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Cefepime-taniborbactam Exhibits Limited Cross-resistance with Ceftazidime-avibactam and Ceftolozane-tazobactam against Carbapenem-nonsusceptible Enterobacterales and Multidrug-resistant *Pseudomonas aeruginosa* from the United States 2018-2022

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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 multidrug resistant (MDR) *Pseudomonas aeruginosa* [2]. In this study we evaluated the activity of cefepime-taniborbactam (FTB) and comparators against clinical isolates of Enterobacterales and *P. aeruginosa* from the US and assessed FTB cross-resistance to ceftazidime-avibactam (CZA) and ceftolozane-tazobactam (CT) in resistant subsets.

METHODS

MICs of cefepime with taniborbactam fixed at 4 µg/mL (FTB) and comparators were determined using the CLSI reference broth microdilution method [3] against Enterobacterales (n=4,932) and *P. aeruginosa* (n=1,508) collected in 2018-2022 in the United States. Quality control (QC) testing was performed each day of testing as specified by the CLSI [3, 4]. Isolates were collected from community and hospital infections from 42 sites. Isolates were sourced primarily from (n/percent of total): respiratory tract (2,503/38.9%), urinary tract (1,850/28.7%), intra-abdominal (817/12.7%), blood (760/11.8%), and skin and soft tissue (509/7.9%). The distribution of Enterobacterales species is shown in Figure 1. 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 [4]. Resistant phenotypes were based on 2024 CLSI breakpoints [4]. As cefepime-taniborbactam breakpoints have not yet been established, a provisional susceptible breakpoint of ≤16 µg/mL was considered for comparative purposes [2]. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2024 breakpoints.

RESULTS

Figure 1. Distribution of 4,932 Enterobacterales isolates by species

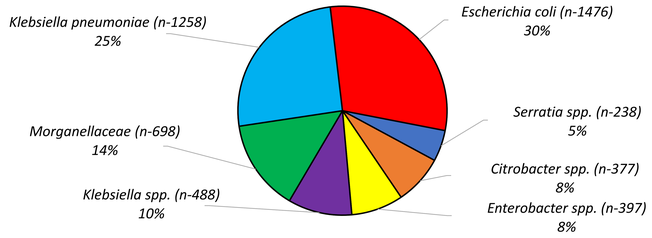
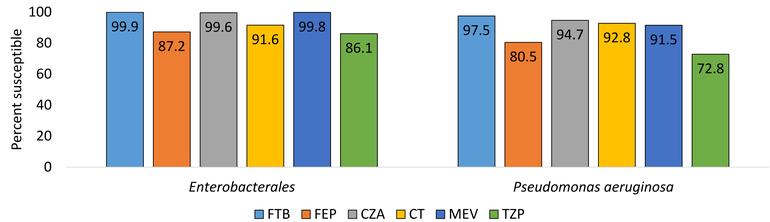
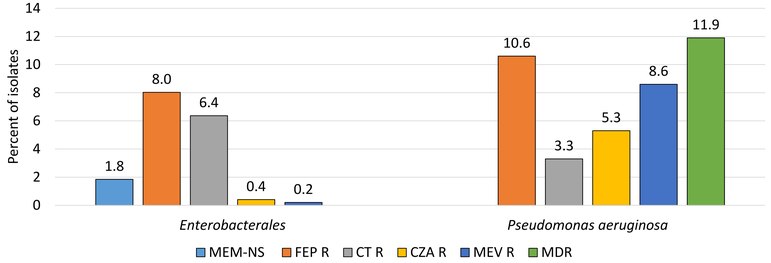


Figure 2. Antimicrobial susceptibility of US isolates of Enterobacterales and *P. aeruginosa*



FTB, cefepime-taniborbactam; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam
Percent susceptible for FTB is based on a provisional susceptible breakpoint of ≤16 µg/mL, for comparative purposes only

Figure 3. Prevalence of resistant phenotypes among US isolates of Enterobacterales and *P. aeruginosa*



MEM-NS, meropenem-nonsusceptible; FEP R, cefepime resistant; CT R, ceftolozane-tazobactam resistant; CZA R, ceftazidime-avibactam resistant; MEV R, meropenem-vaborbactam resistant; MDR, multidrug-resistant. For MEV against *P. aeruginosa*, resistance is based on EUCAST 2024 breakpoint.

Table 1. Antimicrobial susceptibility among US isolates of Enterobacterales and *P. aeruginosa*, including resistant subsets

