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Antimicrobial Activity of Cefepime in Combination with Taniborbactam (formerly VNRX-5133) against a European 2018-2019 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 2018-2019 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 1,166 *P. aeruginosa* from community and hospital infections collected from 86 sites in 23 countries in Europe in 2018-2019. Isolates were sourced from (n/percent of total): respiratory tract infections (688/59.0%), urinary tract infections (195/16.7%), intraabdominal infections (92/7.9%), skin/soft tissue infections (104/8.9%), and bloodstream infections (87/7.5%). 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 2020 EUCAST breakpoints v10.0 [2]. As cefepime-taniborbactam breakpoints have not yet been established, the EUCAST cefepime non-resistant breakpoint of ≤8 mg/L [2] was considered for comparative purposes. Quality cotrol testing was performed each day of testing using ranges provided by the CLSI M100 Ed. 30 (2020) [3]. The presence of metallo-β-lactamase genes was assessed via PCR and Sanger sequencing for 95 randomly selected isolates with meropenem MIC ≥8 mg/L and 45 isolates with cefepime or ceftazidime MIC ≥16 mg/L, and via WGS for 18 isolates exhibiting cefepime-taniborbactam MIC values ≥16 mg/L.

RESULTS

Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against 1,166 *Pseudomonas aeruginosa* from Europe

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}
All (1,166)	Cefepime-taniborbactam	95.4	--	4.6	2	8
	Cefepime	80.9	--	19.1	4	16
	Ceftazidime	76.4	--	23.6	4	>32
	Ceftazidime-avibactam	90.7	--	9.3	2	8
	Ceftolozane-tazobactam	89.4	--	10.6	1	8
	Ciprofloxacin	74.0	--	26.0	0.25	>4
	Gentamicin	--	--	--	2	>16
	Imipenem	64.6	--	35.4	4	>8
	Meropenem	71.0	14.1	14.9	0.5	>8
	Meropenem-vaborbactam	86.2	--	13.8	0.5	16
	Piperacillin-tazobactam	71.5	--	28.5	8	128
Cefepime NS (223)	Cefepime-taniborbactam	80.3	--	19.7	8	16
	Cefepime	0	--	100	16	>32
	Ceftazidime	11.2	--	88.8	>32	>32
	Ceftazidime-avibactam	54.3	--	45.7	8	>16
	Ceftolozane-tazobactam	51.6	--	48.4	4	>16
	Ciprofloxacin	31.8	--	68.2	>4	>4
	Gentamicin	--	--	--	8	>16
	Imipenem	23.8	--	76.2	>8	>8
	Meropenem	23.8	25.6	50.7	>8	>8
	Meropenem-vaborbactam	50.7	--	49.3	8	>16
	Piperacillin-tazobactam	5.4	--	94.6	128	>128
Meropenem NS (338)	Cefepime-taniborbactam	86.7	--	13.3	8	16
	Cefepime	49.7	--	50.3	16	>32
	Ceftazidime	44.4	--	55.6	16	>32
	Ceftazidime-avibactam	69.8	--	30.2	8	>16
	Ceftolozane-tazobactam	66.9	--	33.1	2	>16
	Ciprofloxacin	40.2	--	59.8	4	>4
	Gentamicin	--	--	--	4	>16
	Imipenem	4.7	--	95.3	>8	>8
	Meropenem	0.0	48.5	51.5	>8	>8
	Meropenem-vaborbactam	52.4	--	47.6	8	>16
	Piperacillin-tazobactam	33.4	--	66.6	64	>128
Piperacillin-tazobactam NS (332)	Cefepime-taniborbactam	88.0	--	12.1	8	16
	Cefepime	36.5	--	63.6	16	>32
	Ceftazidime	23.8	--	76.2	32	>32
	Ceftazidime-avibactam	68.7	--	31.3	8	>16
	Ceftolozane-tazobactam	65.4	--	34.6	4	>16
	Ciprofloxacin	41.6	--	58.4	2	>4
	Gentamicin	--	--	--	4	>16
	Imipenem	31.9	--	68.1	>8	>8
	Meropenem	32.2	22.6	45.2	8	>8
	Meropenem-vaborbactam	56.9	--	43.1	8	>16
	Piperacillin-tazobactam	0	--	100	64	>128
Ceftazidime-avibactam NS (108)	Cefepime-taniborbactam	75.0	--	25.0	8	32
	Cefepime	5.6	--	94.4	32	>32
	Ceftazidime	1.9	--	98.2	>32	>32
	Ceftazidime-avibactam	0	--	100	>16	>16
	Ceftolozane-tazobactam	19.4	--	80.6	>16	>16
	Ciprofloxacin	18.5	--	81.5	>4	>4
	Gentamicin	--	--	--	>16	>16
	Imipenem	6.5	--	93.5	>8	>8
	Meropenem	5.6	18.5	75.9	>8	>8
	Meropenem-vaborbactam	24.1	--	75.9	>16	>16
	Piperacillin-tazobactam	3.7	--	96.3	128	>128
Ceftolozane-tazobactam NS (124)	Cefepime-taniborbactam	77.4	--	22.6	8	16
	Cefepime	12.9	--	87.1	32	>32
	Ceftazidime	7.3	--	92.7	>32	>32
	Ceftazidime-avibactam	29.8	--	70.2	>16	>16
	Ceftolozane-tazobactam	0	--	100	>16	>16
	Ciprofloxacin	15.3	--	84.7	>4	>4
	Gentamicin	--	--	--	>16	>16
	Imipenem	9.7	--	90.3	>8	>8
	Meropenem	9.7	21.0	69.4	>8	>8
	Meropenem-vaborbactam	31.5	--	68.6	>16	>16
	Piperacillin-tazobactam	7.26	--	93	128	>128
Meropenem-vaborbactam NS (161)	Cefepime-taniborbactam	78.9	--	21.1	8	16
	Cefepime	31.7	--	68.3	16	>32
	Ceftazidime	24.8	--	75.2	32	>32
	Ceftazidime-avibactam	49.1	--	50.9	16	>16
	Ceftolozane-tazobactam	47.2	--	52.8	8	>16
	Ciprofloxacin	20.5	--	79.5	>4	>4
	Gentamicin	--	--	--	>16	>16
	Imipenem	0.6	--	99.4	>8	>8
	Meropenem	0.0	1.2	98.8	>8	>8
	Meropenem-vaborbactam	0	--	100	>16	>16
	Piperacillin-tazobactam	11.2	--	88.8	64	>128
MBL (VIM)+ (8)	Cefepime-taniborbactam	50.0	--	50.0	nc	nc
	Cefepime	0	--	100	nc	nc
	Ceftazidime	0	--	100	nc	nc
	Ceftazidime-avibactam	0	--	100	nc	nc
	Ceftolozane-tazobactam	0	--	100	nc	nc
	Ciprofloxacin	12.5	--	87.5	nc	nc
	Gentamicin	--	--	--	nc	nc
	Imipenem	0	--	100	nc	nc
	Meropenem	0.0	12.5	87.5	nc	nc
	Meropenem-vaborbactam	12.5	--	87.5	nc	nc

