P-1521

Susceptibility of Carbapenem-Resistant Enterobacterales (CRE) and Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA) With and Without Carbapenemases to Cefepime-Taniborbactam and Comparators: GEARS Antimicrobial Surveillance Program, United States, 2018-2022

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

M. Wise[1], M. Hackel[1], D. Sahm[1]

[1]IHMA, Inc., Schaumburg, IL, USA

INTRODUCTION

Taniborbactam is a novel β-lactamase inhibitor that inhibits serine-β-lactamases and NDM & VIM (but not IMP) metallo-β-lactamases, restoring the activity of cefepime against most isolates of Enterobacterales and *P. aeruginosa* carrying these enzymes. This study examined the *in vitro* antimicrobial activity of cefepime-taniborbactam (FTB) against recent clinical isolates from the US, focusing on genotypically-characterized carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *P. aeruginosa* (CRPA).

METHODS

As a part of the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) program, 4,932 Enterobacterales and 1,508 *P. aeruginosa* isolates were collected from 42 hospitals in the United States from 2018-2022. 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 2024 CLSI breakpoints [2]. CRE was defined by resistance to meropenem; CRPA was defined by resistance to meropenem and/or imipenem. As cefepime-taniborbactam interpretive breakpoints have not yet been established, a provisional susceptible breakpoint of ≤16 µg/mL was used for comparative purposes. 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 values ≥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 (if any) 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 variation previously implicated in elevated resistance to cephalosporins was noted [5-9].

RESULTS

Figure 1. Taxonomic distribution of the 73 isolates of CRE collected in the United States (2018-2022)

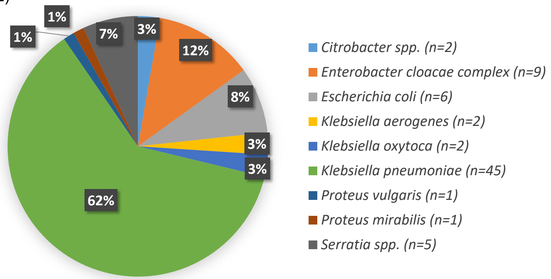
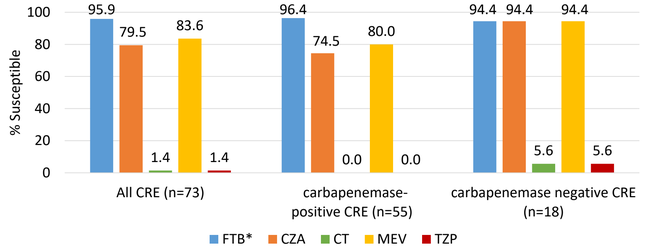


Figure 2. Susceptibility of CRE collected in the United States (2018-2022) to cefepime-taniborbactam and comparator agents



* Corresponds to percentage of isolates inhibited by ≤16 µg/mL cefepime-taniborbactam, for comparative purposes.
Abbreviations: FTB, cefepime-taniborbactam; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MEM-R, meropenem-resistant. CRE designation based on resistance to meropenem.

Figure 3. Carbapenemases carried by the 55 carbapenemase-positive CRE collected in the United States (2018-2022)

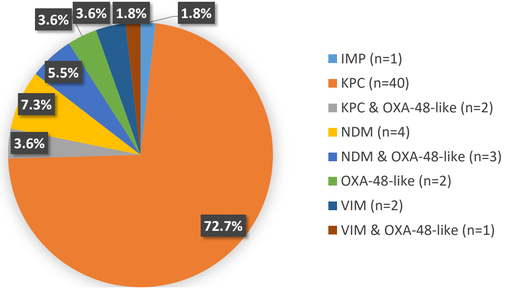
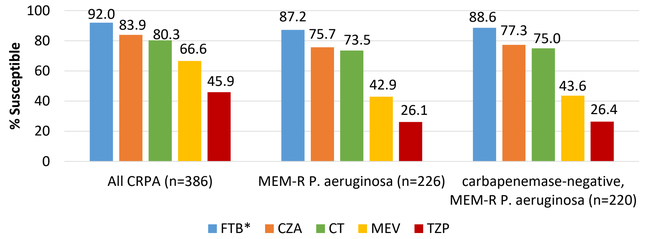
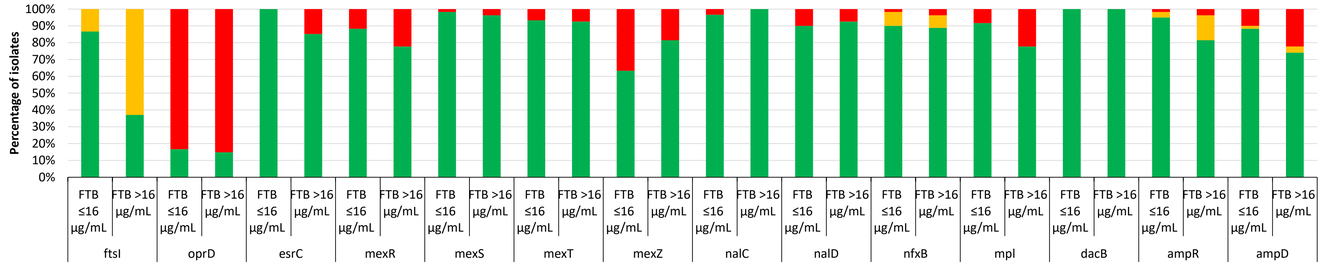