Organism Group / Resistant Subset	N (% of total)	Percent Susceptible					
		FTB[a]	FEP	CZA	CT	MEV[b]	TZP
All Enterobacterales	4,932 (100%)	99.9	87.2	99.6	91.6	99.8	86.1
MEM-nonsusceptible	91 (1.8%)	96.7	6.5	80.4	4.3	87.0	4.3
FEP-resistant	396 (8.0%)	98.7	0	96.5	60.9	97.0	45.7
CT-resistant	314 (6.4%)	98.7	36.0	93.6	0	96.2	3.5
CZA-resistant	20 (0.4%)	90.0	10.0	0	0	50.0	10.0
MEV-resistant	10 (0.2%)	90.0	0	20.0	0	0	0
All *P. aeruginosa*	1,508 (100%)	97.5	80.5	94.7	92.8	91.5	72.8
FEP-resistant	160 (10.6%)	76.9	0	59.4	40.6	63.1	3.1
CT-resistant	50 (3.3%)	54.0	2.0	38.0	0	56.0	6.0
CZA-resistant	80 (5.3%)	65.0	6.3	0	28.7	42.5	5.0
MEV-resistant	129 (8.6%)	80.6	31.8	64.3	69.8	0	15.5
CRPA	386 (25.6%)	92.0	56.0	83.9	80.3	66.6	45.9
MDR	180 (11.9%)	82.2	10.0	63.9	56.1	55.6	1.7

FTB, cefepime-taniborbactam; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MEM, meropenem; CRPA, carbapenem-resistant *P. aeruginosa*; MDR, multidrug-resistant
[a]"Percent Susceptible" is based on a provisional susceptible breakpoint of ≤16 µg/mL, for comparative purposes only.
[b]For MEV against *P. aeruginosa*, "Percent Susceptible" is based on EUCAST 2024 breakpoint.

Table 2. *In vitro* activity of (A) cefepime-taniborbactam and ceftazidime-avibactam against meropenem-nonsusceptible Enterobacterales, (B) cefepime-taniborbactam and ceftolozane-tazobactam against carbapenem-nonsusceptible *P. aeruginosa*, and (C) cefepime-taniborbactam and ceftolozane-tazobactam against MDR *P. aeruginosa*

A. Meropenem-nonsusceptible Enterobacterales

		Cefepime-taniborbactam, No. (%)		No. of isolates (%)
		Susceptible	Nonsusceptible	
Ceftazidime-avibactam	Susceptible	73 (80.2)	1 (1.1)	74 (81.3)
	Nonsusceptible	15 (16.5)	2 (2.2)	17 (18.7)
No. of isolates (% of total)		88 (96.7)	3 (3.3)	91 (100)

Percent susceptible/nonsusceptible based on total number of isolates (n=91)

B. Carbapenem-nonsusceptible *P. aeruginosa*

		Cefepime-taniborbactam, No. (%)		No. of isolates (%)
		Susceptible	Nonsusceptible	
Ceftolozane-tazobactam	Susceptible	306 (79.3)	4 (1.0)	310 (80.3)
	Nonsusceptible	49 (12.7)	27 (7.0)	76 (19.7)
No. of isolates (% of total)		355 (92.0)	31 (8.0)	386 (100)

Percent susceptible/nonsusceptible based on total number of isolates (n=386)

C. MDR *P. aeruginosa*

		Cefepime-taniborbactam, No. (%)		No. of isolates (%)
		Susceptible	Nonsusceptible	
Ceftolozane-tazobactam	Susceptible	98 (54.4)	3 (1.7)	101 (56.1)
	Nonsusceptible	50 (27.8)	29 (16.1)	79 (43.9)
No. of isolates (% of total)		148 (82.2)	32 (17.8)	180 (100)

Percent susceptible/nonsusceptible based on total number of isolates (n=180)

RESULTS SUMMARY

- Among Enterobacterales, 1.8% of isolates were nonsusceptible to meropenem (MEM; Table 1). FTB was the most active agent, inhibiting 96.7% of MEM-nonsusceptible Enterobacterales isolates at ≤16 µg/mL whereas 80.4% were susceptible to CZA and 87.0% were susceptible to meropenem-vaborbactam (MEV).
- Among *P. aeruginosa*, 11.9% of isolates were MDR (Table 1). FTB was the most active agent, inhibiting 82.2% of MDR *P. aeruginosa* isolates at ≤16 µg/mL whereas 56.1% were susceptible to CT and 63.9% were susceptible to CZA (Table 1).
- Among MEM-nonsusceptible Enterobacterales (n=91), 80.2% were susceptible to both FTB and CZA, 16.5% were susceptible to FTB but not to CZA, one isolate (1.1%), was susceptible to CZA but not to FTB, and two isolates (2.2%) were nonsusceptible to both agents (Table 2A).
- Analyzing cross-resistance among carbapenem-nonsusceptible *P. aeruginosa* isolates (n=386), 79.3% were susceptible to both CT and FTB, 12.7% were susceptible to FTB but not to CT, four isolates (1.0%) were susceptible to CT but not to FTB , and 7.0% were nonsusceptible to both agents (Table 2B).
- Among MDR *P. aeruginosa* (n=180), 54.4% were susceptible to both FTB and CT, 27.8% were susceptible to FTB but not to CT, three isolates (1.7%) were susceptible to CT but not to FTB, and 16.1% were nonsusceptible to both agents (Table 2C).

CONCLUSIONS

FTB was active *in vitro* against recent clinical isolates of Enterobacterales and *P. aeruginosa* from the US including most isolates resistant to CZA and CT in key resistant subsets. These data support continued development of FTB as a potential treatment option for patients with challenging infections due to carbapenem-resistant Enterobacterales and carbapenem-resistant and MDR *P. aeruginosa*.

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DISCLOSURES

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