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Antimicrobial Activity of Cefepime in Combination with VNRX-5133 Against a Global 2018 Surveillance Collection of *Pseudomonas aeruginosa*

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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*. The activity of cefepime /VNRX-5133 (FEP/VNRX-5133) and comparator agents was evaluated against recent clinical isolates of *P. aeruginosa* collected in a 2018 surveillance study.

MATERIALS & METHODS

MICs of cefepime with VNRX-5133 fixed at 4 µg/mL (FEP/VNRX-5133) and comparators were determined following CLSI guidelines [1] against 1,136 clinical isolates of *P. aeruginosa* from community and hospital infections collected globally in 2018. Isolates were collected in (n/percent of total): Africa (17/1.5%), Asia (87/7.7%), Europe (500/44.0%), Latin America (125/11.0%), Middle East (42/3.7%), North America (330/29.0%) and South Pacific (35/3.1%). Isolates were sourced from (n/percent of total): respiratory tract infections (823/72.4%), urinary tract infections (232/20.4%), intraabdominal infections (80/7.0%), and bloodstream infections (1/0.1%). Avibactam was tested at a fixed concentration of 4 µg/mL in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 µg/mL in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 µg/mL in combination with meropenem. Resistant phenotypes were based on 2019 CLSI breakpoints [2]. As cefepime/VNRX-5133 breakpoints have not yet been established, the cefepime CLSI susceptible breakpoint of ≤8 µg/mL and intermediate breakpoint of 16 µg/mL [2] were applied to *P. aeruginosa* for comparative purposes.

RESULTS

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

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}
All (1,136)	Cefepime/VNRX-5133	94.2	3.4	2.5	2	8
	Cefepime	80.2	8.7	11.1	4	32
	Ceftazidime	75.8	5.3	18.9	4	> 32
	Ceftazidime-avibactam	90.2	--	9.8	4	8
	Ceftolozane-tazobactam	89.2	3.6	7.2	1	8
	Ciprofloxacin	70.2	5.6	24.3	0.25	> 4
	Gentamicin	81.3	6.6	12.2	2	16
	Imipenem	43.4	22.2	34.4	4	> 8
	Meropenem	73.0	5.4	21.7	0.5	> 8
	Meropenem-vaborbactam	na	na	na	0.5	16
	Piperacillin-tazobactam	71.1	18.3	10.6	8	128
FEP NS (225)	Cefepime/VNRX-5133	70.7	16.9	12.4	8	32
	Cefepime	0	44.0	56.0	32	> 32
	Ceftazidime	9.3	7.1	83.6	> 32	> 32
	Ceftazidime-avibactam	53.8	--	46.2	8	> 16
	Ceftolozane-tazobactam	50.7	15.6	33.8	4	> 16
	Ciprofloxacin	24.4	6.7	68.9	4	> 4
	Gentamicin	43.1	15.1	41.8	8	> 16
	Imipenem	14.2	9.8	76.0	> 8	> 8
	Meropenem	26.7	7.6	65.8	8	> 8
	Meropenem-vaborbactam	na	na	na	8	> 16
	Piperacillin-tazobactam	4.4	46.7	48.9	64	> 128
MEM NS (307)	Cefepime/VNRX-5133	82.4	9.8	7.8	8	16
	Cefepime	46.3	19.9	33.9	16	> 32
	Ceftazidime	40.4	12.1	47.6	16	> 32
	Ceftazidime-avibactam	67.4	--	32.6	8	> 16
	Ceftolozane-tazobactam	64.2	10.8	25.1	2	> 16
	Ciprofloxacin	34.5	6.5	59.0	4	> 4
	Gentamicin	53.8	11.7	34.5	4	> 16
	Imipenem	1.6	3.3	95.1	> 8	> 8
	Meropenem	0	19.9	80.1	8	> 8
	Meropenem-vaborbactam	na	na	na	8	> 16
	Piperacillin-tazobactam	30.0	43.3	26.7	32	> 128
TZP NS (328)	Cefepime/VNRX-5133	82.0	10.4	7.6	8	16
	Cefepime	34.5	28.4	37.2	16	> 32
	Ceftazidime	22.6	13.1	64.3	32	> 32
	Ceftazidime-avibactam	68.0	--	32.0	8	> 16
	Ceftolozane-tazobactam	65.2	11.6	23.2	4	> 16
	Ciprofloxacin	37.8	8.5	53.7	2	> 4
	Gentamicin	58.2	10.7	31.1	4	> 16
	Imipenem	19.2	13.1	67.7	8	> 8
	Meropenem	34.5	7.3	58.2	8	> 8
	Meropenem-vaborbactam	na	na	na	8	> 16
	Piperacillin-tazobactam	0	63.4	36.6	64	> 128

