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In Vitro Activity of Cefepime-Taniborbactam and Comparators Against Genotypically Characterized Carbapenem-Resistant Enterobacterales (CRE) and Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA) from the United States, 2018-2021

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INTRODUCTION

Taniborbactam, a cyclic boronate-based β-lactamase inhibitor with activity against serine-β-lactamases, as well as NDM & VIM metallo-β-lactamases (MBLs), is in development in combination with the fourth-generation cephalosporin, cefepime, for treatment of complicated urinary tract infections. This study examined the *in vitro* activity of cefepime-taniborbactam against recent clinical isolates from the United States, with a focus on carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).

METHODS

From 2018-2021, as part of the GEARS Antimicrobial Surveillance Program, 4,220 Enterobacterales and 1,222 *P. aeruginosa* were collected from 38 clinical sites in the United States. MICs of cefepime with taniborbactam fixed at 4 µg/mL and comparator antimicrobial agents were determined by broth microdilution according to CLSI guidelines [1] and interpreted using 2023 CLSI breakpoints [2]. CRE was defined by resistance to meropenem; CRPA was defined by resistance to meropenem and/or imipenem. As cefepime-taniborbactam breakpoints have not yet been established, a provisional non-resistant breakpoint of ≤16 µg/mL was considered for comparative purposes only. Isolates resistant to meropenem were screened for acquired β-lactamases by multiplex PCR followed by Sanger sequencing, as previously described [3]. Isolates with cefepime-taniborbactam MIC ≥16 µg/mL were characterized by whole genome sequencing (WGS) and resistance genes identified by comparison to the ResFinder database [4]. Analysis of genes of interest for *P. aeruginosa* (including PBP3 [*ftsI*], efflux pump regulatory genes [*esrC, mexR, mexS, mexT, mexZ, nalC, nalD, nfxB*], major porin [*oprD*], and AmpC regulatory genes [*mpl, dacB, ampR, ampD*]) utilized tBLASTn to find the gene with the lowest E value in each WGS assembly to a reference sequence, and mutations encoding amino acid changes were identified. Gross disruptions were defined as any mutation that caused a stop codon to be read in-frame upstream of the stop codon in the reference sequence. For loci deduced to encode intact proteins, specific amino acid variations previously implicated in elevated resistance to cephalosporins were noted [5-9].

RESULTS

Table 1. Susceptibility of CRE and CRPA isolated in the United States (2018-2021) to cefepime-taniborbactam and comparator agents

Organism group (n)	Drug[a]									
	Cefepime-taniborbactam		Ceftazidime-avibactam		Ceftolozane-tazobactam		Meropenem-vaborbactam		Piperacillin-tazobactam	
	% S[c]	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)
Enterobacterales										
All CRE[d] (n=68)	**97.1**	**8**	**80.9**	**>16**	**1.5**	**>8**	**85.3**	**16**	**1.5**	**>128**
carbapenemase-positive CRE (n=51)	**98.0**	**2**	**76.5**	**>16**	**0**	**>8**	**82.4**	**>16**	**0**	**>128**
carbapenemase negative CRE (n=17)	**94.1**	**8**	**94.1**	**8**	**5.9**	**>8**	**94.1**	**4**	**5.9**	**>128**
P. aeruginosa										
All CRPA[e] (n=308)	**92.9**	**16**	**84.7**	**16**	**80.8**	**16**	**68.5**	**>16**	**44.5**	**>128**
MEM-R *P. aeruginosa* (n=177)	**88.7**	**32**	**75.7**	**>16**	**74.0**	**>16**	**44.1**	**>16**	**23.2**	**>128**
carbapenemase-negative, MEM-R *P. aeruginosa* (n=170)	**90.6**	**16**	**77.6**	**16**	**76.5**	**16**	**44.7**	**>16**	**22.9**	**>128**

[a]FTB, cefepime-taniborbactam (taniborbactam fixed at 4 µg/mL); CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MEM, meropenem; S, susceptible; R, resistant.
[b]EUCAST breakpoints applied for meropenem-vaborbactam for *P. aeruginosa*.
[c]Corresponds to percentage of isolates inhibited by ≤16 µg/mL cefepime-taniborbactam, for comparative purposes.
[d]CRE defined as resistant to meropenem (MIC ≥ 4 µg/mL).
[e]CRPA defined as resistant to meropenem and/or imipenem (MIC ≥ 8 µg/mL).

Figure 1. Taxonomic distribution of the 68 isolates of CRE identified in this study

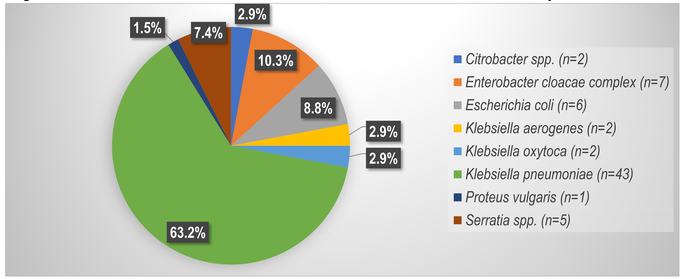


Figure 2. Carbapenemases carried by the 51 carbapenemase-positive CRE in this study

