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Antimicrobial Activity of Cefepime in Combination with VNRX-5133 Against a Collection of β-lactamase-producing *Enterobacteriaceae*

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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 difficult to treat organisms, including cephalosporin and carbapenem resistant *Pseudomonas aeruginosa* and *Enterobacteriaceae* producing serine β-lactamases from all classes, and NDM- and VIM- type metallo-β-lactamases. In this analysis, we evaluated the activity of cefepime in combination with VNRX-5133 and comparators against 369 molecularly characterized β-lactamase-producing *Enterobacteriaceae* clinical isolates.

MATERIALS & METHODS

MICs of cefepime with VNRX-5133 fixed at 4 mg/L (cefepime/VNRX-5133) were determined following CLSI M07-A10 guidelines [1] against 369 β-lactamase-producing *Enterobacteriaceae* from community and hospital infections collected globally in 2012-2013. The distribution of species included is shown in Figure 1. The presence of metallo- β-lactamase (MBL), serine- β-lactamase (KPC), extended-spectrum- β-lactamase (ESBL) and oxacillinase (OXA) genes was assessed via multiplex PCR, followed by amplification of full-length genes and sequencing. The distribution of enzymes by species is shown in Figure 2. As cefepime/VNRX-5133 breakpoints have not yet been established, the CLSI cefepime 2 g q8h susceptible dose dependent (SDD) breakpoint of ≤8 mg/L was considered for comparative purposes [2].

RESULTS

Table 1. *In vitro* activity of cefepime/VNRX-5133 against β-lactamase producing *Enterobacteriaceae*

Enzyme Group	Drug	% Susceptible*	MIC (mg/L)			
			MIC_{50}	MIC_{90}	Range	Mode
All β-lactamase producers (369)	Cefepime/VNRX-5133	97.8	0.12	2	≤0.06 - >128	≤0.06
	Cefepime	24.4	64	>128	≤0.06 - >128	>128
NDM (9)	Cefepime/VNRX-5133	88.9	na	na	0.5 - 16	4
	Cefepime	0	na	na	64 - >128	>128
VIM (20)	Cefepime/VNRX-5133	80.0	1	16	≤0.06 - >128	0.5
	Cefepime	5.0	>128	>128	4 - >128	>128
KPC (70)	Cefepime/VNRX-5133	98.6	0.25	1	≤0.06 - 16	≤0.06
	Cefepime	10.0	>128	>128	1 - >128	>128
ESBL (245)	Cefepime/VNRX-5133	99.2	0.12	1	≤0.06 - 16	≤0.06
	Cefepime	30.6	32	>128	≤0.06 - >128	>128
OXA (25)	Cefepime/VNRX-5133	100	0.25	4	≤0.06 - 8	≤0.06
	Cefepime	28.0	128	>128	0.5 - >128	>128

*% susceptible based on the cefepime 2 g q8h susceptible dose dependent (SDD) breakpoint of ≤8 mg/L; na, $MIC_{50/90}$ not calculated for n<10

Figure 1. Distribution of 369 β-lactamase producing *Enterobacteriaceae* by species

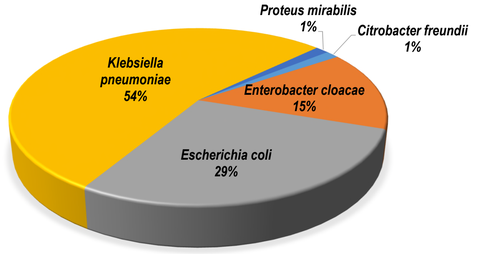


Figure 2. Distribution of β-Lactamases by species

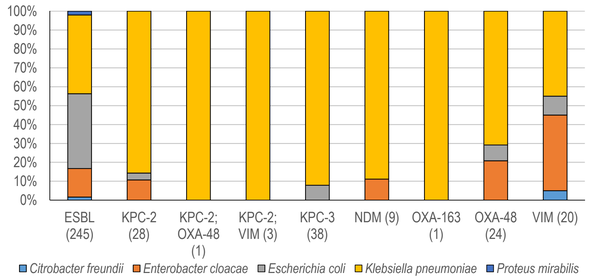
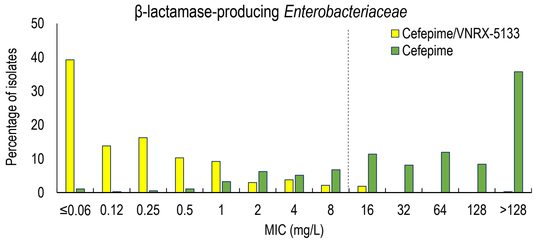
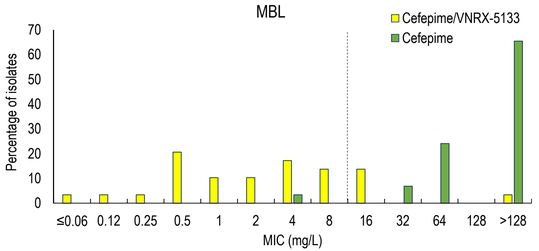