Cefepime/VNRX-5133, cefepime with VNRX-5133 fixed at 4 µg/mL; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; NS, non-susceptible based on 2019 CLSI breakpoints; $MIC_{50/90}$ in µg/mL; cefepime CLSI susceptible breakpoint of ≤8 µg/mL has been applied to cefepime/VNRX-5133 for comparative purposes

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

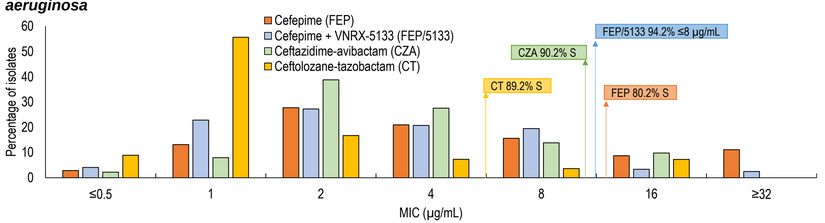


Figure 2. MIC distribution of cefepime, cefepime/VNRX-5133, and comparators against 225 cefepime-non-susceptible *Pseudomonas aeruginosa*

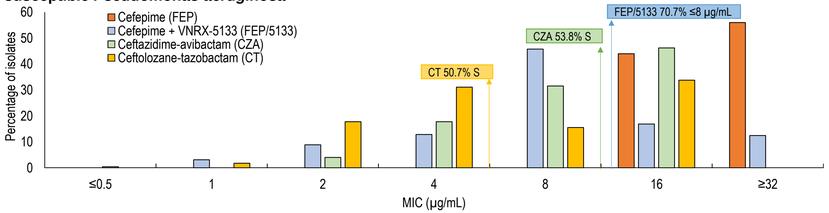


Figure 3. MIC distribution of cefepime, cefepime/VNRX-5133, and comparators against 307 meropenem-non-susceptible *Pseudomonas aeruginosa*

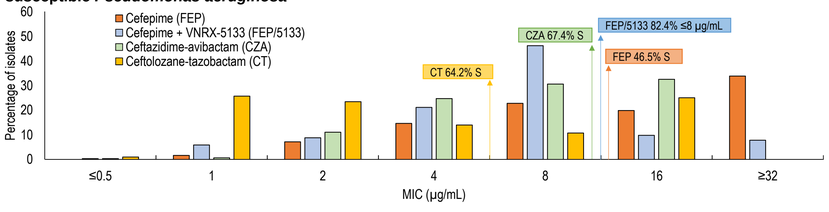
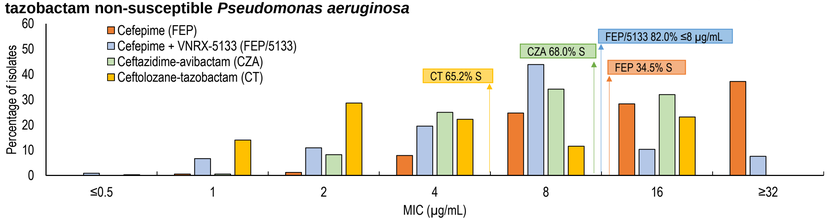


Figure 4. MIC distribution of cefepime, cefepime/VNRX-5133, and comparators against 328 piperacillin-tazobactam non-susceptible *Pseudomonas aeruginosa*



RESULTS SUMMARY

- Cefepime/VNRX-5133 showed potent *in vitro* activity against *P. aeruginosa*, with $MIC_{50/90}$ values of 2/8 µg/mL against all isolates tested (Table 1).
- 94.2% and 97.5% of *P. aeruginosa* isolates were inhibited by cefepime/VNRX-5133 concentrations of ≤8 and ≤16 µg/mL, respectively.
- Cefepime/VNRX-5133 maintained activity against the resistant subsets of *P. aeruginosa*, (Table 1, Figure 1 - Figure 4)

CONCLUSIONS

- Cefepime in combination with VNRX-5133 demonstrated potent *in vitro* activity against *P. aeruginosa*, including cefepime-, piperacillin-tazobactam-, and meropenem-non-susceptible isolates and was the most active of all compounds tested based on percent susceptible.
- By MIC_{50} and MIC_{90}, VNRX-5133 potentiated cefepime activity by 2- to at least 4-fold against *P. aeruginosa*, overall and within each resistant subset.

REFERENCES

1. Clinical and Laboratory Standards Institute. 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eleventh Edition*. CLSI document M07-A11 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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