>8	81.9	82.9	0.25/>8	≤ 0.12–>8
Levofloxacin	91.9	91.9	0.25/0.5	≤ 0.12–>4	96.7	96.7	0.25/0.25	≤ 0.12–>4
Teicoplanin	100.0	100.0	≤ 2/ ≤ 2	≤ 2	100.0	100.0	≤ 2/ ≤ 2	≤ 2
Tetracycline	98.0	96.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>8	94.8	94.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>8
Tigecycline	100.0[b]	100.0	0.06/0.12	0.03–0.5	100.0[b]	100.0	0.06/0.12	≤ 0.015–0.25
TMP-SMX	98.8	98.8	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	100.0	100.0	≤ 0.5/ ≤ 0.5	≤ 0.5–2
Vancomycin	100.0	100.0	0.5/1	0.25–1	100.0	100.0	0.5/1	0.25–2
MRSA	(377)				(180)			
Tedizolid	100.0	100.0	0.12/0.12	0.03–0.25	100.0	100.0	0.12/0.12	0.03–0.25
Linezolid	100.0	100.0	1/1	0.25–2	100.0	100.0	1/1	≤ 0.12–2
Ceftaroline	91.8	91.8	1/1	0.25–2	74.4	74.4	1/2	0.25–4
Clindamycin	57.0	57.0	≤ 0.25/>2	≤ 0.25–>2	78.3	78.3	≤ 0.25/>2	≤ 0.25–>2
Erythromycin	9.3	10.1	>8 />8	≤ 0.12–>8	40.0	40.6	>8/>8	≤ 0.12–>8
Levofloxacin	17.5	17.5	>4/>4	≤ 0.12–>4	13.3	13.3	>4/>4	≤ 0.12–>4
Teicoplanin	100.0	99.5	≤ 2/ ≤ 2	≤ 2–8	100.0	98.9	≤ 2/ ≤ 2	≤ 2–4
Tetracycline	92.3	88.9	≤ 0.5/2	≤ 0.5–>8	91.1	90.6	≤ 0.5/1	≤ 0.5–>8
Tigecycline	100.0[b]	100.0	0.06/0.12	≤ 0.015–0.5	100.0[b]	100.0	0.06/0.12	≤ 0.015–0.25
TMP-SMX	93.6	93.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	98.9	98.9	≤ 0.5/ ≤ 0.5	≤ 0.5–>4
Vancomycin	100.0	100.0	1/1	0.5–2	100.0	100.0	0.5/1	0.25–2
CoNS	(3)				(31)			