Figure 3. MIC distribution of cefepime and cefepime/VNRX-5133 against 369 β-lactamase-producing *Enterobacteriaceae*



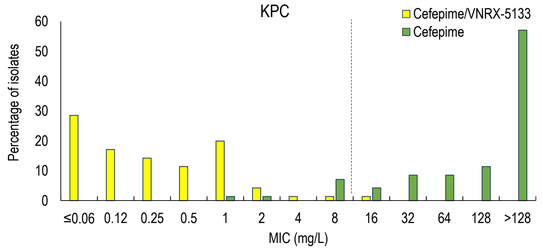
Dashed line indicates cefepime susceptible dose dependent (SDD) breakpoint

Figure 4. MIC distribution of cefepime and cefepime/VNRX-5133 against 29 MBL-producing *Enterobacteriaceae*



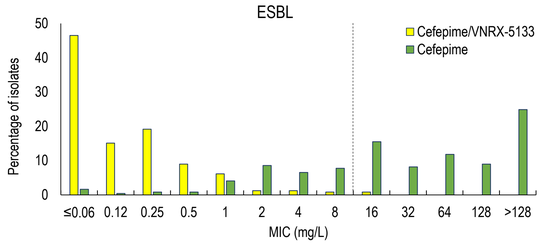
MBL consist of (n): NDM (9); VIM (20)
Dashed line indicates cefepime susceptible dose dependent (SDD) breakpoint

Figure 5. MIC distribution of cefepime and cefepime/VNRX-5133 against 70 KPC-producing *Enterobacteriaceae*



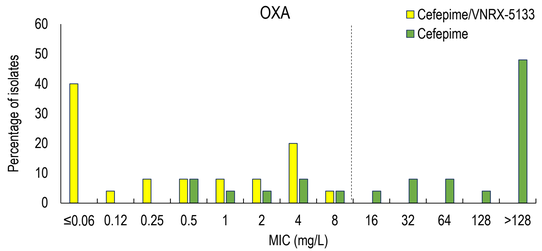
KPC consist of (n): KPC-2 (28); KPC-2+OXA-48 (1); KPC-2+VIM (3); KPC-3 (38)
Dashed line indicates cefepime susceptible dose dependent (SDD) breakpoint

Figure 6. MIC distribution of cefepime and cefepime/VNRX-5133 against 245 ESBL-producing *Enterobacteriaceae*



Dashed line indicates cefepime susceptible dose dependent (SDD) breakpoint

Figure 7. MIC distribution of cefepime and cefepime/VNRX-5133 against 25 OXA-producing *Enterobacteriaceae*



OXA consist of (n): OXA-48 (24); OXA-163 (1)
Dashed line indicates cefepime susceptible dose dependent (SDD) breakpoint

RESULTS SUMMARY

- The combination of cefepime and VNRX-5133 demonstrated potent *in vitro* activity against this collection of β-lactamase-producing *Enterobacteriaceae* with an MIC_{90} value of 2 mg/L compared to >128 mg/L for cefepime alone (Table 1, Figure 3).
- VNRX-5133 substantially potentiated cefepime *in vitro* activity against all subsets of β-lactamase-producing isolates, with cefepime/VNRX-5133 MIC_{90} values ranging from 1 mg/L to 16 mg/L (Table 1; Figure 4 through Figure 7)
- Cefepime/VNRX-5133 inhibited 97.8% of isolates overall at the cefepime SDD breakpoint of ≤8 mg/L, including NDM-producers (88.9%), VIM-producers (80.0%), KPC-producers (98.6%), ESBL-producers (99.2%) and OXA-producers (100%) (Table 1).

CONCLUSIONS

- Cefepime in combination with VNRX-5133 demonstrated potent *in vitro* activity against β-lactamase-producing *Enterobacteriaceae*, including serine- and metallo-β-lactamase-producing 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

1. Clinical and Laboratory Standards Institute. 2015. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Tenth Edition*. CLSI document M07-A10 Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2019. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Ninth Informational Supplement*. CLSI Document M100S 2019. Wayne, PA.

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