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Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Clinical Isolates of Enterobacterales from 2018-2020 Global Surveillance

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INTRODUCTION

Taniborbactam, (formerly VNRX-5133), is a novel 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 greatly enhances 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 *in vitro* activity of the investigational combination cefepime-taniborbactam and comparator agents against recent clinical isolates of Enterobacterales collected during 2018-2020 surveillance.

METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined following CLSI M07-A11 guidelines [2] against 13,730 Enterobacterales collected globally (Figure 1, Figure 2). Quality control (QC) testing was performed each day of testing as specified by the CLSI [2]. Isolates were from community and hospital infections collected from 266 sites in 56 countries from 2018 to 2020. Isolates were sourced from (n/percent of total): respiratory tract infections (4,550/33.1%), urinary tract infections (3,241/23.6%), intraabdominal infections (2,309/16.8%), bloodstream infections (2,346/17.7%), skin/soft tissue infections (1,192/8.7%), and unknown (2/<0.1%). 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. Resistant phenotypes were based on 2021 CLSI breakpoints [3]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤8 µg/mL was considered for comparative purposes. A set of 1178 Enterobacterales with meropenem MIC ≥4 µg/mL (n=573) or with cefepime/ceftazidime MIC ≥2 µg/mL (n=605) was evaluated for the presence of MBL, KPC, ESBL, and OXA-48 group genes via PCR and Sanger sequencing. Seventy-four isolates with cefepime-taniborbactam MIC values of ≥16 µg/mL were interrogated by whole genome sequencing (WGS).

RESULTS

Figure 1. Distribution of 13,730 Enterobacterales isolates by species

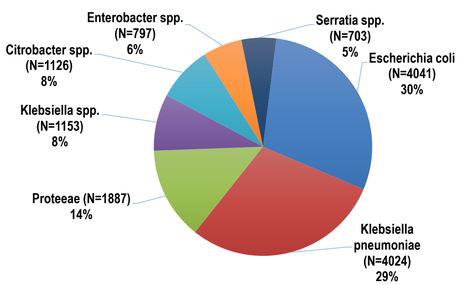
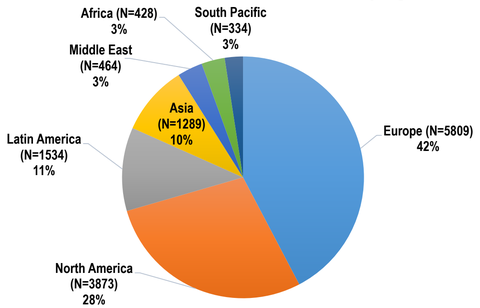


Figure 2. Distribution of 13,730 Enterobacterales isolates by region



Escherichia coli (n=4041), *Klebsiella pneumoniae* (n=4024), *Klebsiella* spp. consist of (n): *K. oxytoca* (759); *K. aerogenes* (390); *K. variicola* (4), Proteeae consist of (n): *Morganella morganii* (389); *Proteus mirabilis* (758); *P. vulgaris* (358); *Providencia alcalifaciens* (3); *P. rettgeri* (164); *P. stuartii* (213); *Providencia* sp. (2), *Serratia* spp. consist of (n): *S. fonticola* (1); *S. liquefaciens* (58); *S. marcescens* (530); *S. odorifera* (2); *S. rubidaea* (5); *S. ureilytica* (24); *Serratia* sp. (83), *Citrobacter* spp. consist of (n): *C. amalonaticus* (7); *C. braakii* (53); *C. farmeri* (4); *C. freundii* (681); *C. koseri* (374); *C. sedlakii* (2); *C. youngae* (1); *Citrobacter* sp. (4), *Enterobacter* spp. consist of (n): *E. asburiae* (54); *E. bugandensis* (27); *E. cloacae* (585); *E. cloacae* complex (58); *E. kobei* (17); *E. ludwigii* (8); *E. xiangfangensis* (24); *Enterobacter* sp. (23)

Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against 13,730 Enterobacterales

