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Antimicrobial Activity of Cefepime in Combination with Taniborbactam (formerly VNRX-5133) Against a European 2018-2020 Surveillance Collection of *Pseudomonas aeruginosa*

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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). 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 *P. aeruginosa* collected in Europe during 2018-2020 surveillance.

MATERIALS & METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined following CLSI M07-A11 guidelines [1] against 2,035 *P. aeruginosa* from community and hospital infections collected from 109 sites in 25 countries in Europe in 2018-2020. Isolates were sourced from (n/percent of total): respiratory tract infections (1,097/53.9%), urinary tract infections (285/14.0%), skin/soft tissue infections (259/12.7%), bloodstream infections (226/11.1%), and intraabdominal infections (168/8.3%). 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. Resistant phenotypes were based on 2021 EUCAST breakpoints v11.0 [2]. As FTB breakpoints have not yet been established, the EUCAST cefepime non-resistant breakpoint of ≤8 mg/L [2] was considered for comparative purposes. Quality control testing was performed each day of testing using ranges provided by the CLSI M100 Ed. 31 (2021) [3]. The presence of metallo-β-lactamase genes was assessed via PCR with Sanger sequencing, or whole genome sequencing (WGS), for 253 isolates with meropenem MIC ≥8 mg/L and by PCR/Sanger for 44 randomly selected isolates with cefepime or ceftazidime MIC ≥16 mg/L. Fifty isolates exhibiting FTB MIC values ≥16 mg/L were subjected to WGS.

RESULTS

Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against 2,035 *P. aeruginosa* from Europe

