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Comparative *In Vitro* Activities of Ceftaroline and Tedizolid against Clinical Strains of *Staphylococcus aureus* and *Enterococcus*: Results from the China Antimicrobial Surveillance Network (CHINET) in 2018

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ABSTRACT The *in vitro* activities of ceftaroline and tedizolid were compared against *Staphylococcus aureus*, *Enterococcus faecalis*, and *Enterococcus faecium* clinical isolates collected from the China Antimicrobial Surveillance Network. Ceftaroline demonstrated potent activity against *S. aureus* isolates ($MIC_{50/90}$, ≤0.25/1 mg/liter). Tedizolid was also highly active against *S. aureus* ($MIC_{50/90}$, 0.25/0.5 mg/liter) and *Enterococcus* ($MIC_{50/90}$, 0.5/0.5 mg/liter) isolates. Our results support the clinical usefulness of ceftaroline and tedizolid in treating Gram-positive infections.

KEYWORDS ceftaroline, tedizolid, antimicrobial susceptibility testing, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*

Staphylococcus aureus and *Enterococcus* spp. represent the major Gram-positive pathogens causing bacteremia, infective endocarditis, and pneumonia, as well as bloodstream, skin and soft tissue, and urinary tract infections (1). According to data from the China Antimicrobial Surveillance Network (CHINET) (2), *S. aureus* accounted for 9.3% (23,323/249,758) of all clinical isolates, while *Enterococcus faecalis* and *Enterococcus faecium* accounted for 3.1% (7,676/249,758) and 4.2% (10,413/249,758), respectively. Ceftaroline, a novel broad-spectrum β-lactam cephalosporin, was approved in 2010 by the U.S. Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (3) due to its activity against methicillin-resistant *S. aureus* (MRSA). Tedizolid is an oxazolidinone antibacterial agent. In 2014, tedizolid was approved in the United States for the treatment of ABSSSI caused by susceptible strains of *S. aureus*, *Streptococcus*, and *E. faecalis* (4). Currently, the antimicrobial activity and spectrum of ceftaroline and tedizolid have not been studied extensively with clinical strains in China. Here, we compared the *in vitro* activities of ceftaroline, tedizolid, and other comparators against a large panel of clinical isolates with the purpose to support the clinical use of ceftaroline and tedizolid.

A total of 2,058 nonduplicate clinical isolates of *S. aureus* ($n = 1,191$), *E. faecalis* ($n = 417$), and *E. faecium* ($n = 450$) were collected from 44 hospitals in 26 provinces or cities across China in 2018, as part of CHINET. *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 isolates were used as quality controls for antimicrobial susceptibility testing. MICs were determined by the reference broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI) (5). The results were interpreted according to 2019 CLSI breakpoints for all the agents tested with the exception

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TABLE 1 MIC frequency distribution of ceftaroline and tedizolid against *S. aureus*, *E. faecalis*, and *E. faecium*

Organism[a]	Antimicrobial agent	No. (cumulative %) of isolates at MIC (mg/liter) of:					
		0.125	0.25	0.5	1	2	4
S. aureus (n = 1,191)	Ceftaroline		716 (60.1)	299 (85.2)	167 (99.2)	8 (99.9)	1 (100.0)
	Tedizolid	22 (1.8)	834 (71.9)	335 (100)			
MRSA (n = 411)	Ceftaroline		25 (6.1)	225 (60.8)	152 (97.8)	8 (99.8)	1 (100.0)
	Tedizolid	9 (2.2)	299 (74.9)	103 (100.0)			
MSSA (n = 780)	Ceftaroline		691 (88.6)	74 (98.1)	15 (100.0)		
	Tedizolid	13 (1.7)	535 (70.3)	232 (100.0)			
Enterococcus spp. (n = 867)	Tedizolid	5 (0.6)	208 (24.6)	623 (96.4)	30 (99.9)	1 (100.0)	
E. faecalis (n = 417)	Tedizolid	4 (1.0)	105 (26.1)	283(94.0)	25 (100.0)		
E. faecium (n = 450)	Tedizolid	1 (0.2)	103 (23.1)	340 (98.7)	5 (99.8)	1 (100.0)	

[a]MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

of tigecycline, for which CLSI criteria were not available (6). Tigecycline MICs were interpreted by FDA breakpoints for *S. aureus* (susceptible, ≤0.5 mg/liter) and *E. faecalis* (susceptible, ≤0.25 mg/liter) (7).