Tedizolid		100.0	0.12	0.06–0.12		100.0	0.12/0.12	0.06–0.25
Linezolid	100.0	100.0	0.5	0.25–0.5	100.0	100.0	0.5/1	0.25–1
Ceftaroline			≤ 0.06	≤ 0.06–0.25			0.5/2	≤ 0.06–2
Clindamycin	66.7	66.7	≤ 0.25	≤ 0.25–>2	80.6	77.4	≤ 0.25/>2	≤ 0.25–>2
Erythromycin	33.3	33.3	>8	0.25–>8	19.4	19.4	>8/>8	≤ 0.12–>8
Levofloxacin	66.7	66.7	0.5	0.12–>4	29.0	29.0	4/>4	≤ 0.12–>4
Oxacillin	66.7	66.7	≤ 0.25	≤ 0.25–2	12.9	12.9	>2/>2	≤ 0.25–>2
Teicoplanin	100.0	100.0	≤ 2	≤ 2–4	93.5	83.9	4/8	≤ 2–>16
Tetracycline	100.0	100.0	≤ 0.5	≤ 0.5	80.6	74.2	≤ 0.5/>8	≤ 0.5–>8
Tigecycline		100.0	0.06	0.03–0.06		100.0	0.06/0.25	0.03–0.5
TMP-SMX	66.7	66.7	≤ 0.5	≤ 0.5–>4	61.3	61.3	1/>4	≤ 0.5–>4
Vancomycin	100.0	100.0	1	0.5–2	100.0	100.0	1/2	0.5–2
Streptococcus pneumoniae	(129)				(233)			
Tedizolid			0.12/0.25	0.03–0.25			0.12/0.25	0.06–0.25
Linezolid	100.0	100.0	1/1	≤ 0.12–2	100.0	100.0	1/1	0.25–2
Amoxicillin-clavulanic acid	87.6		≤ 1/4	≤ 1–>4	90.1		≤ 1/2	≤ 1–>4
Ceftaroline	100.0[c]	98.4	0.03/0.12	≤ 0.015–0.5	100.0[c]	99.6	≤ 0.015/0.12	≤ 0.015–0.5
Ceftriaxone	67.4[d] 93.8[c]	67.4	0.12/1	≤ 0.06–>2	70.0[d] 89.7[c]	70.0	≤ 0.06/2	≤ 0.06–>2
Clindamycin	77.5	78.3	≤ 0.25/>1	≤ 0.25–>1	69.1	70.0	≤ 0.25/>1	≤ 0.25–>1
Erythromycin	41.9	41.9	>2/>2	≤ 0.12–>2	61.4	61.4	≤ 0.12/>2	≤ 0.12–>2
Levofloxacin	98.4	98.4	1/1	0.5–>4	99.1	99.1	1/1	0.5–>4
Penicillin	45.0[e] 45.0[f] 91.5[g]	45.0[d] 45.0[c]	0.25/2	≤ 0.06–4	48.1[e] 48.1[f] 91.0[g]	48.1d 48.1c	0.12/2	≤ 0.06–>8
Tetracycline	72.1	72.1	≤ 0.5/>4	≤ 0.5–>4	63.5	63.5	≤ 0.5/>4	≤ 0.5–>4
TMP-SMX	62.8	64.3	≤ 0.5/>4	≤ 0.5–>4	63.9	75.5	≤ 0.5/>4	≤ 0.5–>4
Vancomycin	100.0	100.0	0.25/0.5	≤ 0.12–0.5	100.0	100.0	0.25/0.25	≤ 0.12–0.5
β-hemolytic streptococci	(11)				(6)			
Tedizolid	100.0	100.0	0.12/0.25	0.12–0.25	100.0	100.0	0.12	0.12–0.25
Linezolid	100.0	100.0	1/1	0.5–1	100.0	100.0	1	0.5–1
Amoxicillin-clavulanic acid	100.0	100.0	≤ 1/ ≤ 1	≤ 1	100.0	100.0	≤ 1	≤ 1
Ceftaroline	100.0	100.0	≤ 0.015/ ≤ 0.015	≤ 0.015	100.0	100.0	0.015	≤ 0.008–0.03
Ceftriaxone	100.0	100.0	≤ 0.06/ ≤ 0.06	≤ 0.06	100.0	100.0	0.06	0.03–0.12
Clindamycin	100.0	100.0	≤ 0.25/ ≤ 0.25	≤ 0.25	100.0	100.0	≤ 0.25	≤ 0.25
Erythromycin	72.7	72.7	≤ 0.12/2	≤ 0.12–>32	100.0	100.0	≤ 0.12	≤ 0.12
Levofloxacin	100.0	100.0	0.5/1	0.25–1	100.0	100.0	0.5	0.5–1
Penicillin	100.0	100.0	≤ 0.06/ ≤ 0.06	≤ 0.06	100.0	100.0	≤ 0.06	≤ 0.06
Tetracycline	36.4	36.4	>8/>8	≤ 0.5–>8	16.7	16.7	>8	≤ 0.25–>8

