P-1514

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

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

M. Hackel[1], M. Wise[1], G. Moeck[2], D. Sahm[1]

[1]IHMA, Inc., Schaumburg, IL, USA; [2]Venatorx Pharmaceuticals, Inc., Malvern, PA, USA

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

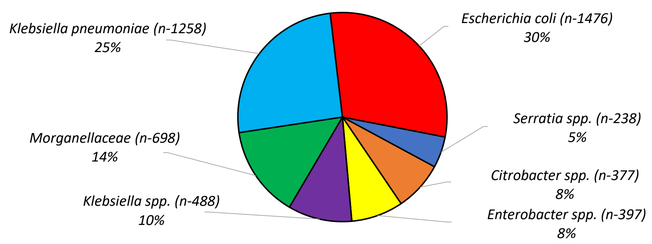
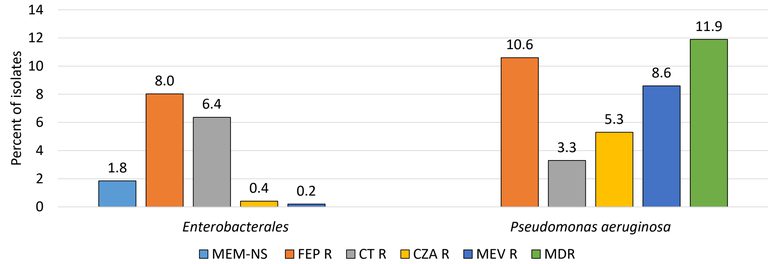


Figure 3. Prevalence of resistant phenotypes among US isolates of Enterobacterales and *P. aeruginosa*



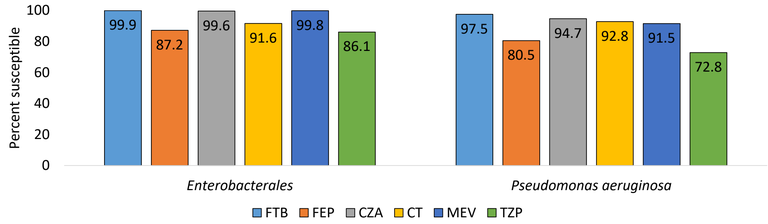
MEM-NS, meropenem-nonsusceptible; FEP R, cefepime resistant; CT R, ceftolozane-tazobactam resistant; CZA R, ceftazidime-avibactam resistant; MEV R, meropenem-vaborbactam resistant; MDR, multidrug-resistant. For MEV against *P. aeruginosa*, resistance is based on EUCAST 2024 breakpoint.

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.

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

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. (%) Susceptible	Nonsusceptible	No. of isolates (%)
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. (%) Susceptible	Nonsusceptible	No. of isolates (%)
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. (%) Susceptible	Nonsusceptible	No. of isolates (%)
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*.

REFERENCES

1. Hamrick JC, Docquier J, Uehara T, Myers CL, Six DA, Chatwin CL, John KJ, Vernacchio SF, Cusick SM, Trout REL, Pozzi C, De Luca F, Benvenuti M, Mangani S, Liu B, Jackson RW, Moeck G, Xerri L, Burns CJ, Pevear DC, Daigle DM. 2020. *VNRX-5133 (Taniborbactam), a Broad-Spectrum Inhibitor of Serine- and Metallo-β-Lactamases, Restores Activity of Cefepime in Enterobacterales and Pseudomonas aeruginosa*. Antimicrob Agents Chemother 64:10.1128/aac.01963-19.https://doi.org/10.1128/aac.01963-19.
2. Karlowsky JA, Hackel MA, Wise MG, Six DA, Uehara T, Daigle DM, Cusick SM, Pevear DC, Moeck G, Sahm DF. 2023. *In Vitro Activity of Cefepime-Taniborbactam and Comparators against Clinical Isolates of Gram-Negative Bacilli from 2018 to 2020: Results from the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) Program*. Antimicrob Agents Chemother 67:e01281-22.
3. Clinical and Laboratory Standards Institute. 2024. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Twelfth Edition*. CLSI document M07-A12 Wayne, PA.
4. Clinical and Laboratory Standards Institute. 2024. *Performance Standards for Antimicrobial Susceptibility Testing; Thirty-fourth Informational Supplement*. CLSI Document M100 2024. Wayne, PA.

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.

Presented at IDWeek 2024, October 16-19, 2024 in Los Angeles, CA