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Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Resistant Clinical Isolates from the United States 2018-2021

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INTRODUCTION

Taniborbactam is a novel, investigational cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D) [1]. Taniborbactam restores the activity of cefepime against many difficult to treat organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. In this study, we evaluated the activity of cefepime-taniborbactam (FTB) and comparator agents against nonsusceptible (NS)/resistant (R) clinical isolates of Enterobacterales and *P. aeruginosa* from the United States (US) from a 2018-2021 global surveillance study.

METHODS

MICs of cefepime with taniborbactam fixed at 4 µg/mL and comparators were determined using the CLSI reference method [2] against Enterobacterales (n=4,220) and *P. aeruginosa* (n=1,222) from the United States collected in 2018-2021. Quality control (QC) testing was performed each day of testing as specified by the CLSI [2, 3]. Isolates were collected from community and hospital infections from 35 sites. Avibactam was tested at a fixed concentration of 4 µg/mL in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 µg/mL in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 µg/mL in combination with meropenem [3]. CLSI 2023 breakpoints were applied for this analysis, with the EUCAST 2023 meropenem-vaborbactam breakpoint applied against *P. aeruginosa* [3, 4]. Resistant phenotypes were based on CLSI 2023 breakpoints [3]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤16 µg/mL was considered for comparative purposes. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2023 breakpoints.

RESULTS

Figure 1. Distribution of Enterobacterales isolates by species

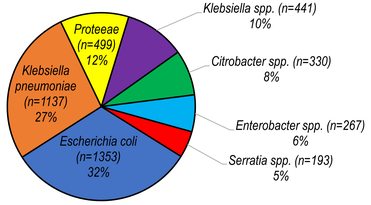
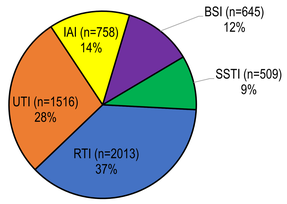


Figure 2. Distribution of isolates by infection sources



BSI, bloodstream infection; IAI, intraabdominal infection; RTI, respiratory tract infection; SSTI, skin/soft tissue infection UTI, urinary tract infection

Table 1. Activity of cefepime-taniborbactam and comparators against Enterobacterales

Resistance Phenotype	N (%)	MIC$_{90}$ (µg/mL)/Percent susceptible					
		FTB[a]	FEP	CZA	CT	MEV	TZP
Enterobacterales	**4,220 (100%)**	**0.12/99.9**	**8/86.9**	**0.5/99.6**	**2/91.8**	**≤0.06/99.8**	**32/89.7**
FEP NS	554 (13.1%)	1/99.3	>16/0	2/97.1	>8/62.8	0.12/98.2	>128/59.6
TZP NS	434 (10.3%)	1/99.1	>16/48.4	2/96.3	>8/30	0.25/97.7	>128/0
MEM NS	83 (2.0%)	4/97.6	>16/7.2	>16/81.9	>8/4.8	8/88.0	>128/4.8
MEV NS	10 (0.2%)	8/90.0	>16/0	>16/20	>8/0	>16/0	>128/0
CZA NS	18 (0.4%)	8/94.4	>16/11.1	>16/0	>8/0	>16/55.6	>128/11.1
MDR	251 (5.9%)	2/98.4	>16/10.0	4/94.0	>8/39.4	1/96.0	>128/35.5

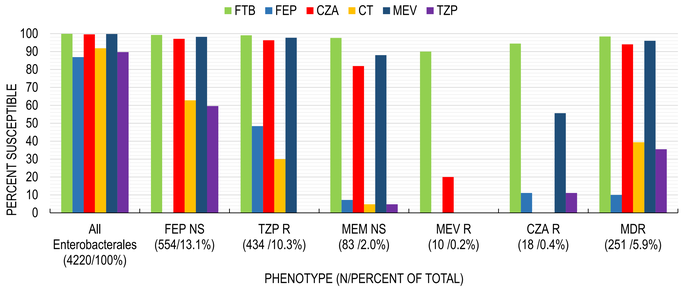
FTB, cefepime with taniborbactam fixed at 4 µg/mL; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant; NS, nonsusceptible; R, resistant.
[a]Corresponds to a provisional susceptible breakpoint of ≤16 µg/mL for comparative purposes only

Table 2. Activity of cefepime-taniborbactam and comparators against *P. aeruginosa*

Resistance Phenotype	N (%)	MIC$_{90}$ (µg/mL)/Percent susceptible					
		FTB[a]	FEP[b]	CZA	CT	MEV	TZP[b]
P. aeruginosa	**1222/100**	**8/97.7**	**32/80.8**	**8/94.6**	**4/92.7**	**8/91.9**	**>128/72.8**
FEP NS	235/19.2	32/88.1	>32/0	>16/74.0	>16/63.8	>16/71.1	>128/9.8
TZP NS	332/27.2	16/92.5	>32/36.1	16/81.0	16/75.3	>16/73.9	>128/0
MEM NS	261/21.4	16/91.2	>32/49.0	>16/79.7	16/76.6	>16/62.1	>128/33.0
MEV Rb	99/8.1	>32/81.8	>32/31.3	>16/62.6	>16/70.7	>16/0	>128/12.1
CZA R	66/5.4	>32/68.2	>32/7.6	>16/0	>16/28.8	>16/43.9	>128/4.5
CT NS	89/7.3	>32/74.2	>32/4.5	>16/47.2	>16/0	>16/67.4	>128/7.9
MDR	164/13.4	32/85.4	>32/18.9	>16/67.1	>16/59.1	>16/61.0	>128/10.4