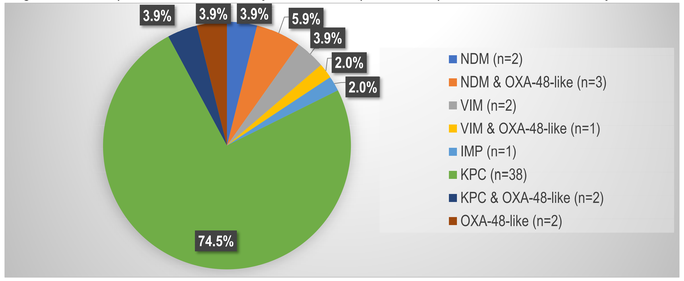


Figure 3. MIC frequency distribution of cefepime-taniborbactam and cefepime alone against 68 CRE isolated in the United States (2018-2021)

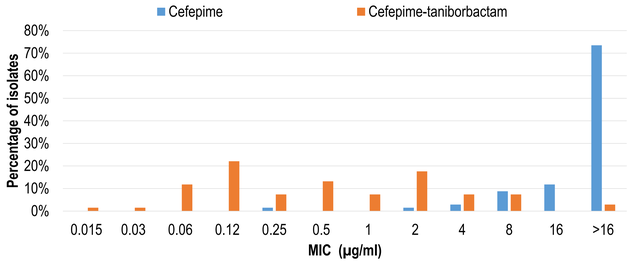


Figure 4. MIC frequency distribution of cefepime-taniborbactam and cefepime alone against the 308 CRPA isolated in the United States (2018-2021)

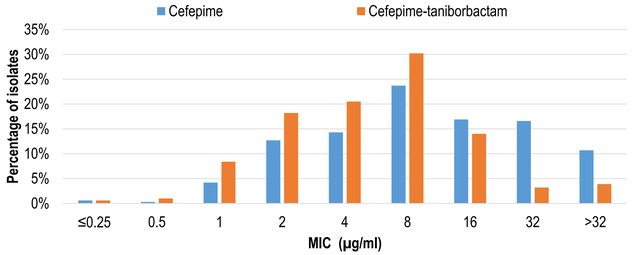
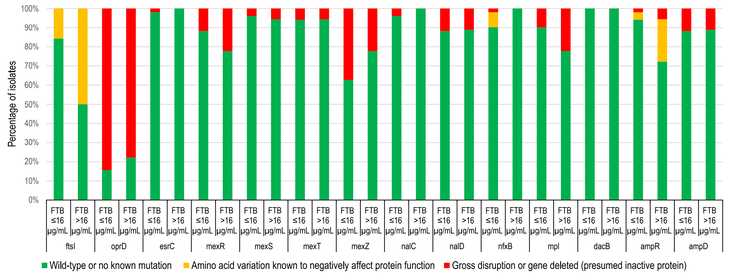


Figure 5. Analysis of genes of interest among carbapenemase-negative CRPA testing with cefepime-taniborbactam (FTB) MIC ≤16 µg/mL (*n*=51) and FTB MIC >16 µg/mL (*n*=18)



RESULTS SUMMARY

- In total, 66/68 (97.1%) of the CRE isolates were inhibited by ≤16 µg/mL of cefepime-taniborbactam (Table 1).
- Overall, 63.2% of the CRE were identified as *Klebsiella pneumoniae* (Fig. 1).
- The majority of CRE (51/68; 75.0%) produced a carbapenemase (Fig. 2) and 98.0% of these isolates were inhibited by ≤16 µg/mL cefepime-taniborbactam, a substantially greater percentage than the most active comparator, meropenem-vaborbactam (82.4% susceptible; Table 1).
- While KPC was the most prevalent carbapenemase among CRE (74.5%), a metallo-β-lactamase (NDM, VIM, or IMP) was identified in 17.6% of carbapenemase-positive isolates
- Cefepime-taniborbactam at ≤16 µg/mL inhibited 92.9% of all CRPA (n=308), 88.7% of meropenem-resistant *P. aeruginosa* (n=177), and 90.6% of carbapenemase-negative, meropenem-resistant *P. aeruginosa* (n=170) whereas the most active comparator, ceftazidime-avibactam, covered 84.7%, 75.7%, and 77.6% of these resistant subsets, respectively (Table 1).
- Taniborbactam strongly potentiated cefepime activity against CRE (Fig. 3). This effect was also evident, although less pronounced, against CRPA (Fig. 4).
- In carbapenemase-negative CRPA where WGS data were available (n=69), sequence variations, gross disruptions, or gene deletions in certain genes of interest may have contributed to reduced susceptibility to the tested agents. For example, *ftsI* mutations appeared in 9/18 (50.0%) of isolates with cefepime-taniborbactam MIC >16 µg/mL versus 8/51 (15.7%) isolates with cefepime-taniborbactam MIC ≤16 µg/mL. Mutations in the gene for AmpR, a global regulator of PDC expression, also appeared to be more common in isolates with elevated cefepime-taniborbactam MICs. Since WGS analysis was performed primarily on isolates with cefepime-taniborbactam MIC ≥16 µg/mL, confirmation of putative phenotype-genotype associations would require further investigation.

CONCLUSIONS

Cefepime-taniborbactam inhibited ≥94.1% of CRE isolates from the US, regardless of carbapenemase carriage. Similarly potent *in vitro* activity was observed for cefepime-taniborbactam against US isolates of CRPA, including meropenem-resistant strains without a detected carbapenemase which represented 96.0% of all meropenem-resistant *P. aeruginosa* strains. The continued development of cefepime-taniborbactam appears warranted.

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DISCLOSURES

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