*For cefepime, ceftazidime, imipenem, meropenem and piperacillin/tazobactam tested, the susceptible category includes 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, ceftazidime with avibactam fixed at 4 mg/L; ceftolozane-tazobactam, ceftolozane with tazobactam fixed at 4 mg/L; meropenem-vaborbactam, meropenem with vaborbactam fixed at 8 mg/L; NS, non-susceptible based on 2020 EUCAST breakpoints; MBL+, metallo-β-lactamase gene present (8 VIM; 2 isolates expressing IMP were encountered, both of which had cefepime-taniborbactam MICs of ≥16 mg/L); breakpoint of ≤8 mg/L has been applied to cefepime-taniborbactam for comparative purposes; $MIC_{50/90}$ in mg/L; --, no breakpoint available; nc, $MIC_{50/90}$ not calculated for n<15

Figure 1. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 1,166 *Pseudomonas aeruginosa* from Europe

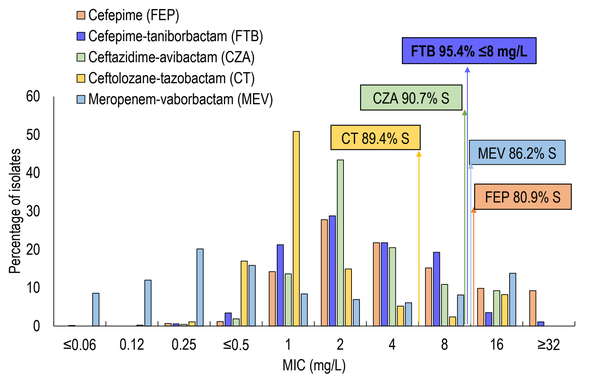


Figure 2. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 223 cefepime-non-susceptible *Pseudomonas aeruginosa* from Europe