Vancomycin	100.0	100.0	0.25/0.5	0.25–0.5	100.0	100.0	0.25	0.25–0.5
Viridans group streptococci	(4)				(13)			
Tedizolid	100.0	100.0	0.12	0.06–0.12	100.0	100.0	0.12/0.12	0.03–0.12
Linezolid	100.0		0.5	0.5–1	100.0		0.5/1	0.25–1
Amoxicillin-clavulanic acid		100.0	≤ 1	≤ 1		53.8	≤ 1/4	≤ 1–>4
Ceftriaxone	100.0	100.0	0.12	0.12–0.5	84.6	76.9	0.25/2	≤ 0.06–4
Clindamycin	100.0	100.0	≤ 0.25	≤ 0.25	84.6	84.6	≤ 0.25/2	≤ 0.25–>2
Erythromycin	50.0		≤ 0.12	≤ 0.12–2	38.5		1/>4	≤ 0.12–>4
Levofloxacin	100.0		0.5	0.25–1	100.0		1/2	0.5–2
Penicillin	50.0	100.0	0.12	≤ 0.03–0.25	53.8	53.8	≤ 0.06/2	≤ 0.06–>4
Tetracycline	100.0		≤ 0.25	≤ 0.25–1	69.2		≤ 0.5/>8	≤ 0.5–>8
Vancomycin	100.0	100.0	0.5	0.25–1	100.0	100.0	0.25/0.5	0.25–0.5

Activity of tedizolid and comparators against CAP/HCAP isolates

The activity of tedizolid and comparators against isolates causing CAP/HCAP in US and European hospital patients is shown in **Table 3**. In contrast to HAP findings, isolates from patients with CAP were predominantly *S. pneumoniae* (51.9/89.6% of all CAP isolates [US/Europe]) followed by *S. aureus* (44.1/36.6% of all CAP isolates [US/Europe]) (**Tables 1 and 3**). Tedizolid was active against all CAP pathogens with 100.0% inhibited by ≤ 0.5 mg/L (**Table 3**). As with the HAP isolates, linezolid, ceftaroline, teicoplanin, tigecycline (staphylococci), and vancomycin all were active against these GPC.

Table 3 Activity of tedizolid and comparator antimicrobial agents when tested against isolates causing CAP/HCAP in US and European hospitals (2014–2016). Note: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; TMP-SMX, trimethoprim-sulfamethoxazole. [a]Criteria as published by CLSI and EUCAST. [b]Breakpoints from FDA Package Insert revised 12/2014. [c]Using non-meningitis breakpoints. [d]Using meningitis breakpoints. [e]Using oral breakpoints. [f]Using parenteral, meningitis breakpoints. [g]Using parenteral, non-meningitis breakpoints.

Organism group (no. tested)	**United States**				**Europe**			
antimicrobial agent	**CLSI[a]**	**EUCAST[a]**	**$MIC_{50/90}$**	**MIC range**	**CLSI[a]**	**EUCAST[a]**	**$MIC_{50/90}$**	**MIC range**
	%S	**%S**			**%S**	**%S**		
Staphylococcus aureus	-1,234				-520			
Tedizolid	100	100	0.12/0.12	0.015–0.5	100	100	0.12/0.25	0.06–0.25
Linezolid	100	100	01-Jan	≤ 0.12–4	100	100	01-Jan	0.25–2
Ceftaroline	98.5	98.5	0.25/1	≤ 0.06–2	96.5	96.5	0.25/1	0.12–2
Clindamycin	80.2	80.1	≤ 0.25/>2	≤ 0.25–>2	91	90.4	≤ 0.25/ ≤ 0.25	≤ 0.25–>2
Erythromycin	40	40.8	8/>8	≤ 0.12–>8	61.9	61.9	0.25/>8	≤ 0.12–>8
Levofloxacin	58.3	58.3	0.25/>4	≤ 0.12–>4	73.3	73.3	0.25/>4	≤ 0.12–>4
Oxacillin	57.7	57.7	0.5/>2	≤ 0.25–>2	74.8	74.8	0.5/>2	≤ 0.25–>2
Teicoplanin	100	100	≤ 2/ ≤ 2	≤ 2–≤ 2	100	99.8	≤ 2/ ≤ 2	≤ 2–4
Tetracycline	95	92.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>8	95.8	95.4	≤ 0.5/ ≤ 0.5	≤ 0.5–>8
Tigecycline	100.0[b]	100	0.06/0.12	≤ 0.015–0.5	100.0[b]	100	0.06/0.12	0.03–0.25