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Range
All (13,731)	Cefepime-taniborbactam	99.5	--	0.5	0.06	0.25	≤0.008 - > 16
	Cefepime	77.3	5.3	17.4	≤0.25	> 16	≤0.25 - > 16
	Ceftazidime	74.2	2.3	23.4	0.5	> 16	≤0.03 - > 16
	Ceftazidime-avibactam	97.8	--	2.2	≤0.12	0.5	≤0.12 - > 16
	Ceftolozane-tazobactam	87.1	2.4	10.5	0.5	8	≤0.25 - > 8
	Gentamicin	83.8	0.8	15.4	0.5	> 16	≤0.12 - > 16
	Levofloxacin	69.8	4.2	26.0	0.12	> 8	≤0.004 - > 8
	Meropenem	94.8	0.6	4.6	0.03	0.12	≤0.004 - > 64
	Meropenem-vaborbactam	97.4	0.3	2.2	≤0.06	0.12	≤0.06 - > 16
	Piperacillin Tazobactam	84.2	4.9	10.9	≤4	128	≤4 - > 128
Cefepime-NS (3,114)	Cefepime-taniborbactam	97.6	--	2.4	0.12	2	≤0.008 - > 16
	Cefepime	0.0	23.3	76.8	> 16	> 16	4 - > 16
	Ceftazidime	10.2	7.1	82.8	> 16	> 16	0.06 - > 16
	Ceftazidime-avibactam	90.5	--	9.5	0.25	8	≤0.12 - > 16
	Ceftolozane-tazobactam	57.2	5.0	37.8	2	> 8	≤0.25 - > 8
	Gentamicin	47.1	1.9	51.1	16	> 16	≤0.12 - > 16
	Levofloxacin	21.1	8.3	70.6	> 8	> 8	0.015 - > 8
	Meropenem	78.0	2.1	19.9	0.06	32	≤0.004 - > 64
	Meropenem-vaborbactam	88.9	1.5	9.7	≤0.06	8	≤0.06 - > 16
	Piperacillin Tazobactam	54.0	10.7	35.3	16	> 128	≤4 - > 128
Meropenem-NS (721)	Cefepime-taniborbactam	91.1	--	8.9	1	8	0.015 - > 16
	Cefepime	4.9	4.4	90.7	> 16	> 16	≤0.25 - > 16
	Ceftazidime	3.7	1.9	94.3	> 16	> 16	0.06 - > 16
	Ceftazidime-avibactam	62.4	--	37.6	2	> 16	≤0.12 - > 16
	Ceftolozane-tazobactam	2.6	2.1	95.3	> 8	> 8	0.5 - > 8
	Gentamicin	35.9	2.9	61.2	> 16	> 16	≤0.12 - > 16
	Levofloxacin	10.7	6.0	83.4	> 8	> 8	0.03 - > 8
	Meropenem	0.0	11.7	88.4	32	> 64	2 - > 64
	Meropenem-vaborbactam	51.3	6.4	42.3	4	> 16	≤0.06 - > 16
	Piperacillin-tazobactam	1.3	2.8	96.0	> 128	> 128	≤4 - > 128
Piperacillin-tazobactam-NS (2,165)	Cefepime-taniborbactam	96.7	--	3.3	0.25	4	0.015 - > 16
	Cefepime	33.9	9.6	56.6	> 16	> 16	≤0.25 - > 16
	Ceftazidime	19.7	2.2	78.2	> 16	> 16	0.06 - > 16
	Ceftazidime-avibactam	86.8	--	13.2	0.5	> 16	≤0.12 - > 16
	Ceftolozane-tazobactam	27.9	9.6	62.5	> 8	> 8	≤0.25 - > 8
	Gentamicin	57.4	1.9	40.8	1	> 16	≤0.12 - > 16
	Levofloxacin	34.9	6.6	58.5	4	> 8	0.008 - > 8
	Meropenem	67.1	3.5	29.4	0.12	64	≤0.004 - > 64
	Meropenem-vaborbactam	83.8	2.1	14.1	≤0.06	> 16	≤0.06 - > 16