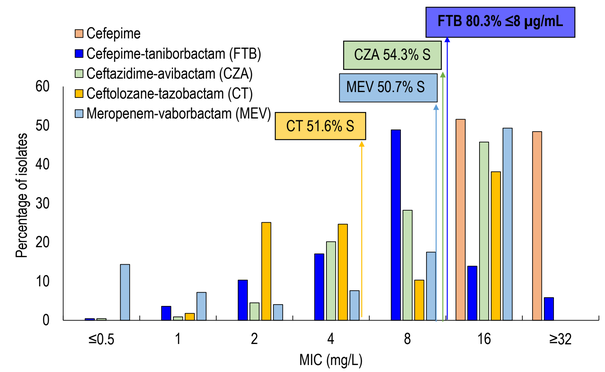


Figure 3. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 338 meropenem-non-susceptible *Pseudomonas aeruginosa* from Europe

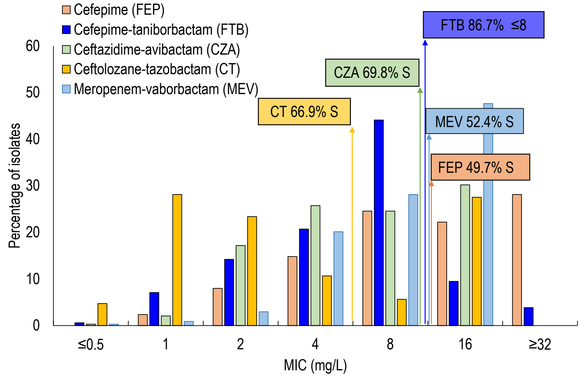
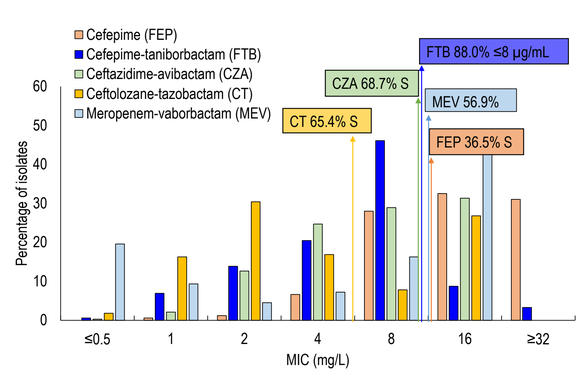


Figure 4. MIC distribution of cefepime, cefepime-taniborbactam, and comparators against 332 piperacillin-tazobactam non-susceptible *Pseudomonas aeruginosa* from Europe



RESULTS SUMMARY

- Cefepime-taniborbactam demonstrated potent *in vitro* activity ($MIC_{50/90}$, 2/8 mg/L; 95.4% inhibited at ≤8 mg/L) against *P. aeruginosa* isolates from Europe (Table 1).
- Provisional susceptibility rates to cefepime-taniborbactam and ceftolozane-tazobactam, respectively, were 75.0% and 19.4% vs ceftazidime-avibactam nonsusceptible (NS) isolates, 77.4% and 0% vs ceftolozane-tazobactam NS isolates, 78.9% and 47.2% vs meropenem-vaborbactam NS isolates, and 88.0% and 65.4% vs piperacillin-tazobactam NS isolates (Table 1).
- Cefepime-taniborbactam was the only agent inhibiting 50% and 100% of the (non-IMP) MBL producers at ≤8 mg/L and ≤16 mg/L, respectively (Table 1).
- WGS analysis suggested possible explanations for most of the isolates exhibiting cefepime-taniborbactam MIC values ≥16 mg/L (18/19 isolates, 94.7%), including the presence of IMP-type enzymes that are outside the inhibitory spectrum of taniborbactam; and non-transferable mechanisms including disruptions of negative regulators of efflux and variation in PBP3-coding gene implicated in elevated resistance to cephalosporins and aztreonam.

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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