Ceftaroline inhibited 99.2% of the *S. aureus* strains at a concentration of 1 mg/liter (breakpoint for susceptibility), showing excellent activity against MRSA ($MIC_{50/90}$, 0.5/1 mg/liter) and methicillin-susceptible *S. aureus* (MSSA) ($MIC_{50/90}$, 0.25/0.5 mg/liter) strains (Table 1). Tedizolid inhibited 100% of the *S. aureus* strains at a concentration of 0.5 mg/liter ($MIC_{50/90}$, 0.25/0.5 mg/liter). Nine (0.8%) strains of *S. aureus* were susceptible-dose dependent to ceftaroline (MIC, 2 to 4 mg/liter) (Table 1). Tedizolid was highly active ($MIC_{50/90}$, 0.5/0.5 mg/liter) against *Enterococcus* isolates by inhibiting 100% of the 867 strains at a concentration of 2 mg/liter (Table 1).

Overall, 99.2%, 100%, and 100% of the *S. aureus* strains tested were susceptible to ceftaroline, tedizolid, and linezolid, respectively, but had relatively lower susceptibility to the comparators erythromycin (31.7%), clindamycin (58.3%), gentamicin (77.8%), and levofloxacin (77.7%). In terms of susceptibility rates, vancomycin (100%), tedizolid (100%), linezolid (100%), tigecycline (98.2), and trimethoprim-sulfamethoxazole (95.6%) were similar to ceftaroline. Tedizolid and ceftaroline inhibited 100% and 97.8% of the MRSA isolates, respectively, which was much higher than erythromycin, clindamycin, gentamicin, and levofloxacin (14.1% to 67.2%). All MSSA strains were susceptible to ceftaroline, tedizolid, linezolid, tigecycline, and vancomycin and better than any other antibiotic tested (Table 2).

Tedizolid inhibited most of the *Enterococcus* strains, similar to linezolid, tigecycline, and vancomycin (95.5% to 99.1%) and better than all of the other antibiotics tested. More *E. faecalis* strains than *E. faecium* strains were susceptible to ampicillin (98.1% versus 8.4%), nitrofurantoin (98.8% versus 12.9%), levofloxacin (64% versus 7.1%), tigecycline (100% versus 98.2%), and vancomycin (99.8% versus 94.7%) (Table 2).

Gram-positive pathogens develop resistance to virtually all antimicrobials currently available in clinical practice because of an immense pool of resistant genes (8). Data from the CHINET program showed that *S. aureus* and *Enterococcus* strains were the most frequently isolated Gram-positive pathogens (2, 9, 10).

Sader et al. (11) reported the activity of ceftaroline against 21,056 clinical strains of *S. aureus* isolated from 42 medical centers in the United States, showing $MIC_{50/90}$ values of 0.25/0.25 mg/liter against MSSA (100% susceptible) and 0.5/1 mg/liter against MRSA (97.2% susceptible). This is consistent with our results (modal MIC, 0.25 mg/liter). Andrey et al. (12) reported that 24% of the strains were resistant to ceftaroline (MIC, ≥2 mg/liter) according to EUCAST breakpoints. We found a much lower incidence (0.8%, 9/1,191) of ceftaroline-nonsusceptible *S. aureus* (MIC, 2 to 4 mg/liter). The percentage of ceftaroline resistance should be interpreted cautiously because the collection of clinical strains and the breakpoints are different.

The MIC values of tedizolid in our study were similar to those in previous reports,

TABLE 2 Activities of ceftaroline, tedizolid, and comparators against clinical isolates