Figure 4. Susceptibility of CRPA collected in the United States (2018-2022) to cefepime-taniborbactam and comparator agents



* Corresponds to percentage of isolates inhibited by ≤16 µg/mL cefepime-taniborbactam, for comparative purposes.
Abbreviations: CRPA, carbapenem-resistant *P. aeruginosa*; FTB, cefepime-taniborbactam; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MEM-R, meropenem-resistant. Note, EUCAST breakpoints applied for meropenem-vaborbactam against *P. aeruginosa*. CRPA designation based on resistance to meropenem and/or imipenem.

Figure 5. Analysis of genes of interest among carbapenemase-negative CRPA testing with FTB MIC ≤16 µg/mL (n=60) and FTB MIC >16 µg/mL (n=27)



RESULTS SUMMARY

- In total, 73 CRE were collected and the majority (62%) were identified as *Klebsiella pneumoniae* (Fig. 1), followed by isolates of *Enterobacter cloacae* complex (12%) and *Escherichia coli* (8%).
- 70/73 (95.9%) of the 73 CRE isolates were inhibited by ≤16 µg/mL FTB, approximately 16 and 12 percentage points higher than that inhibited by ceftazidime-avibactam and meropenem-vaborbactam, respectively (Fig. 2). Ceftolozane/tazobactam and piperacillin/tazobactam were inactive versus the isolates of CRE in this collection.
- Most CRE (55/73; 75.3%) produced a carbapenemase (40 KPC, 7 NDM, 2 VIM, 2 OXA-48-like, 2 KPC+OXA-48, 1 IMP, and 1 VIM+OXA-48; Fig. 3), and 96.4% were inhibited by ≤16 µg/mL FTB (Fig. 2). The most active comparator was meropenem-vaborbactam (80.0% susceptible). FTB, ceftazidime-avibactam and meropenem-vaborbactam each inhibited 17/18 (94.4%) of CRE that did not carry a carbapenemase.
- At ≤16 µg/mL, FTB inhibited 92.0% of all CRPA (n=386) and 87.2% of meropenem-resistant CRPA (n=226), both values the highest among comparator agents (Fig. 4). Among meropenem-resistant CRPA, only 6 isolates (2.7%) carried a carbapenemase (2 IMP, 1 IMP+VIM, 1 VIM, 1 GES, 1 NDM) and FTB inhibited two of the three non-IMP carrying isolates.
- FTB at ≤16 µg/mL inhibited 88.6% of meropenem-resistant, carbapenemase-negative *P. aeruginosa* (n=220), again the highest value among comparators.
- Analysis of individual genes of interest (ftsI, oprD, and negative regulators of efflux and AmpC expression) in the carbapenemase-negative subset of CRPA that had WGS data available revealed multiple mutations putatively accounting for reduced susceptibility to FTB (Fig. 5), as well as to many of the tested comparators (not shown). Segregating the isolates by FTB MIC values (≤16 µg/mL [n=60] and >16 µg/mL [n=27]), showed that the proportion of isolates with ftsI mutations was higher (63%) in the elevated FTB MIC group compared to the lower FTB MIC group (13%). Mutations in the gene coding for MexR (a MarR family protein that negatively regulates multidrug efflux systems in *P. aeruginosa*), as well as those coding for AmpD and AmpR, key global regulators of the expression the intrinsic AmpC in *P. aeruginosa*, also appeared to be more common in the group with elevated FTB MICs, although this observation should be confirmed in additional studies.

CONCLUSIONS

Cefepime-taniborbactam at ≤16 µg/mL inhibited >94% of CRE isolates collected in the US, regardless of carbapenemase carriage. Similarly potent activity was observed for FTB against CRPA isolates, most of which lacked a carbapenemase. Cefepime-taniborbactam could be an important option for use against CRE and CRPA, as currently available therapies have variable or limited activity, especially against NDM- and VIM-carriers.

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DISCLOSURES

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