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Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Resistant Clinical Isolates of Enterobacterales from 2018-2021 Global Surveillance

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INTRODUCTION

Taniborbactam is a novel, investigational 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) [1]. Taniborbactam restores the activity of cefepime against many difficult to treat organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. In this study we evaluated the activity of cefepime-taniborbactam and comparator agents against resistant clinical isolates of Enterobacterales and *P. aeruginosa* from a 2018-2021 global surveillance study.

METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined using the ISO 20776-1:2019 reference method [2] against Enterobacterales (n=17,827) and *P. aeruginosa* (n=6,417) collected in 2018-2021. Quality control (QC) testing was performed each day of testing as specified by the CLSI [3, 4]. Isolates were collected from community and hospital infections from 266 sites in 56 countries from 2018 to 2021. Isolates were sourced primarily from (n/percent of total): respiratory tract (10,156/41.9%), urinary tract (5,703/23.5%), intra-abdominal (3,661/15.1%), blood (2,874/11.9%), and skin and soft tissue (1,846/7.6%). Avibactam was tested at a fixed concentration of 4 mg/L in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 mg/L in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 mg/L in combination with meropenem [4]. Resistant phenotypes were based on 2022 EUCAST breakpoints [5]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤16 mg/L was considered for comparative purposes. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2022 breakpoints.

RESULTS SUMMARY

- Overall, 24.0% and 20.2% of Enterobacterales isolates were nonsusceptible to cefepime and piperacillin-tazobactam, respectively (Table 1). A total of 15.3% of isolates were MDR, and 4.8% were nonsusceptible to meropenem. *K. pneumoniae* (n=5,196) accounted for 47.1, 51.2, 57.1, and 78.4% of cefepime nonsusceptible, piperacillin-tazobactam nonsusceptible, MDR, and meropenem nonsusceptible isolates among Enterobacterales species within each subset, respectively.
- Cefepime-taniborbactam had potent activity against Enterobacterales overall, with an MIC_{90} value of 0.25 mg/L and 99.5% inhibited at ≤16 mg/L (Figure 1).
- Cefepime-taniborbactam maintained activity against resistant subsets of Enterobacterales (MIC_{90} range, 2 to 32 mg/L; 81.2% to 97.9% inhibited at ≤16 mg/L) including MDR isolates (MIC_{90}, 4 µg/mL; 96.8% inhibited at ≤16 mg/L) (Table 1, Figure 1). Greater than 80% of isolates that were nonsusceptible to ceftazidime-avibactam and/or meropenem-vaborbactam were inhibited at ≤16 mg/L cefepime-taniborbactam.
- From 21.9% to 29.9% of *P. aeruginosa* isolates were NS/R to cefepime, piperacillin-tazobactam and/or meropenem (Table 2). Between 10.7% and 14.8% of isolates were resistant to ceftolozane-tazobactam, ceftazidime-avibactam and/or meropenem-vaborbactam.
- Cefepime-taniborbactam was the most active tested agent against *P. aeruginosa* overall, with an MIC_{90} value of 8 mg/L and 96.5% inhibited at ≤16 mg/L (Figure 2).
- Percentages of *P. aeruginosa* isolates in the nonsusceptible subsets that were inhibited by ≤16 mg/L cefepime-taniborbactam ranged from 72.0% for ceftazidime-avibactam resistant isolates to 89.1% for piperacillin-tazobactam resistant isolates. These compared to 0% to 65.9% susceptible to comparators (Table 2, Figure 2).
- Against MDR *P. aeruginosa* (21.1% of total isolates), cefepime-taniborbactam maintained activity, with 84.1% of isolates inhibited at ≤16 mg/L, a substantially greater percentage than the most active comparators, CZA (53.3% S) and CT (46.5% S) (Table 2, Figure 2).

CONCLUSIONS

- Cefepime-taniborbactam demonstrated potent *in vitro* activity against contemporary isolates of Enterobacterales and *P. aeruginosa* from global surveillance, including MDR isolates and isolates nonsusceptible to cefepime, meropenem, piperacillin-tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam.
- These results support the continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram-negative pathogens.

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DISCLOSURES

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RESULTS

Table 1. Activity of cefepime-taniborbactam and comparators against Enterobacterales

Resistance Phenotype	N (%)	MIC_{90} (mg/L)/Percent susceptible					
		FTB[a]	FEP	CZA	CT	MEV	TZP
Enterobacterales	**17827 (100%)**	**0.25/99.5**	**>16/76.0**	**0.5/97.7**	**8/86.9**	**0.12/97.6**	**128/79.8**
FEP NS	4279 (24.0%)	2/97.9	>16/0	8/90.5	>8/55.3	8/90.1	>128/42.3
TZP R	3596 (20.2%)	4/97.5	>16/31.4	>16/89.0	>8/39.4	16/88.2	>128/0
MEM NS	861 (4.8%)	16/90.2	>16/1.3	>16/57.7	>8/1.2	>16/50.4	>128/0.4
MEV R	427 (2.4%)	32/82.4	>16/0.2	>16/30.9	>8/0.9	>16/0	>128/0.2
CZA R	408 (2.3%)	32/81.2	>16/1	>16/0	>8/0.2	>16/27.9	>128/2.9
MDR	2725 (15.3%)	4/96.8	>16/9.5	>16/85.9	>8/40.4	>16/82.5	>128/34.5