Organism[a]	Antimicrobial agent	MIC (mg/liter)			Susceptibility (%)[b]	
		Range	50%	90%	Susceptible	Resistant
S. aureus (*n* = 1,191)	Ceftaroline	≤0.25 to 4	≤0.25	1	99.2	0.8[c]
	Tedizolid	0.125 to 0.5	0.25	0.5	100	0
	Linezolid	0.5 to 4	2	2	100	0
	Erythromycin	≤0.5 to >16	>16	>16	31.7	66.1
	Clindamycin	≤0.5 to >16	≤0.5	>16	58.3	40.2
	Gentamicin	≤1 to >32	≤1	32	77.8	20.3
	Levofloxacin	≤0.25 to >32	≤0.25	32	77.7	21.2
	Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	1	95.6	4.4
	Tigecycline	≤0.06 to 2	0.125	0.25	98.2	0
	Vancomycin	≤0.12 to 2	1	1	100	0
MRSA (*n* = 411)	Ceftaroline	≤0.25 to 4	0.5	1	97.8	2.2[c]
	Tedizolid	0.125 to 0.5	0.25	0.5	100	0
	Linezolid	0.5 to 4	2	2	100	0
	Erythromycin	≤0.5 to >16	>16	>16	14.1	83.5
	Clindamycin	≤0.5 to >16	>16	>16	34.3	63.5
	Gentamicin	≤1 to >32	≤1	>32	67.2	31.6
	Levofloxacin	≤0.25 to >32	0.5	>32	59.1	40.1
	Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	0.5	97.6	2.5
	Tigecycline	≤0.06 to 2	0.125	0.5	94.6	0
	Vancomycin	≤0.12 to 2	1	1	100	0
MSSA (*n* = 780)	Ceftaroline	≤0.25 to 1	≤0.25	0.5	100	0
	Tedizolid	0.125 to 0.5	0.25	0.5	100	0
	Linezolid	0.5 to 4	2	2	100	0
	Erythromycin	≤0.5 to >16	>16	>16	41	56.9
	Clindamycin	≤0.5 to >16	≤0.5	32	70.9	27.9
	Gentamicin	≤1 to >32	≤1	16	83.5	14.4
	Levofloxacin	≤0.25 to >32	≤0.25	4	87.6	11.3
	Trimethoprim-sulfamethoxazole	≤0.25 to >8	≤0.25	1	94.6	5.4
	Tigecycline	≤0.06 to 0.5	0.125	0.25	100	0
	Vancomycin	≤0.12 to 2	1	1	100	0
Enterococcus spp. (*n* = 867)	Tedizolid	0.125 to 2	0.5	0.5	96.4	3.6[c]
	Linezolid	≤0.06 to >8	2	2	95.5	3.8
	Ampicillin	≤1 to >64	4	>64	51.6	48.4
	Nitrofurantoin	2 to >256	32	256	54.2	28.4
	Levofloxacin	≤0.25 to >32	32	>32	34.5	62.6
	Erythromycin	≤0.5 to >16	>16	>16	5.2	79.8
	Tigecycline	≤0.06 to 2	0.125	0.25	99.1	0
	Vancomycin	≤0.12 to >8	1	2	97.1	0
E. faecalis (*n* = 417)	Tedizolid	0.125 to 1	0.5	0.5	94.0	6.0[c]
	Linezolid	≤0.06 to 8	2	2	92.1	6.5
	Ampicillin	≤1 to >64	≤1	2	98.1	1.9
	Nitrofurantoin	2 to 128	8	16	98.8	0.5
	Levofloxacin	≤0.25 to >32	2	32	64	34.3
	Erythromycin	≤0.5 to >16	>16	>16	5.3	72.2
	Tigecycline	≤0.06 to 0.25	≤0.06	0.125	100	0
	Vancomycin	≤0.12 to >8	1	2	99.8	0
E. faecium (*n* = 450)	Tedizolid	0.125 to 2	0.5	0.5	98.7	1.3[c]
	Linezolid	0.5 to >8	2	2	98.7	1.3
	Ampicillin	≤1 to >64	>64	>64	8.4	91.6
	Nitrofurantoin	8 to >256	128	256	12.9	54.2
	Levofloxacin	0.5 to >32	>32	>32	7.1	88.9
	Erythromycin	≤0.5 to >16	>16	>16	5.1	86.9
	Tigecycline	≤0.06 to 2	0.125	0.25	98.2	0
	Vancomycin	0.25 to >8	1	2	94.7	0

[a]MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.
[b]Tedizolid breakpoints for *Staphylococcus* spp.: susceptible, ≤0.5 mg/liter; intermediate, 1 mg/liter; resistant, ≥2 mg/liter; for *Enterococcus* spp.: susceptible, ≤0.5 mg/liter. Ceftaroline breakpoints for *S. aureus*: susceptible, ≤1 mg/liter; susceptible-dose dependent, 2 to 4 mg/liter; resistant, ≥8 mg/liter. Linezolid breakpoints for *S. aureus*: susceptible, ≤4 mg/liter; resistant, ≥8 mg/liter; for *Enterococcus* spp.: susceptible, ≤2 mg/liter; intermediate, 4 mg/liter; resistant, ≥8 mg/liter.
[c]Nonsusceptible.

e.g., $MIC_{50/90}$ values of 0.25/0.5 mg/liter against 1,839 strains of MRSA collected from the Asia Pacific region (13). Most (96.4%) of the *Enterococcus* isolates were susceptible to tedizolid, with a modal MIC of 0.5 mg/liter, which was 4- to 8-fold lower than that of linezolid. In this study, we found that 3.6% of *Enterococcus* strains were nonsusceptible

to tedizolid (MIC, 1 to 2 mg/liter), and all of these strains were not susceptible to linezolid (data not shown).

In summary, ceftaroline and tedizolid have demonstrated good activity against clinical isolates of Gram-positive organisms in our surveillance program. Both drugs have shown promise for treatment of Gram-positive pathogens.

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