TMP-SMX	98.9	98.9	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	99.6	99.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>4
Vancomycin	100	100	0.5/1	≤ 0.12–2	100	100	0.5/1	0.25–2
MSSA	-712				-389			
Tedizolid	100	100	0.12/0.12	0.03–0.25	100	100	0.12/0.25	0.06–0.25
Linezolid	100	100	01-Jan	≤ 0.12–2	100	100	01-Jan	0.25–2
Ceftaroline	100	100	0.25/0.25	≤ 0.06–0.5	100	100	0.25/0.25	0.12–0.5
Clindamycin	92.8	92.8	≤ 0.25/ ≤ 0.25	≤ 0.25–>2	97.7	97.2	≤ 0.25/ ≤ 0.25	≤ 0.25–>2
Erythromycin	63.3	64	0.25/>8	≤ 0.12–>8	75.6	75.6	0.25/>8	≤ 0.12–>8
Levofloxacin	86.7	86.7	0.25/4	≤ 0.12–>4	92.5	92.5	0.25/0.5	≤ 0.12–>4
Teicoplanin	100	100	≤ 2/ ≤ 2	≤ 2	100	100	≤ 2/ ≤ 2	≤ 2
Tetracycline	96.5	94.4	≤ 0.5/ ≤ 0.5	≤ 0.5–>8	96.9	96.7	≤ 0.5/ ≤ 0.5	≤ 0.5–>8
Tigecycline	100.0[b]	100	0.06/0.12	≤ 0.015–0.25	100.0[b]	100	0.06/0.12	0.03–0.25
TMP-SMX	99.4	99.4	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	100	100	≤ 0.5/ ≤ 0.5	≤ 0.5–1
Vancomycin	100	100	0.5/1	≤ 0.12–2	100	100	0.5/1	0.25–2
MRSA	-522				-131			
Tedizolid	100	100	0.12/0.12	0.015–0.5	100	100	0.12/0.25	0.06–0.25
Linezolid	100	100	01-Jan	≤ 0.12–4	100	100	01-Jan	0.5–2
Ceftaroline	96.6	96.6	01-Jan	0.25–2	86.3	86.3	01-Feb	0.25–2
Clindamycin	63	62.6	≤ 0.25/>2	≤ 0.25–>2	71	70.2	≤ 0.25/>2	≤ 0.25–>2
Erythromycin	8.2	9	>8/>8	≤ 0.12–>8	21.4	21.4	>8/>8	≤ 0.12–>8
Levofloxacin	19.7	19.7	>4/>4	≤ 0.12–>4	16	16	>4/>4	0.12–>4
Teicoplanin	100	100	≤ 2/ ≤ 2	≤ 2	100	99.2	≤ 2/ ≤ 2	≤ 2
Tetracycline	92.9	90.2	≤ 0.5/1	≤ 0.5–>8	92.4	91.6	≤ 0.5/ ≤ 0.5	≤ 0.5–>8
Tigecycline	100.0[b]	100	0.06/0.12	≤ 0.015–0.5	100.0[b]	100	0.06/0.12	0.03–0.25
TMP-SMX	98.1	98.1	≤ 0.5/ ≤ 0.5	≤ 0.5–>4	98.5	98.5	≤ 0.5/ ≤ 0.5	≤ 0.5–>4
Vancomycin	100	100	01-Jan	0.25–2	100	100	0.5/1	0.5–2
CoNS	-13				-8			
Tedizolid		100	0.06/0.12	0.015–0.12		100	0.12	0.06–0.12
Linezolid	100	100	0.5/1	≤ 0.12–1	100	100	0.5	0.5–1
Ceftaroline			0.25/1	≤ 0.06–2			0.5	0.12–2
Clindamycin	69.2	53.8	≤ 0.25/>2	≤ 0.25–>2	75	75	≤ 0.25	≤ 0.25–>2
Erythromycin	23.1	23.1	>8/>8	≤ 0.06–>8	12.5	12.5	>8	0.25–>8
Levofloxacin	46.2	46.2	2/>4	0.06–>4	12.5	12.5	>4	≤ 0.12–>4
Oxacillin	30.8	30.8	>2/>2	≤ 0.25–>2	12.5	12.5	>2	≤ 0.25–>2
Teicoplanin	100	100	≤ 2/4	≤ 2–4	100	100	≤ 2	≤ 2–4
Tetracycline	92.3	92.3	≤ 0.5/1	≤ 0.5–>8	100	87.5	≤ 0.5	≤ 0.5–4
Tigecycline		100	0.06/0.12	0.03–0.12		100	0.06	0.06–0.25
TMP-SMX	46.2	46.2	4/>4	≤ 0.5–>4	37.5	37.5	>4	≤ 0.5–>4

