P0268

Activity of Cefepime-Taniborbactam (FTB) Against Enterobacterales and *P. aeruginosa* Collected Globally in 2018-2021 Stratified by β-lactamase Carriage

IHMA
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

The novel cyclic boronate-based broad-spectrum β-lactamase inhibitor, taniborbactam, inhibits serine-β-lactamases, as well as NDM and VIM metallo-β-lactamases (Ambler Classes A, B, C and D) [1]. Taniborbactam is being developed in combination with cefepime for use against cephalosporin-, carbapenem-, and multidrug-resistant Enterobacterales and *Pseudomonas aeruginosa*. The *in vitro* activity of cefepime-taniborbactam (FTB) and comparators was evaluated against a recent global collection of clinical isolates of Enterobacterales and *P. aeruginosa* in the context of their β-lactamase carriage.

METHODS

- 17,827 Enterobacterales and 6,417 *P. aeruginosa* isolates collected from 59 countries in 2018-2021 were a part of this study (Figure 1).
- MICs of cefepime with taniborbactam fixed at 4 mg/L and comparator agents were determined using the ISO 20776-1:2019 reference method [2] and interpreted using 2022 EUCAST breakpoints [3].
- For FTB, a provisional susceptible MIC breakpoint of ≤16 mg/L was employed for comparative purposes only.
- Organisms with FTB MIC ≥16 mg/L were characterized by whole genome sequencing, while those resistant to meropenem by CLSI breakpoints [4] were screened for acquired β-lactamase carriage by PCR followed by Sanger sequencing, as previously described [5]. Additionally, 945 Enterobacterales isolates with FTB MIC values ≤8 mg/L and meropenem MIC values ≤2 µg/mL testing with cefepime and/or ceftazidime MIC values ≥2 mg/L were screened by PCR/Sanger. Also, 638 *P. aeruginosa* isolates with FTB MIC values ≤8 mg/L and meropenem MIC values ≤4 mg/L testing with cefepime and/or ceftazidime MIC values ≥16 mg/L were screened by PCR/Sanger.

RESULTS SUMMARY

- Regions contributing the most isolates to this study included Europe (43%), North America (27%) and Latin America (11%) (Figure 1).
- Against Enterobacterales carrying NDM or VIM metallo-β-lactamases, FTB was the most active agent tested as 75.3% and 94.7% of the respective groups were inhibited at ≤16 mg/L (Table 1, Figure 2). The most active comparator, MEV, inhibited 10.0% and 50.0% of the NDM- and VIM-carrying isolates, respectively.
- FTB also demonstrated potent activity against Enterobacterales harboring KPC, OXA-48 group, ESBL and AmpC-type serine-β-lactamases with 100%, 99.1%, 99.1%, and 97.3% of the isolates inhibited at ≤16 mg/L, respectively (Table 1, Figure 2). Ceftazidime-avibactam, and meropenem-vaborbactam (with the exception of the OXA-48 group), also demonstrated a high extent of coverage of these genotypically defined groups.
- FTB inhibited 82.7% of VIM-carrying isolates of *P. aeruginosa* at ≤16 mg/L, whereas all comparator agents were inactive versus this group (Table 2, Figure 3).
- FTB was the most active agent against *P. aeruginosa* harboring GES, PER, and VEB-type enzymes with 98.7%, 93.8% and 93.3% of the respective groups inhibited at ≤16 mg/L (Table 2, Figure 3).

CONCLUSIONS

Taniborbactam restored cefepime activity against most isolates of Enterobacterales carrying NDM and VIM-type metallo-β-lactamases, as well as isolates carrying serine β-lactamases including carbapenemases. Against *P. aeruginosa* carrying VIM-type metallo-β-lactamases, and GES-, PER- and VEB-type serine β-lactamases, cefepime-taniborbactam demonstrated greater activity than the tested currently available β-lactam/β-lactamase inhibitor combinations. Based on these *in vitro* data, cefepime-taniborbactam may represent a viable therapeutic option for use against difficult-to-treat β-lactamase-harboring Gram-negative pathogens. Continued development is warranted.

