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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 Europe 2018-2023

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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 Europe 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 mg/L (FTB) and comparators were determined using the ISO 20776-1:2019 reference method [3] against Enterobacterales (n=9,984) and *P. aeruginosa* (n=4,134) collected in 26 European countries in 2018-2023 (Figure 1). The distribution of Enterobacterales species is shown in Figure 2. Quality control (QC) testing was performed each day of testing as specified by the CLSI [4]. Isolates were collected from community and hospital infections and were sourced from (n/percent of total): respiratory tract (6,682/47.3%), urinary tract (3,103/22.0%), intra-abdominal (2,224/15.9%), blood (1,373/9.7%), skin and soft tissue (714/5.1%), and unknown (2/<0.1). Avibactam was tested at a fixed concentration of 4 mg/L in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 mg/L in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 mg/L in combination with meropenem [5]. Resistant phenotypes were based on 2024 EUCAST breakpoints [5]. As cefepime-taniborbactam breakpoints have not yet been established, a provisional susceptible breakpoint of ≤16 mg/L was considered for comparative purposes [2]. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2024 breakpoints.

RESULTS SUMMARY

- The prevalence of resistant phenotypes is shown in Figure 3.
- Among Enterobacterales, 5.3% of isolates were nonsusceptible to meropenem (MEM; Table 1). FTB was the most active agent, inhibiting 92.0% of MEM-nonsusceptible Enterobacterales isolates at ≤16 µg/mL whereas 60.6% were susceptible to CZA and 54.1% were susceptible to meropenem-vaborbactam (MEV).
- Among *P. aeruginosa*, 18.8% of isolates were MDR (Table 1). FTB was the most active agent, inhibiting 82.3% of MDR *P. aeruginosa* isolates at ≤16 µg/mL whereas 31.7% were susceptible to CT and 42.4% were susceptible to CZA (Table 1).
- Among MEM-nonsusceptible Enterobacterales (n=525), 59.6% were susceptible to both FTB and CZA, 32.4% were susceptible to FTB but not to CZA, five isolates (0.9%), were susceptible to CZA but not to FTB, and 37 isolates (7.0%) were nonsusceptible to both agents (Table 2A).
- Analyzing cross-resistance among carbapenem-resistant *P. aeruginosa* isolates (n=1,496), 63.4% were susceptible to both CT and FTB, 27.5% were susceptible to FTB but not to CT, 12 isolates (0.8%) were susceptible to CT but not to FTB , and 8.4% were nonsusceptible to both agents (Table 2B).
- Among MDR *P. aeruginosa* (n=776), 30.4% were susceptible to both FTB and CT, 51.9% were susceptible to FTB but not to CT, 10 isolates (1.3%) were susceptible to CT but not to FTB, and 16.4% were nonsusceptible to both agents (Table 2C).

CONCLUSIONS

FTB was active *in vitro* against recent clinical isolates of Enterobacterales and *P. aeruginosa* from Europe 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, carbapenem-resistant *P. aeruginosa*, and MDR *P. aeruginosa*.

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DISCLOSURES

This project has been funded in whole or in part with federal funds from the Department of Health and Human Services; Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract numbers HHSO100201900007C and 75A50122C00080.