Vancomycin	100	100	01-Feb	0.5–2	100	100	1	0.5–2
Streptococcus pneumoniae	-1,452				-1,272			
Tedizolid			0.12/0.25	0.03–0.25			0.12/0.25	0.015–0.5
Linezolid	100	100	01-Jan	≤ 0.12–2	100	100	01-Jan	≤ 0.12–2
Amoxicillin-clavulanic acid	92.4		≤ 1/2	≤ 1–>4	92.5		≤ 1/2	≤ 1–>4
Ceftaroline	99.9[c]	99.5	≤ 0.015/0.12	≤ 0.015–1	99.8[c]	99.3	≤ 0.015/0.12	≤ 0.015–1
Ceftriaxone	84.9[d]	84.9	≤ 0.06/1	≤ 0.06–>2	84.6[d]	84.6	≤ 0.06/1	≤ 0.06–>2
	96.4[c]				94.8[c]			
Clindamycin	84.4	85.1	≤ 0.25/>1	≤ 0.25–>1	80.7	81.4	≤ 0.25/>1	≤ 0.25–>1
Erythromycin	52.5	52.5	≤ 0.12/>2	≤ 0.12–>2	71.7	71.7	≤ 0.12/>2	≤ 0.12–>2
Levofloxacin	98.6	98.6	01-Jan	0.25–>4	98.3	98.3	01-Jan	0.25–>4
Penicillin	59.2[e]	59.2[d]	≤ 0.06/2	≤ 0.06–8	67.0[e]	67.0[d]	≤ 0.06/2	≤ 0.06–>8
	59.2[f]	59.2[c]			67.0[f]	67.0[c]		
	95.3[g]				94.7[g]			
Tetracycline	78.1	78.1	≤ 0.5/>4	≤ 0.5–>4	73.7	73.7	≤ 0.5/>4	≤ 0.5–>4
TMP-SMX	70.1	77.5	≤ 0.5/>4	≤ 0.5–>4	67.7	74.1	≤ 0.5/>4	≤ 0.5–>4
Vancomycin	100	100	0.25/0.25	≤ 0.12–1	100	100	0.25/0.25	≤ 0.12–0.5
β-hemolytic streptococci	-79				-41			
Tedizolid	100	100	0.12/0.25	0.06–0.25	100	100	0.12/0.12	0.06–0.25
Linezolid	100	100	01-Jan	0.5–2	100	100	01-Jan	0.5–2
Amoxicillin-clavulanic acid	100	100	≤ 1/ ≤ 1	≤ 1	100	100	≤ 1/ ≤ 1	≤ 1
Ceftaroline	100	100	≤ 0.015/ ≤ 0.015	≤ 0.015–0.03	100	100	≤ 0.015/ ≤ 0.015	≤ 0.015–0.03
Ceftriaxone	100	100	≤ 0.06/ ≤ 0.06	≤ 0.06–0.12	100	100	≤ 0.06/0.12	≤ 0.06–0.25
Clindamycin	87.3	87.3	≤ 0.25/>2	≤ 0.25–>2	90.2	95.1	≤ 0.25/ ≤ 0.25	≤ 0.25–>2
Erythromycin	62	62	≤ 0.12/>4	≤ 0.12–>4	80.5	80.5	≤ 0.12/2	≤ 0.12–>16
Levofloxacin	98.7	98.7	0.5/1	0.25–>4	100	100	0.5/1	0.25–2
Penicillin	100	100	≤ 0.06/ ≤ 0.06	≤ 0.06	100	100	≤ 0.06/ ≤ 0.06	≤ 0.06
Tetracycline	57	57	≤ 0.5/>8	≤ 0.5–>8	58.5	58.5	≤ 0.5/>8	≤ 0.5–>8
Vancomycin	100	100	0.25/0.5	0.25–0.5	100	100	0.25/0.5	0.25–0.5
Viridans group streptococci	-13				-34			
Tedizolid			0.06/0.12	0.03–0.12			0.12/0.12	0.06–0.25
Linezolid	100		0.5/1	0.25–1	100		0.5/1	0.25–1
Amoxicillin-clavulanic acid		84.6	≤ 1/ ≤ 1	≤ 1–2		61.8	≤ 1/4	≤ 1–>4
Ceftriaxone	100	92.3	0.25/0.5	0.06–1	94.1	88.2	0.25/1	≤ 0.06–4
Clindamycin	100	100	≤ 0.25/ ≤ 0.25	≤ 0.25	76.5	76.5	≤ 0.25/>2	≤ 0.25–>2
Erythromycin	53.8		≤ 0.12/2	≤ 0.12–8	41.2		1/>4	≤ 0.12–>4
Levofloxacin	100		01-Jan	0.25–2	91.2		01-Feb	0.25–>4