REFERENCES

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DISCLOSURES

This project began with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services; Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201900007C and 75A50122C00080, and The Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z, and continues with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201900007C.

RESULTS

Figure 1. Geographic region (n) of the 24,244 isolates in this study

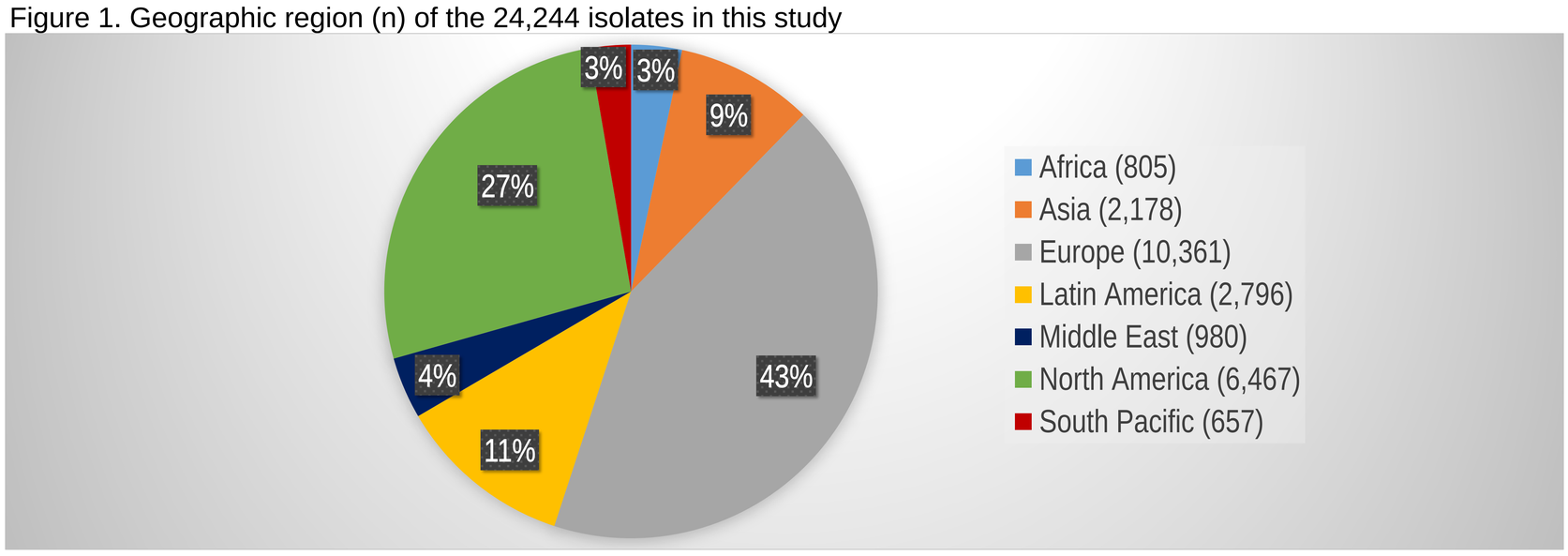


Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against molecularly characterized Enterobacterales isolates (n=1,819 in total), by genotypic subset

Genotype	N (%)[a]	MIC_{90} (mg/L)/Percent susceptible					
		FTB[b]	FEP	CZA	CT	MEV	TZP
MBL[c]	329 (18.1%)	>16/77.5	>16/0	>16/0.6	>8/0	>16/14.6	>128/0
NDM	291 (16.0%)	>16/75.3	>16/0	>16/0.3	>8/0	>16/10.0	>128/0
VIM	38 (2.1%)	16/94.7	>16/0	>16/2.6	>8/0	>16/50.0	>128/0
KPC[d]	311 (17.1%)	4/100	>16/1.0	8/94.5	>8/1.3	4/96.5	>128/0.3
OXA-48 group[e]	217 (11.9%)	4/99.1	>16/4.1	4/95.9	>8/3.2	>16/40.6	>128/0
ESBL[f]	789 (43.4%)	1/99.1	>16/3.3	1/98.6	>8/75.5	0.12/99.7	>128/58.2
AmpC[g]	75 (4.1%)	2/97.3	16/73.3	2/97.3	>8/56.0	0.12/100	>128/54.7