RESULTS

Figure 1. Distribution of 14,118 European isolates by country

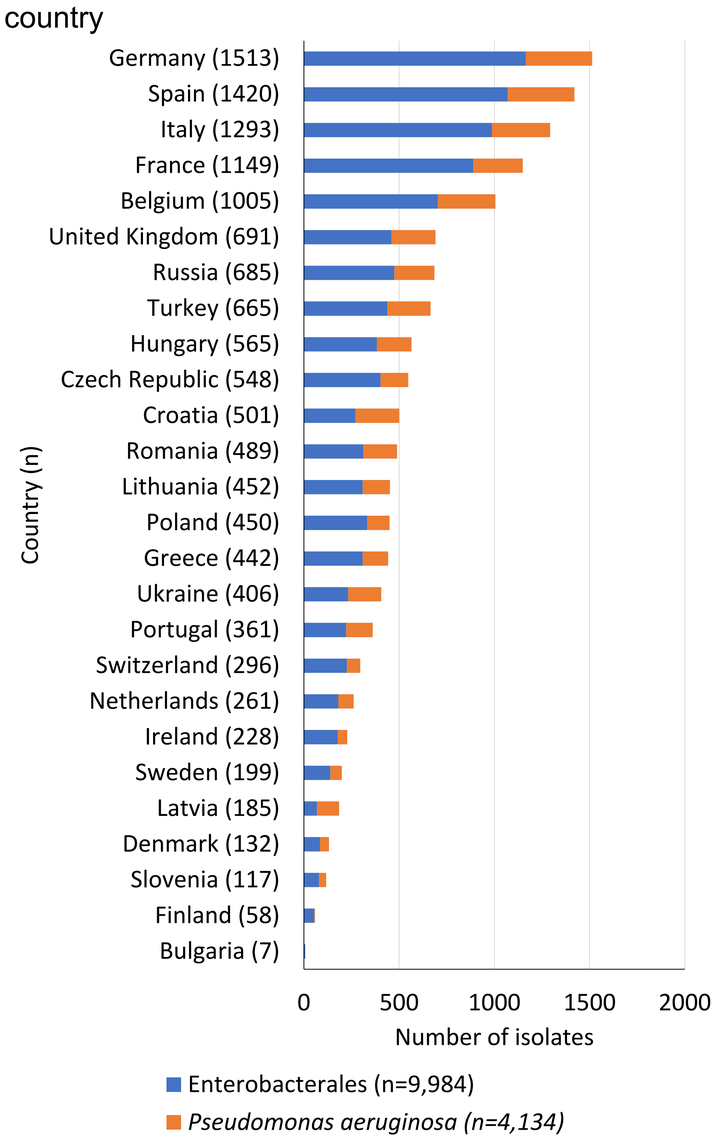
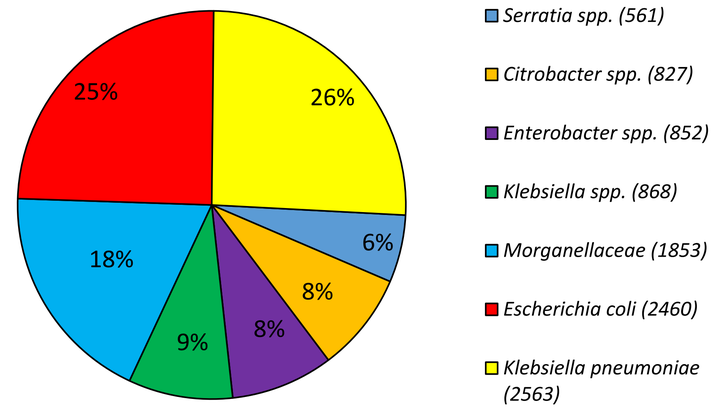
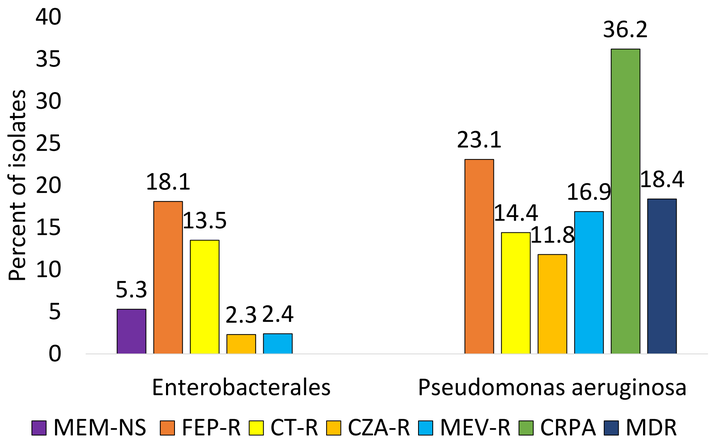