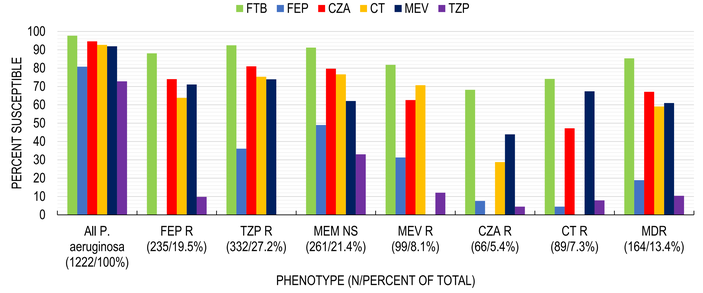
FTB, cefepime with taniborbactam fixed at 4 µg/mL; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant; NS, nonsusceptible; R, resistant.
[a]Corresponds to a provisional susceptible breakpoint of ≤16 µg/mL for comparative purposes only
[b]EUCAST breakpoints (susceptible ≤8 µg/mL/resistant ≥16 µg/mL) applied for *P. aeruginosa*

Fig 3. Antimicrobial susceptibility of Enterobacterales overall and by and resistant subset



FTB, cefepime with taniborbactam fixed at 4 µg/mL; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant; R, resistant; NS, non-susceptible; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤16 µg/mL for comparative purposes

Fig 4. Antimicrobial susceptibility of *P. aeruginosa* overall and by and resistant subsets



FTB, cefepime with taniborbactam fixed at 4 µg/mL; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant; R, resistant; MEV R based on EUCAST 2023 breakpoint; NS, non-susceptible; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤16 µg/mL for comparative purposes

RESULTS SUMMARY

- *E. coli* (32% of total isolates) and *K. pneumoniae* (27% of total isolates) were the most common species of Enterobacterales represented in this surveillance collection (Figure 1).
- Overall, 13.1% and 10.3% of Enterobacterales isolates from the United States were nonsusceptible to cefepime and piperacillin-tazobactam, respectively (Table 1). A total of 5.9% of isolates were MDR, and 2.0% were nonsusceptible to meropenem. *K. pneumoniae* (n=1,137) accounted for 37.2, 31.3, 60.2, and 41.4% of cefepime nonsusceptible, piperacillin-tazobactam nonsusceptible, MDR, and meropenem nonsusceptible isolates among Enterobacterales species within each subset, respectively.
- Cefepime-taniborbactam had potent activity against Enterobacterales overall, with an MIC$_{90}$ value of 0.12 µg/mL and 99.9% inhibited at ≤16 µg/mL (Table 1, Figure 2).
- Cefepime-taniborbactam maintained activity against resistant subsets of Enterobacterales (MIC$_{90}$ range, 1 to 8 µg/mL; 90.0% to 99.3% inhibited at ≤16 µg/mL) including MDR isolates (MIC$_{90}$, 2 µg/mL; 98.4% inhibited at ≤16 µg/mL) (Table 1, Figure 1). Greater than 90% of isolates that were nonsusceptible to ceftazidime-avibactam and/or meropenem-vaborbactam were inhibited at ≤16 µg/mL cefepime-taniborbactam.
- From 19.2% to 27.2% of *P. aeruginosa* isolates were nonsusceptible to cefepime, piperacillin-tazobactam and/or meropenem (Table 2). Between 5.4% and 8.1% of isolates were nonsusceptible/resistant to ceftolozane-tazobactam, ceftazidime-avibactam and/or meropenem-vaborbactam.
- Cefepime-taniborbactam was the most active tested agent against *P. aeruginosa* overall, with an MIC$_{90}$ value of 8 µg/mL and 97.7% inhibited at ≤16 µg/mL (Table 2, Figure 3).
- Percentages of *P. aeruginosa* isolates in the nonsusceptible subsets that were inhibited by ≤16 µg/mL cefepime-taniborbactam ranged from 68.2% for ceftazidime-avibactam resistant isolates to 92.5% for piperacillin-tazobactam nonsusceptible isolates. These compared to 0% to 81.0% susceptible to comparators (Table 2, Figure 3).
- Against MDR *P. aeruginosa* (13.4% of total isolates), cefepime-taniborbactam maintained activity, with 85.4% of isolates inhibited at ≤16 µg/mL, a substantially greater percentage than the most active comparators, ceftazidime-avibactam (67.1% susceptible), meropenem-vaborbactam (61.0% susceptible), and ceftolozane-tazobactam (59.1% susceptible) (Table 2, Figure 3).

CONCLUSIONS

- Cefepime-taniborbactam demonstrated potent *in vitro* activity against recent Enterobacterales and *P. aeruginosa* from the United States, including MDR isolates and isolates nonsusceptible to cefepime, meropenem, piperacillin-tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, and/or meropenem-vaborbactam.
- These data support continued development of cefepime-taniborbactam as a potential treatment option for challenging infections due to resistant Gram-negative pathogens.

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DISCLOSURES

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