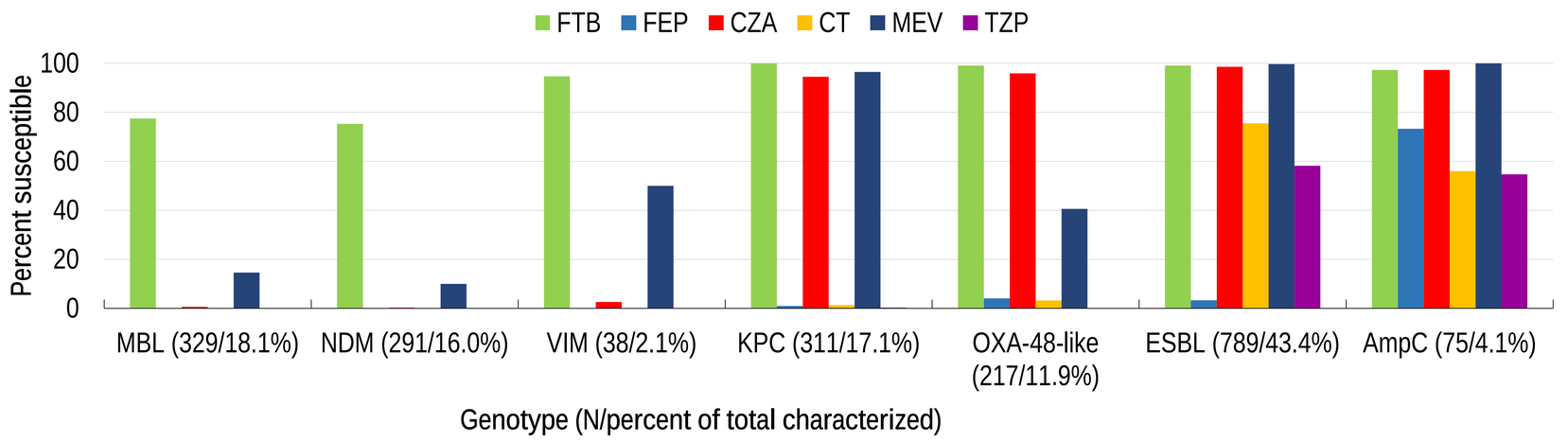
Abbreviations: FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam.
[a]Percentage is based on total molecularly characterized isolates (Enterobacterales, n=1,819).
[b]"Percent susceptible" corresponds to percentage of isolates inhibited by ≤16 mg/L FTB (for comparative purposes only).
[c]Excludes IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition [1].
[d]Excludes isolates co-producing MBLs.
[e]Excludes isolates co-producing MBLs and/or KPC.
[f]Excludes isolates co-producing carbapenemases.
[g]Excludes isolates co-producing carbapenemases and ESBLs.

Table 2. *In vitro* activity of cefepime-taniborbactam and comparator agents against molecularly characterized *P. aeruginosa* isolates (n=1,591 in total), by genotypic subset

Genotype	N (%)[a]	MIC_{90} (mg/L)/Percent susceptible					
		FTB[b]	FEP[c]	CZA	CT	MEV	TZP[c]
VIM	231 (14.5%)	>32/82.7	>32/3.5	>16/2.6	>16/0.9	>16/6.1	>128/2.2
GES[d]	78 (4.9%)	16/98.7	>32/46.2	>16/66.7	>16/1.3	>16/26.9	>128/5.1
PER[d]	16 (1.0%)	16/93.8	>32/0	>16/12.5	>16/0	>16/25.0	>128/25.0
VEB[d]	45 (2.8%)	16/93.3	>32/0	>16/2.2	>16/0	>16/4.4	>128/0

