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Antimicrobial Activity of Cefepime in Combination with VNRX-5133 Against a Global 2018 Surveillance Collection of Clinical Isolates

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INTRODUCTION

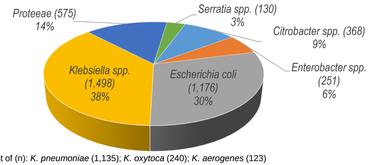
VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D). VNRX-5133 greatly enhances the activity of cefepime against many difficult to treat organisms, including cephalosporin and carbapenem resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*. In this study, the activity of cefepime in combination with VNRX-5133 and comparator agents was evaluated against recent clinical isolates collected in a 2018 surveillance study.

MATERIALS & METHODS

MICs of cefepime with VNRX-5133 fixed at 4 mg/L (FEP/VNRX-5133) and comparators were determined following CLSI M07-A11 guidelines [1] against 5,184 clinical isolates (3,998 *Enterobacteriaceae*, 1,136 *P. aeruginosa* and 50 methicillin-susceptible *Staphylococcus aureus* (MSSA) from community and hospital infections collected globally in 2018. The species distribution of the *Enterobacteriaceae* is shown in Figure 1. Isolates were collected in (n/percent of total): Asia/South Pacific (520/10.0%), Africa/Middle East (266/5.1%), Europe (2,496/48.1%), Latin America (437/8.4%), and North America (1,465/28.3%). Isolates were sourced from (n/percent of total): respiratory tract infections (2,400/46.3%), urinary tract infections (1,765/34.0%), intraabdominal infections (860/16.6%), skin/soft tissue infections (158/3.0%), and bloodstream infections (1/<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. Resistant phenotypes were based on 2018 EUCAST breakpoints v8.1 [2]. As cefepime/VNRX-5133 breakpoints have not yet been established, the cefepime EUCAST non-resistant breakpoint of ≤4 mg/L [2] and the cefepime 2 g q8h CLSI susceptible dose dependent (SDD) breakpoint of ≤8 µg/mL [3] were considered for *Enterobacteriaceae,* and the EUCAST cefepime non-resistant breakpoint of ≤8 mg/L [2] was applied to *P. aeruginosa* for comparative purposes.

RESULTS

Figure 1. Distribution of 3,998 *Enterobacteriaceae* isolates by species



Klebsiella spp. consist of (n): *K. pneumoniae* (1,135); *K. oxytoca* (240); *K. aerogenes* (123)
Proteeae consist of (n): *Morganella morganii* (116); *Proteus mirabilis* (226); *P. vulgaris* (109); *Providencia rettgeri* (49); *P. stuartii* (75)
Serratia spp. consist of (n): *S. marcescens* (127); *S. liquefaciens* (1); *Serratia*, non-speciated (2)
Citrobacter spp. consist of (n): *C. freundii* (244); *C. koseri* (124)
Enterobacter spp. consist of (n): *E. asburiae* (25); *E. cloacae* (204); *E. kobei* (14); *E. ludwigii* (6); *Enterobacter*, non-speciated (2)

Table 1. *In vitro* activity of cefepime/VNRX-5133 and comparator agents against 3,998 *Enterobacteriaceae*