Phenotype (n; percent of total)	Antimicrobial	%S	%I*	%R	MIC_{50}	MIC_{90}
All (2,035)	Cefepime-taniborbactam	95.6	--	4.4	2	8
	Cefepime	0.0	79.0	21.0	4	32
	Ceftazidime	0.0	75.8	24.2	4	>32
	Ceftazidime-avibactam	89.9	--	10.1	2	16
	Ceftolozane-tazobactam	88.1	--	11.9	1	8
	Ciprofloxacin	0.0	74.7	25.3	0.12	>4
	Gentamicin	na	na	na	2	>16
	Imipenem	0.0	65.9	34.2	2	>8
	Meropenem	70.8	13.2	16.0	0.5	>8
	Meropenem-vaborbactam	84.7	--	15.3	0.5	16
	Piperacillin-tazobactam	0.0	69.9	30.1	8	128
TZP NS (612; 30.1%)	Cefepime-taniborbactam	87.4	--	12.6	8	16
	Cefepime	0.0	33.7	66.3	16	>32
	Ceftazidime	0.0	25.2	74.8	32	>32
	Ceftazidime-avibactam	68.0	--	32.0	8	>16
	Ceftolozane-tazobactam	63.1	--	36.9	4	>16
	Ciprofloxacin	0.0	42.2	57.8	2	>4
	Gentamicin	na	na	na	4	>16
	Imipenem	0.0	31.4	68.6	>8	>8
	Meropenem	31.7	21.2	47.1	8	>8
	Meropenem-vaborbactam	54.4	--	45.6	8	>16
	Piperacillin-tazobactam	0	0	100	64	>128
MEM NS (595; 29.2%)	Cefepime-taniborbactam	86.6	--	13.5	8	16
	Cefepime	0.0	44.7	55.3	16	>32
	Ceftazidime	0.0	41.3	58.7	16	>32
	Ceftazidime-avibactam	67.9	--	32.1	8	>16
	Ceftolozane-tazobactam	63.0	--	37.0	2	>16
	Ciprofloxacin	0.0	40.3	59.7	4	>4
	Gentamicin	na	na	na	4	>16
	Imipenem	0.0	5.4	94.6	>8	>8
	Meropenem	0.0	45.2	54.8	>8	>8
	Meropenem-vaborbactam	47.7	--	52.3	16	>16
	Piperacillin-tazobactam	0.0	29.8	70.3	64	>128
FEP R (428; 21.0%)	Cefepime-taniborbactam	79.4	--	20.6	8	16
	Cefepime	0	0	100	32	>32
	Ceftazidime	0.0	11.0	89.0	>32	>32
	Ceftazidime-avibactam	54.2	--	45.8	8	>16
	Ceftolozane-tazobactam	50.5	--	49.5	4	>16
	Ciprofloxacin	0.0	32.9	67.1	>4	>4
	Gentamicin	na	na	na	16	>16
	Imipenem	0.0	22.9	77.1	>8	>8
	Meropenem	23.1	23.4	53.5	>8	>8
	Meropenem-vaborbactam	47.4	--	52.6	16	>16
	Piperacillin-tazobactam	0.0	5.1	94.9	128	>128
MEV NS (311; 15.3%)	Cefepime-taniborbactam	78.8	--	21.2	8	16
	Cefepime	0.0	27.7	72.4	16	>32
	Ceftazidime	0.0	24.8	75.2	32	>32
	Ceftazidime-avibactam	48.6	--	51.5	16	>16
	Ceftolozane-tazobactam	42.8	--	57.2	16	>16
	Ciprofloxacin	0.0	22.2	77.8	>4	>4
	Gentamicin	na	na	na	>16	>16
	Imipenem	0.0	1.9	98.1	>8	>8
	Meropenem	0.0	2.3	97.8	>8	>8
	Meropenem-vaborbactam	0	--	100	>16	>16
	Piperacillin-tazobactam	0.0	10.3	89.7	64	>128
CT NS (243; 11.9%)	Cefepime-taniborbactam	76.5	--	23.5	8	32
	Cefepime	0.0	12.8	87.2	32	>32
	Ceftazidime	0.0	5.4	94.7	>32	>32
	Ceftazidime-avibactam	26.8	--	73.3	>16	>16
	Ceftolozane-tazobactam	0	--	100	>16	>16
	Ciprofloxacin	0.0	13.6	86.4	>4	>4
	Gentamicin	na	na	na	>16	>16
	Imipenem	0.0	9.5	90.5	>8	>8
	Meropenem	9.5	16.5	74.1	>8	>8
	Meropenem-vaborbactam	26.8	--	73.3	>16	>16
	Piperacillin-tazobactam	0.0	7.0	93.0	128	>128
CZA NS (205; 10.1%)	Cefepime-taniborbactam	73.2	--	26.8	8	>32
	Cefepime	0.0	4.4	95.6	32	>32
	Ceftazidime	0.0	1.0	99.0	>32	>32
	Ceftazidime-avibactam	0	--	100	>16	>16
	Ceftolozane-tazobactam	13.2	--	86.8	>16	>16
	Ciprofloxacin	0.0	14.6	85.4	>4	>4
	Gentamicin	na	na	na	>16	>16
	Imipenem	0.0	7.3	92.7	>8	>8
	Meropenem	6.8	15.6	77.6	>8	>8
	Meropenem-vaborbactam	22.0	--	78.1	>16	>16
	Piperacillin-tazobactam	0.0	4.4	95.6	128	>128
VIM-positive (40)	Cefepime-taniborbactam	70.0	--	30.0	8	32
	Cefepime	0.0	2.5	97.5	32	>32
	Ceftazidime	0.0	2.5	97.5	>32	>32
	Ceftazidime-avibactam	5.0	--	95.0	>16	>16
	Ceftolozane-tazobactam	0.0	--	100	>16	>16
	Ciprofloxacin	0.0	2.5	97.5	>4	>4
	Gentamicin	na	na	na	>16	>16
	Imipenem	0.0	0.0	100	>8	>8
	Meropenem	0.0	5.0	95.0	>8	>8
	Meropenem-vaborbactam	5.0	--	95.0	>16	>16
	Piperacillin-tazobactam	0.0	0.0	100	64	>128

*For cefepime (FEP), ceftazidime, imipenem, ciprofloxacin, and piperacillin/tazobactam (TZP) tested, the intermediate category indicates susceptible, increased exposure [2]
Cefepime-taniborbactam, cefepime with taniborbactam fixed at 4 mg/L; piperacillin-tazobactam, piperacillin with tazobactam fixed at 4 mg/L ; ceftazidime-avibactam (CZA), ceftazidime with avibactam fixed at 4 mg/L; ceftolozane-tazobactam (CT), ceftolozane with tazobactam fixed at 4 mg/L; meropenem-vaborbactam (MEV), meropenem with vaborbactam fixed at 8 mg/L; NS, non-susceptible based on 2021 EUCAST breakpoints; breakpoint of ≤8 mg/L has been applied to cefepime-taniborbactam for comparative purposes; $MIC_{50/90}$ in mg/L; --, no breakpoint available

Figure 1. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 2,035 *Pseudomonas aeruginosa* from Europe

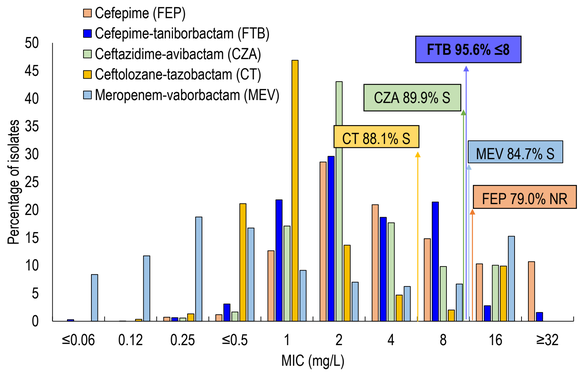


Figure 2. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 428 cefepime-resistant *Pseudomonas aeruginosa* from Europe