Penicillin	69.2	84.6	≤ 0.06/0.5	≤ 0.06–1	58.8	61.8	≤ 0.06/2	≤ 0.06–>8
Tetracycline	76.9		≤ 0.5/>8	≤ 0.5–>8	44.1		8/>8	≤ 0.5–>8
Vancomycin	100	100	0.5/1	0.25–1	100	100	0.5/0.5	0.25–0.5

Discussion

Adequate antimicrobial treatment is key to improving the unacceptably high rates of morbidity and mortality encountered in patients hospitalized with pneumonia [2,3,6,7,9]. Since causative pathogens commonly include MDR GPC, such as MRSA, effective treatments should demonstrate potency against clinically relevant gram-positive pneumonia isolates [12]. Although a clinical trial to evaluate tedizolid for treating ventilator-assisted adult patients with bacterial pneumonia is ongoing, surveillance data can be used to monitor real-world tedizolid activity in patients hospitalized with pneumonia.

This study evaluated the activity *in vitro* of tedizolid and comparators against a 3-year collection of gram-positive clinical isolates implicated in pneumonia, including MRSA. Overall, tedizolid activity was unchanged over three years and was comparable for isolates from both Europe and the US (data not shown). The *in vitro* potency of tedizolid was greater than the *in vitro* potency of the tested comparators, including linezolid. Tedizolid inhibited 100.0% of MRSA isolates at the CLSI and EUCAST approved breakpoint (≤ 0.5 mg/L). Equivalent potency results were observed for tedizolid when tested against isolates from Europe and the US.

In conclusion, tedizolid showed excellent activity against *S. aureus* (including MRSA), CoNS, *S. pneumoniae*, BHS, VGS, and enterococci isolated in 2014 through 2016 from patients hospitalized with pneumonia in the US and Europe.

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