Phenotype (n)	Antimicrobial	%S	mg/L		
			MIC_{50}	MIC_{90}	Range
All (3,998)	FEP/VNRX-5133 (CLSI)	99.7	0.06	0.25	≤0.008 - > 16
	FEP/VNRX-5133 (EUCAST)	99.3	0.06	0.25	≤0.008 - > 16
	Cefepime	78.6	≤0.25	> 16	≤0.25 - > 16
	Ceftazidime	72.8	0.25	> 16	≤0.03 - > 16
	Ceftazidime-avibactam	99.1	≤0.12	0.5	≤0.12 - > 16
	Ceftolozane-tazobactam	83.9	0.5	4	≤0.25 - > 8
	Gentamicin	84.1	0.5	> 16	≤0.12 - > 16
	Levofloxacin	71.6	0.06	> 8	≤0.004 - > 8
	Meropenem	97.5	0.03	0.12	≤0.004 - > 4
	Meropenem-vaborbactam	99.0	≤0.06	0.12	≤0.06 - > 16
	Piperacillin-tazobactam	82.9	≤4	64	≤4 - > 128
FEP NS (857)	FEP/VNRX-5133 (CLSI)	98.6	0.12	1	≤0.008 - > 16
	FEP/VNRX-5133 (EUCAST)	96.6	0.12	1	≤0.008 - > 16
	Cefepime	0	> 16	> 16	2 - > 16
	Ceftazidime	5.6	> 16	> 16	0.12 - > 16
	Ceftazidime-avibactam	95.6	0.25	2	≤0.12 - > 16
	Ceftolozane-tazobactam	49.0	2	> 8	≤0.25 - > 8
	Gentamicin	49.8	4	> 16	≤0.12 - > 16
	Levofloxacin	24.4	8	> 8	0.015 - > 8
	Meropenem	88.8	0.06	> 4	≤0.004 - > 4
	Meropenem-vaborbactam	95.7	≤0.06	0.5	≤0.06 - > 16
	Piperacillin-tazobactam	45.9	16	> 128	≤4 - > 128
MEM NS (101)	FEP/VNRX-5133 (CLSI)	91.1	1	8	≤0.008 - > 16
	FEP/VNRX-5133 (EUCAST)	83.2	1	8	≤0.008 - > 16
	Cefepime	5.0	> 16	> 16	≤0.25 - > 16
	Ceftazidime	5.0	> 16	> 16	0.06 - > 16
	Ceftazidime-avibactam	72.3	2	> 16	≤0.12 - > 16
	Ceftolozane-tazobactam	3.0	> 8	> 8	0.5 - > 8
	Gentamicin	33.7	> 16	> 16	≤0.12 - > 16
	Levofloxacin	6.9	> 8	> 8	0.06 - > 8
	Meropenem	0	> 4	> 4	4 - > 4
	Meropenem-vaborbactam	61.4	2	> 16	≤0.06 - > 16
	Piperacillin-tazobactam	2.0	> 128	> 128	≤4 - > 128
TZP NS (685)	FEP/VNRX-5133 (CLSI)	98.5	0.12	2	≤0.008 - > 16
	FEP/VNRX-5133 (EUCAST)	96.2	0.12	2	≤0.008 - > 16
	Cefepime	32.3	16	> 16	≤0.25 - > 16
	Ceftazidime	17.7	> 16	> 16	0.12 - > 16
	Ceftazidime-avibactam	95.0	0.5	2	≤0.12 - > 16
	Ceftolozane-tazobactam	27.9	4	> 8	≤0.25 - > 8
	Gentamicin	58.0	1	> 16	≤0.12 - > 16
	Levofloxacin	38.5	2	> 8	0.015 - > 8
	Meropenem	85.6	0.06	> 4	≤0.004 - > 4
	Meropenem-vaborbactam	94.5	≤0.06	1	≤0.06 - > 16
	Piperacillin-tazobactam	0	128	> 128	16 - > 128

Cefepime/VNRX-5133, cefepime with VNRX-5133 fixed at 4 mg/L; FEP/VNRX-5133 (CLSI), CLSI cefepime 2 g q8h CLSI susceptible dose dependent (SDD) breakpoint of ≤8 µg/mL; FEP/VNRX-5133 (EUCAST), EUCAST cefepime non-resistant breakpoint of ≤4 mg/L; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; NS, non-susceptible based on 2018 EUCAST breakpoints

Table 2. *In vitro* activity of cefepime/VNRX-5133 and comparator agents against 1,136 *Pseudomonas aeruginosa*