	Piperacillin-tazobactam	0.0	30.8	69.2	> 128	> 128	32 - > 128
ESBL-positive (524)[a]	Cefepime-taniborbactam	99.4	--	0.6	0.12	1	0.015 - > 16
	Cefepime	6.1	20.6	73.3	> 16	> 16	≤0.25 - > 16
	Ceftazidime	10.3	10.9	78.8	> 16	> 16	0.5 - > 16
	Ceftazidime-avibactam	98.5	--	1.5	0.25	1	≤0.12 - > 16
	Ceftolozane-tazobactam	78.8	5.2	16.0	1	> 8	≤0.25 - > 8
	Gentamicin	51.5	1.0	47.5	2	> 16	≤0.12 - > 16
	Levofloxacin	22.1	10.3	67.6	> 8	> 8	0.03 - > 8
	Meropenem	95.0	1.2	3.8	0.03	0.12	≤0.004 - 64
	Meropenem-vaborbactam	99.6	0.2	0.2	≤0.06	0.12	≤0.06 - 16
	Piperacillin-tazobactam	75.8	9.9	14.3	8	> 128	≤4 - > 128
KPC-positive (230)[b]	Cefepime-taniborbactam	100	--	0	1	4	0.015 - 8
	Cefepime	2.2	8.7	89.1	> 16	> 16	0.5 - > 16
	Ceftazidime	1.3	3.9	94.8	> 16	> 16	2 - > 16
	Ceftazidime-avibactam	93.9	--	6.1	2	8	≤0.12 - > 16
	Ceftolozane-tazobactam	0.4	2.6	97.0	> 8	> 8	2 - > 8
	Gentamicin	40.0	2.2	57.8	> 16	> 16	≤0.12 - > 16
	Levofloxacin	10.4	2.6	87.0	> 8	> 8	0.03 - > 8
	Meropenem	1.7	1.7	96.5	32	> 64	0.25 - > 64
	Meropenem-vaborbactam	93.5	4.8	1.7	≤0.06	2	≤0.06 - > 16
	Piperacillin-tazobactam	0.0	2.6	97.4	> 128	> 128	32 - > 128
MBL-positive (229)[c]	Cefepime-taniborbactam	76.0	--	24.0	1.0	> 16	0.03 - > 16
	Cefepime	0.4	0.4	99.1	> 16	> 16	2 - > 16
	Ceftazidime	0	0	100	> 16	> 16	16 - > 16
	Ceftazidime-avibactam	0.9	--	99.1	> 16	> 16	0.25 - > 16
	Ceftolozane-tazobactam	0	0	100	> 8	> 8	> 8 - > 8
	Gentamicin	30.1	6.1	63.8	> 16	> 16	≤0.12 - > 16
	Levofloxacin	10.5	10.5	79.0	> 8	> 8	0.06 - > 8
	Meropenem	0.9	0.0	99.1	64	> 64	0.5 - > 64
	Meropenem-vaborbactam	7.9	7.4	84.7	> 16	> 16	0.5 - > 16
	Piperacillin-tazobactam	0.0	2.2	97.8	> 128	> 128	32 - > 128
OXA-48-positive (165)[b]	Cefepime-taniborbactam	98.2	--	1.8	2	4	0.03 - > 16
	Cefepime	8.5	1.8	89.7	> 16	> 16	≤0.25 - > 16
	Ceftazidime	7.9	1.2	90.9	> 16	> 16	0.5 - > 16
	Ceftazidime-avibactam	95	--	5	1	2	≤0.12 - > 16
	Ceftolozane-tazobactam	3.0	4.2	92.7	> 8	> 8	≤0.25 - > 8
	Gentamicin	24.9	0.0	75.2	> 16	> 16	≤0.12 - > 16
	Levofloxacin	3.6	5.5	90.9	> 8	> 8	0.06 - > 8
	Meropenem	6.7	6.1	87.3	16	64	0.25 - > 64
	Meropenem-vaborbactam	28.5	8.5	63.0	16	> 16	0.25 - > 16
	Piperacillin-tazobactam	0.0	0.6	99.4	> 128	> 128	64 - > 128

