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P1176 Antimicrobial activity of cefepime in combination with VNRX-5133 against a collection of beta-lactamase-producing *Enterobacteriaceae*

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Background: VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase (BL) inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-BLs (Ambler Classes A, B, C and D). In this analysis, we evaluated the activity of cefepime (FEP) in combination with VNRX-5133 and comparators against 440 molecularly characterized BL-producing Enterobacteriaceae clinical isolates.

Materials/methods: MICs of FEP with VNRX-5133 fixed at 4 mg/L (FEP/VNRX-5133) were determined following CLSI M07-A10 guidelines against 440 BL-producing Enterobacteriaceae from community and hospital infections collected globally in 2012-2013. The presence of metallo-BL, serine-BL, extended-spectrum-BL and oxacillinase genes was assessed via multiplex PCR, followed by amplification of full-length genes and sequencing. As FEP/VNRX-5133 breakpoints have not yet been established, the FEP 2 g q8h susceptible dose dependent (SDD) breakpoint of ≤8 mg/L was considered for comparative purposes.

Results: FEP MIC_{90} against this collection of BL-producing Enterobacteriaceae was >128 mg/L (32% SDD). VNRX-5133 substantially potentiated FEP *in vitro* activity, with MIC_{90} values of the combination ranging from 0.5 mg/L to 16 mg/L against the BL-producing subsets (Table). FEP/VNRX-5133 inhibited 98% of isolates overall at the FEP SDD breakpoint of ≤8 mg/L.

Enzyme Group	Enzyme	(N)	FEP/VNRX-5133 MIC (mg/L)										% MIC ≤8 mg/L
			≤0.06	0.12	0.25	0.5	1	2	4	8	16	≥32	
MBL	NDM	(9)				1	1	2	3	1	1		88.9
	VIM	(22)	2	1	1	5	2	1	2	4	4		81.8
Serine	KPC-2	(33)	7	6	4	4	9	2	1				100
	KPC-3	(37)	13	8	6	4	5	1					100
ESBL	ESBL	(313)	149	49	59	28	19	4	3		2		99.4
Oxacillinase	OXA-48	(25)	9	1	3	2	2	2	5	1			100
	OXA-163	(1)	1										100

Dotted line indicates the % susceptible based on the cefepime dose dependent breakpoint of ≤8 mg/L; MBL, metallo-β-lactamase; ESBL, extended-spectrum- β-lactamase

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.