Phenotype (n)	Antimicrobial	%S	mg/L		
			MIC_{50}	MIC_{90}	Range
All (1,136)	FEP/VNRX-5133	94.2	2	8	≤0.06 - > 32
	Cefepime	80.2	4	32	≤0.25 - > 32
	Ceftazidime	75.8	4	> 32	≤0.25 - > 32
	Ceftazidime-avibactam	90.2	4	8	≤0.25 - > 16
	Ceftolozane-tazobactam	89.2	1	8	≤0.12 - > 16
	Ciprofloxacin	70.2	0.25	> 4	≤0.06 - > 4
	Gentamicin	81.3	2	16	≤0.25 - > 16
	Imipenem	65.6	4	> 8	≤0.5 - > 8
	Meropenem	73.0	0.5	> 8	≤0.06 - > 8
	Meropenem-vaborbactam	87.8	0.5	16	≤0.06 - > 16
	Piperacillin-tazobactam	71.1	8	128	≤0.5 - > 128
FEP NS (225)	FEP/VNRX-5133	70.7	8	32	1 - > 32
	Cefepime	0	32	> 32	16 - > 32
	Ceftazidime	9.3	> 32	> 32	2 - > 32
	Ceftazidime-avibactam	53.8	8	> 16	0.5 - > 16
	Ceftolozane-tazobactam	50.7	4	> 16	1 - > 16
	Ciprofloxacin	24.4	4	> 4	≤0.06 - > 4
	Gentamicin	43.1	8	> 16	≤0.25 - > 16
	Imipenem	24.0	> 8	> 8	≤0.5 - > 8
	Meropenem	26.7	8	> 8	0.12 - > 8
	Meropenem-vaborbactam	54.7	8	> 16	≤0.06 - > 16
	Piperacillin-tazobactam	4.4	64	> 128	1 - > 128
MEM NS (307)	FEP/VNRX-5133	82.4	8	16	0.5 - > 32
	Cefepime	46.3	16	> 32	1 - > 32
	Ceftazidime	40.4	16	> 32	2 - > 32
	Ceftazidime-avibactam	67.4	8	> 16	0.5 - > 16
	Ceftolozane-tazobactam	64.2	2	> 16	0.5 - > 16
	Ciprofloxacin	34.5	4	> 4	0.12 - > 4
	Gentamicin	53.8	4	> 16	≤0.25 - > 16
	Imipenem	4.9	> 8	> 8	2 - > 8
	Meropenem	0	8	> 8	4 - > 8
	Meropenem-vaborbactam	54.7	8	> 16	0.5 - > 16
	Piperacillin-tazobactam	30.0	32	> 128	1 - > 128
TZP NS (328)	FEP/VNRX-5133	82.0	8	16	0.5 - > 32
	Cefepime	34.5	16	> 32	1 - > 32
	Ceftazidime	22.6	32	> 32	2 - > 32
	Ceftazidime-avibactam	68.0	8	> 16	1 - > 16
	Ceftolozane-tazobactam	65.2	4	> 16	0.5 - > 16
	Ciprofloxacin	37.8	2	> 4	≤0.06 - > 4
	Gentamicin	58.2	4	> 16	≤0.25 - > 16
	Imipenem	32.3	8	> 8	≤0.5 - > 8
	Meropenem	34.5	8	> 8	0.12 - > 8
	Meropenem-vaborbactam	61.0	8	> 16	≤0.06 - > 16
	Piperacillin-tazobactam	0	64	> 128	32 - > 128

Cefepime/VNRX-5133, cefepime with VNRX-5133 fixed at 4 mg/L; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; NS, non-susceptible based on 2018 EUCAST breakpoints; EUCAST cefepime non-resistant breakpoint of ≤8 mg/L was applied to P. aeruginosa for comparative purposes.

Table 3. *In vitro* activity of cefepime/VNRX-5133 and comparator agents against 50 methicillin-susceptible *Staphylococcus aureus*

Organism (n)	Antimicrobial	mg/L		
		MIC_{50}	MIC_{90}	Range
S. aureus (MSSA) (50)	FEP/VNRX-5133	2	2	0.03 - 8
	Cefepime	2	4	≤0.25 - 8
	Ceftazidime	16	16	8 - > 16
	Ceftazidime-avibactam	16	16	0.5 - > 16
	Ceftolozane-tazobactam	> 8	> 8	4 - > 8
	Gentamicin	0.25	0.5	≤0.12 - 2
	Meropenem	0.12	0.25	0.008 - 0.5
	Meropenem-vaborbactam	0.12	0.12	≤0.06 - 0.25
	Piperacillin Tazobactam	≤4	≤4	≤4 - 8

MSSA, methicillin-susceptible *S. aureus*; cefepime/VNRX-5133, cefepime with VNRX-5133 fixed at 4 mg/L

Figure 2. MIC distribution of cefepime/VNRX-5133 and select comparator agents against 3,998 *Enterobacteriaceae*