Figure 2. Distribution of 9,984 European Enterobacterales isolates by species (n)



Klebsiella spp. includes species other than *pneumoniae*

Figure 3. Prevalence of resistant phenotypes among European 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; CRPA, carbapenem-resistant *P. aeruginosa*; MDR, multidrug-resistant

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

Organism Group / Resistant Subset	N (% of total)	Percent Susceptible					
		FTB[a]	FEP[b]	CZA	CT	MEV	TZP[b]
All Enterobacterales	9984 (100)	99.6	77.8	97.7	86.5	97.6	78.9
MEM-nonsusceptible	525 (5.3)	92.0	1.9	60.6	1.5	54.1	0.2
FEP-R	1810 (18.1)	97.6	0	87.3	48.4	87	34.8
CT-R	1351 (13.5)	96.9	18.1	82.9	0	82.5	8.1
CZA-R	231 (2.3)	84.0	0.4	0	0	30.3	0.4
MEV-R	241 (2.4)	83.8	0.8	33.2	1.7	0	0
All *P. aeruginosa*	4134 (100)	96.6	76.9	88.2	85.6	83.1	68.7
FEP-R	956 (23.1)	85.5	0	50.7	44.9	44.4	6.1
CT-R	594 (14.4)	78.6	11.3	26.4	0	26.1	6.6
CZA-R	487 (11.8)	73.3	3.3	0	10.3	18.7	4.5
MEV-R	699 (16.9)	81.0	23.9	43.3	37.2	0	10.4
CRPA	1496 (36.2)	90.8	49.6	69.9	64.2	53.3	38.8
MDR	776 (18.8)	82.3	0	42.4	31.7	32.2	2.1

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 breakpoint of ≤16 mg/L, for comparative purposes only.
b"Percent susceptible" corresponds to "Percent susceptible, increased exposure".

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

A. Meropenem-nonsusceptible[a] Enterobacterales

		Cefepime-taniborbactam, No. (%)		No. of isolates
		Susceptible	Nonsusceptible	
Ceftazidime-avibactam	Susceptible	313 (59.6)	5 (0.9)	318
	Nonsusceptible	170 (32.4)	37 (7.0)	207
No. of isolates		483	42	525

Percent susceptible/nonsusceptible based on total number of isolates (n=525)
[a]Meropenem MIC ≥4 mg/L
[b]Based on a provisional susceptible breakpoint of ≤16 mg/L, for comparative purposes only.

B. Carbapenem-resistant[a] *P. aeruginosa*

		Cefepime-taniborbactam, No. (%)		No. of isolates
		Susceptible[b]	Nonsusceptible	
Ceftolozane-tazobactam	Susceptible	948 (63.4)	12 (0.8)	960
	Nonsusceptible	411 (27.5)	125 (8.4)	536
No. of isolates		1359	137	1496

Percent susceptible/nonsusceptible based on total number of isolates (n=1,496)
[A]Meropenem MIC >8 mg/L and/or imipenem MIC >4 mg/L
[b]Based on a provisional susceptible breakpoint of ≤16 mg/L, for comparative purposes only.

C. MDR[a] *P. aeruginosa*

		Cefepime-taniborbactam, No. (%)		No. of isolates
		Susceptible[b]	Nonsusceptible	
Ceftolozane-tazobactam	Susceptible	236 (30.4)	10 (1.3)	246
	Nonsusceptible	403 (51.9)	127 (16.4)	530
No. of isolates		639	137	776

Percent susceptible/nonsusceptible based on total number of isolates (n=776)
[a]Resistant to at least one agent from ≥3 drug classes based on EUCAST 2024 breakpoints
[b]Based on a provisional susceptible breakpoint of ≤16 mg/L, for comparative purposes only.

Presented at ESCMID Global 2025 on April 11 - 15, 2025 in Vienna, Austria