Cefepime-taniborbactam, cefepime with taniborbactam fixed at 4 µg/mL; ceftazidime-avibactam, ceftazidime with avibactam fixed at 4 µg/mL; ceftolozane-tazobactam, ceftolozane with tazobactam fixed at 4 µg/mL; meropenem-vaborbactam, meropenem with vaborbactam fixed at 8 µg/mL; piperacillin-tazobactam, piperacillin with tazobactam fixed at 4 µg/mL; NS, nonsusceptible based on 2021 CLSI breakpoints [2]; breakpoint of ≤8 µg/mL has been applied to cefepime-taniborbactam for comparative purposes.
[a]Note organisms could also possess AmpC-type enzymes, or OSBLs, but no carbapenemases
[b]Note organisms could also possess ESBLs, AmpC-type enzymes, or OSBLs, but no other carbapenemases
[c]Includes NDM (n=207) and VIM (n=22). Note organisms could also possess serine carbapenemases, ESBLs, AmpC-type enzymes, or OSBLs

Figure 3. MIC distribution of cefepime-taniborbactam and select comparator agents against 13,730 Enterobacterales

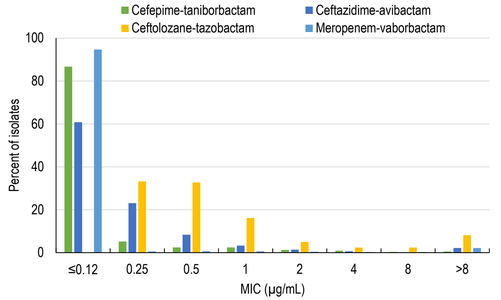
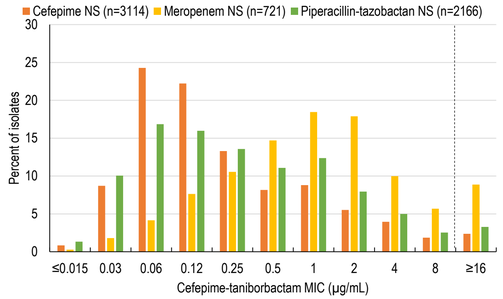
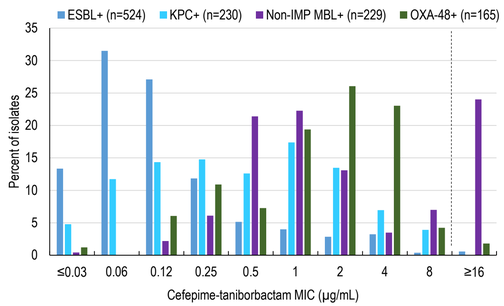


Figure 4. MIC distribution of cefepime-taniborbactam against resistant Enterobacterales



NS, non-susceptible based on 2021 CLSI breakpoints; dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L

Figure 5. MIC distribution of cefepime-taniborbactam against molecularly characterized Enterobacterales



Dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L; MBLs consist of (n): NDM (207), VIM (22)

RESULTS SUMMARY

- Cefepime-taniborbactam showed potent *in vitro* activity against all Enterobacterales, with $MIC_{50/90}$ values of 0.06/0.25 µg/mL and >99% inhibited at the provisional susceptible breakpoint of ≤8 µg/mL (Table 1, Figure 3).
- Cefepime-taniborbactam activity was maintained against resistant subsets of Enterobacterales, with MIC_{90} values of 2 µg/mL against cefepime-non-susceptible, 8 µg/mL against meropenem-non-susceptible and 4 µg/mL against piperacillin-tazobactam-non-susceptible isolates (Table 1, Figure 4).
- Cefepime-taniborbactam maintained activity against ESBL-, KPC-, and OXA-48 group-, harboring isolates with MIC_{90} values of 1 µg/mL, 2 µg/mL, 4 µg/mL, respectively; 98.2% to 100% of MIC values of ≤8 µg/mL) (Table 1, Figure 5).
- Cefepime-taniborbactam inhibited 76.0% of isolates expressing NDM (n=207) or VIM (n=22) MBLs. Whole genome sequence analysis suggested likely explanations for the majority of the non-IMP harboring isolates exhibiting cefepime-taniborbactam MIC values ≥16 µg/mL, including penicillin-binding protein 3 variation observed in 21/24 *E. coli*, and permeability defects and/or possible efflux pump up-regulation in 39/39 (100%) *K. pneumoniae*.

CONCLUSIONS

Taniborbactam significantly restored the in vitro activity of cefepime against Enterobacterales, including isolates nonsusceptible to recently-approved BL/BLI combinations and expressing serine and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram-negative pathogens.

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