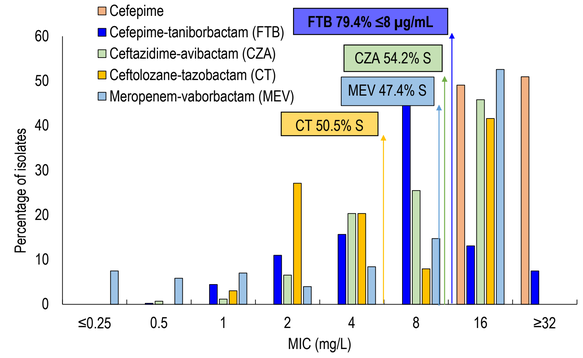


Figure 3. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 595 meropenem-non-susceptible *Pseudomonas aeruginosa* from Europe

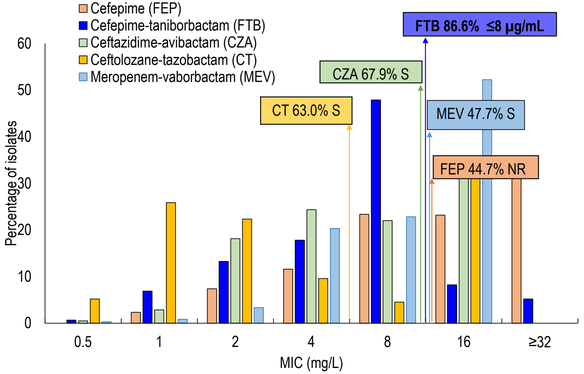
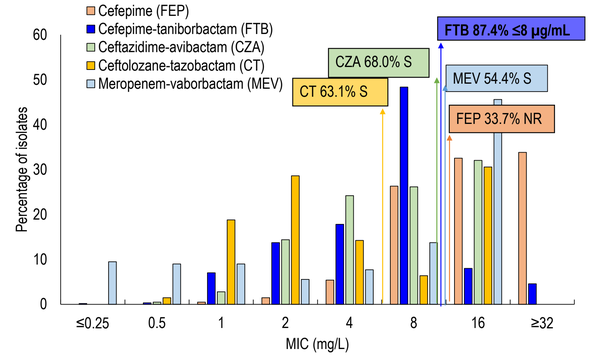


Figure 4. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 612 piperacillin-tazobactam resistant *Pseudomonas aeruginosa* from Europe



RESULTS SUMMARY

- Cefepime-taniborbactam demonstrated potent in vitro activity ($MIC_{50/90}$, 2/8 mg/L; 95.6% inhibited at ≤8 mg/L) against *P. aeruginosa* isolates from Europe (Table 1).
- Provisional susceptibility rates to cefepime-taniborbactam and ceftolozane-tazobactam, respectively, were 73.2% and 13.2% vs ceftazidime-avibactam nonsusceptible (NS) isolates, 76.5% and 0% vs ceftolozane-tazobactam NS isolates, 78.8% and 42.8% vs meropenem-vaborbactam NS isolates, and 87.4% and 63.1% vs piperacillin-tazobactam resistant (R) isolates (Table 1).
- Against 40 VIM-harboring *P. aeruginosa*, cefepime-taniborbactam was more active than any comparator, with 70.0% of the isolates inhibited at ≤8 mg/L (Table 1).
- WGS analysis suggested possible explanations for the majority of the 50 isolates exhibiting cefepime-taniborbactam MIC values ≥16 mg/L including the presence of IMP-type enzymes that are outside the inhibitory spectrum of taniborbactam (n=6), as well as non-transferable mechanisms including disruptions of negative regulators of efflux (n=34) and variation in the PBP3-coding gene (n=9) implicated in elevated resistance to cephalosporins and aztreonam. Several isolates possessed more than one of these putative resistance mechanisms.

CONCLUSIONS

- Cefepime in combination with taniborbactam demonstrated potent *in vitro* activity against *P. aeruginosa* from Europe with different phenotypic resistance profiles, including nonsusceptibility to cefepime, meropenem, and piperacillin/tazobactam, and to the recently introduced protected β-lactam/β-lactamase inhibitors ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam.
- These findings support the continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram negative pathogens.

REFERENCES

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