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P1175 Antimicrobial activity of cefepime in combination with VNRX-5133 against a global 2018 surveillance collection of clinical isolates

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Background: 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*. 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 against 1,027 Enterobacteriaceae, 501 *P. aeruginosa* and 49 methicillin-susceptible *Staphylococcus aureus* (MSSA) from community and hospital infections collected globally in 2018. Resistant phenotypes were based on 2018 EUCAST breakpoints v8.1. As FEP/VNRX-5133 breakpoints have not yet been established, the FEP EUCAST non-resistant breakpoint of ≤4 mg/L and the FEP 2 g q8h CLSI susceptible dose dependent (SDD) breakpoint of ≤8 µg/mL were considered for Enterobacteriaceae for comparative purposes.

Results: FEP/VNRX-5133 showed potent *in vitro* activity against Enterobacteriaceae and *P. aeruginosa*, with $MIC_{50/90}$ values of 0.03/0.12 mg/L and 2/8 mg/L, respectively. Greater than 99% of all Enterobacteriaceae were inhibited at ≤4 mg/L (non-resistant by EUCAST) and 100% at ≤8 mg/L (uppermost of SDD range by CLSI), and 94.4% of *P. aeruginosa* were inhibited at the EUCAST cefepime breakpoint of ≤8 mg/L.

Resistance Phenotype	N	Cefepime/VNRX-5133			
		MIC (mg/L)		%≤4 mg/L[a]	%≤8 mg/L[b]
		MIC_{50}	MIC_{90}		
Enterobacteriaceae	1027	0.03	0.12	99.7	100
Enterobacteriaceae, FEP NS	200	0.12	1	98.5	100
Enterobacteriaceae, MEM NS	19	1	2	94.7	100
Enterobacteriaceae, TZP NS	135	0.12	1	98.4	100
P. aeruginosa	501	2	8	na	94.4
P. aeruginosa, FEP NS	85	8	16	na	70.6
P. aeruginosa, MEM NS	143	8	16	na	84.6
P. aeruginosa, TZP NS	135	8	16	na	82.2
S. aureus, methicillin-susceptible	49	2	2	na	na

FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; NS, nonsusceptible based on 2018 EUCAST breakpoints v8.1

[a] corresponds to Enterobacteriaceae non-resistant to cefepime by EUCAST criteria

[b] corresponds to uppermost of cefepime SDD range by CLSI criteria for Enterobacteriaceae, and cefepime susceptible by EUCAST for *P. aeruginosa*

Conclusions: Cefepime in combination with VNRX-5133 demonstrated potent *in vitro* activity against Enterobacteriaceae, including cefepime-, piperacillin-tazobactam-, or meropenem-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.