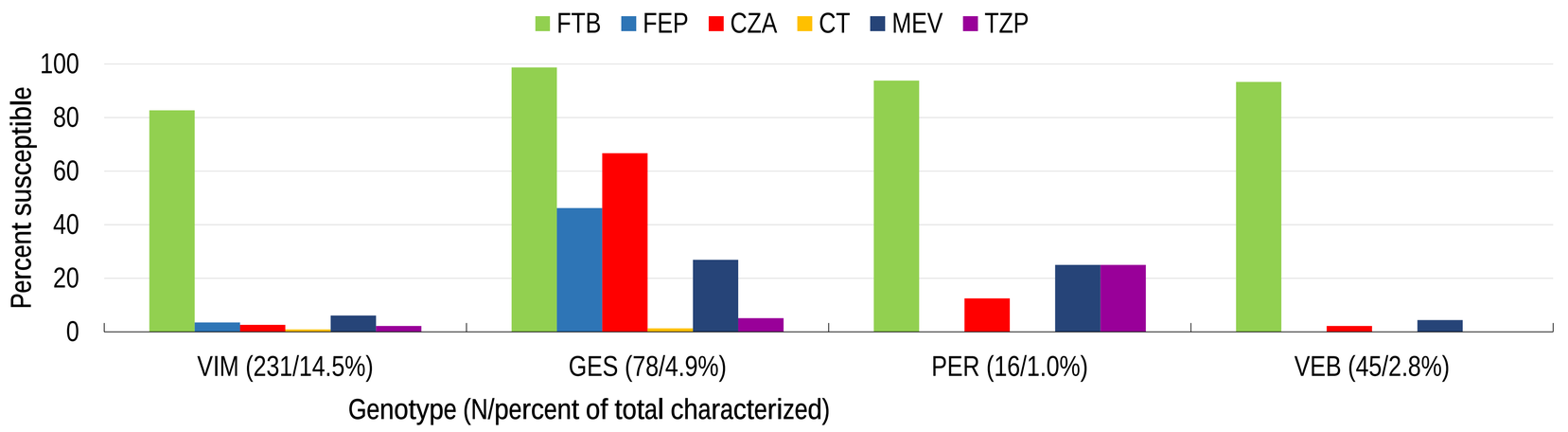
Abbreviations: FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam.
[a]Percentage is based on total molecularly characterized isolates (*P. aeruginosa*, n=1,591)
[b]"Percent susceptible" corresponds to percentage of isolates inhibited by ≤16 mg/L FTB (for comparative purposes only).
[c]For FEP and TZP, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure."
[d]Excludes isolates co-producing MBLs.

Figure 2. Antimicrobial susceptibility of Enterobacterales carrying defined β-lactamases



FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. Total N of Enterobacterales characterized molecularly = 1819. For FTB, percent susceptible corresponds to percentage of isolates inhibited by ≤16 mg/L (for comparative purposes only). MBL-carrying group excludes IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition [1]. KPC-carrying group excludes isolates co-producing MBLs. OXA-48-like-carrying group excludes isolates co-producing MBLs and/or KPC. ESBL-carrying group excludes isolates co-producing carbapenemases. AmpC carrying group excludes isolates co-producing carbapenemases and/or ESBLs.

Figure 3. Antimicrobial susceptibility of *P. aeruginosa* carrying defined β-lactamases



FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. Total N of P. aeruginosa characterized molecularly = 1591. For FTB, percent susceptible corresponds to percentage of isolates inhibited by ≤16 mg/L (for comparative purposes only). GES-, PER- and VEB-carrying groups exclude isolates co-producing MBLs.

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