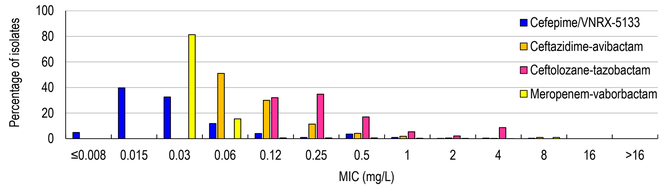
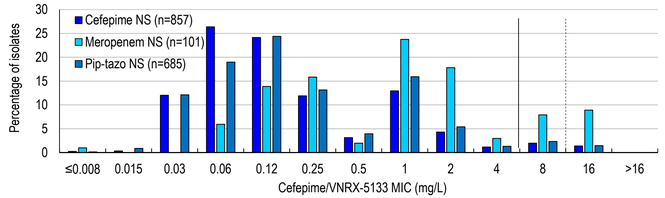
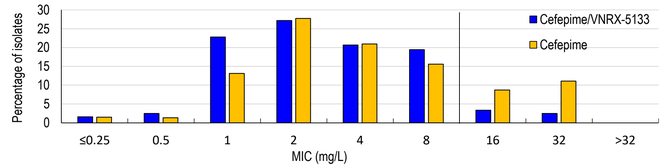


Figure 3. MIC distribution of cefepime/VNRX-5133 against resistant *Enterobacteriaceae*



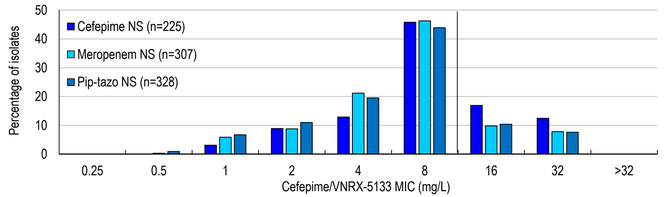
Pip-tazo, piperacillin-tazobactam; NS, non-susceptible based on 2018 EUCAST breakpoints; solid line indicates the EUCAST cefepime non-resistant breakpoint of ≤4 mg/L; dashed line indicates CLSI cefepime 2 g q8h CLSI susceptible dose dependent (SDD) breakpoint of ≤8 µg/mL

Figure 4. MIC distribution of cefepime/VNRX-5133 and cefepime against 1,136 *Pseudomonas aeruginosa*



Solid line indicates the EUCAST cefepime non-resistant breakpoint of ≤8 mg

Figure 5. MIC distribution of cefepime/VNRX-5133 against resistant *Pseudomonas aeruginosa*



Pip-tazo, piperacillin-tazobactam; NS, non-susceptible based on 2018 EUCAST breakpoints; solid line indicates the EUCAST cefepime non-resistant breakpoint of ≤8 mg

RESULTS SUMMARY

- Cefepime/VNRX-5133 showed potent *in vitro* activity against *Enterobacteriaceae*, with $MIC_{50/90}$ values of 0.06/0.25 mg/L against all isolates tested and 99.7% inhibited at ≤4 mg/L (non-resistant by EUCAST breakpoint) (Table 1).
- Activity was maintained against resistant subsets of *Enterobacteriaceae*, with MIC_{90} values of 1 mg/L against cefepime- non-susceptible, 8 mg/L against meropenem-non-susceptible and 2 mg/L against piperacillin-tazobactam-non-susceptible isolates (Table 1, Figure 3).
- Cefepime/VNRX-5133 inhibited 94.2% of *P. aeruginosa* at the EUCAST cefepime breakpoint of ≤8 mg/L, with $MIC_{50/90}$ values of 2/8 mg/L (Table 2).
- Cefepime/VNRX-5133 maintained activity against the resistant subsets of *P. aeruginosa*, and was the most active of all compounds tested based on percent susceptible (Table 2).
- There was little or no potentiation of cefepime activity by VNRX-5133 against the *S. aureus* isolates (Table 3).

CONCLUSIONS

- Cefepime in combination with VNRX-5133 demonstrated potent *in vitro* activity against *Enterobacteriaceae* and *P. aeruginosa*, including cefepime-, meropenem-, or piperacillin-tazobactam-non-susceptible isolates.
- Because this drug combination exhibited substantial potential for the treatment of infections caused by isolates often resistant to first line therapy, further development is warranted.

REFERENCES

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ACKNOWLEDGMENTS

This project has been sponsored by VenatoRx Pharmaceuticals, Inc. and funded in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services (Contract No. HHSN272201300019C) and the Wellcome Trust (Grant No. WT101999/Z/13/Z).