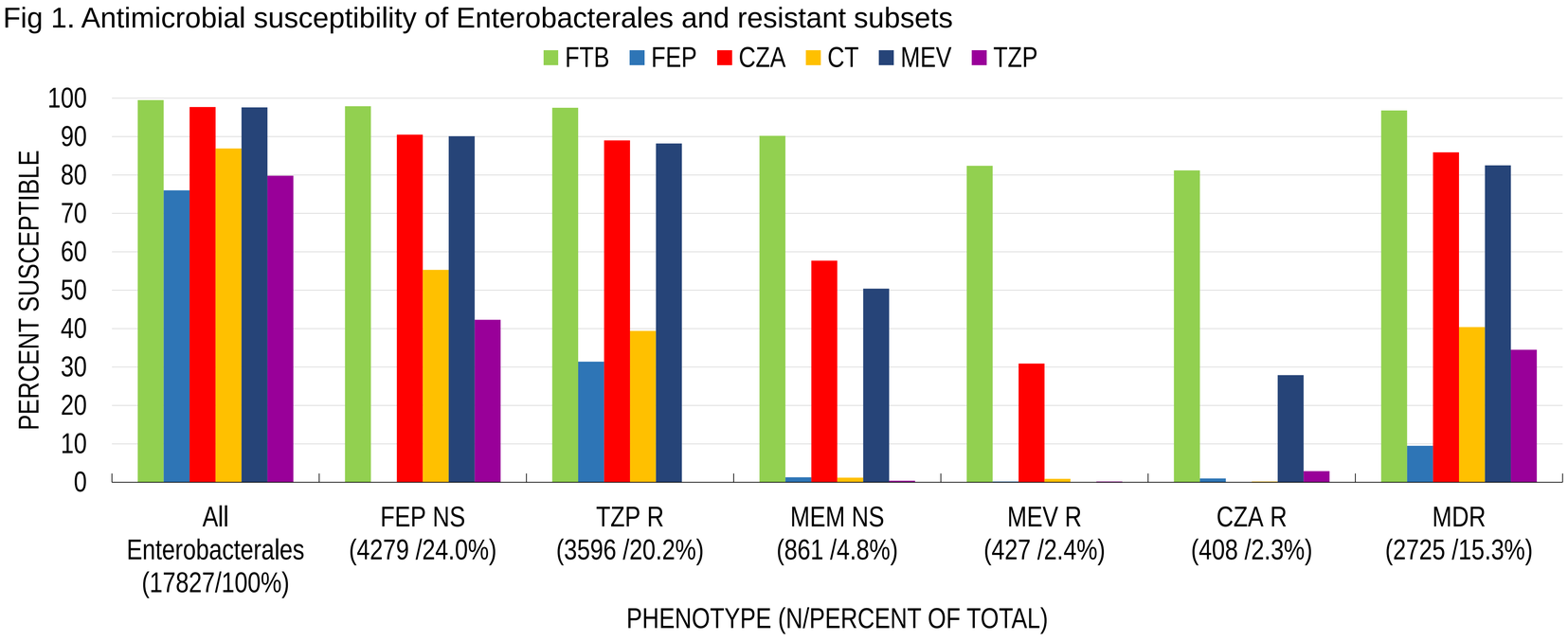
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on 2022 EUCAST breakpoints; NS, nonsusceptible based on 2022 EUCAST breakpoints
[a]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only

Table 2. Activity of cefepime-taniborbactam and comparators against *Pseudomonas aeruginosa*

Resistance Phenotype	N (%)	MIC_{90} (mg/L)/Percent susceptible					
		FTB[a]	FEP[b]	CZA	CT	MEV	TZP[b]
P. aeruginosa	**6417 (100%)**	**8/96.5**	**32/21.9**	**16/89.3**	**8/87.3**	**16/85.2**	**>128/70.1**
FEP R	1408 (21.9%)	**>32/84.1**	**>32/0**	**>16/52.6**	**>16/46.6**	**>16/49.9**	**>128/6.5**
TZP R	1917 (29.9%)	**32/89.1**	**>32/68.6**	**>16/65.9**	**>16/60.1**	**>16/56.2**	**>128/0**
MEM NS	1831 (28.5%)	**32/88.3**	**>32/43.7**	**>16/65.4**	**>16/60.8**	**>16/48.3**	**>128/30.6**
MEV R	947 (14.8%)	**>32/80.0**	**>32/25.6**	**>16/43.6**	**>16/41**	**>16/0**	**>128/11.4**
CZA R	689 (10.7%)	**128/72.0**	**>32/3.0**	**>16/0**	**>16/13.2**	**>16/22.5**	**>128/5.1**
CT R	817 (12.7%)	**64/75.9**	**>32/8.0**	**>16/26.8**	**>16/0**	**>16/31.6**	**>128/6.5**
MDR	1355 (21.1%)	**>32/84.1**	**>32/17.3**	**>16/53.3**	**>16/46.5**	**>16/40.7**	**>128/3.3**

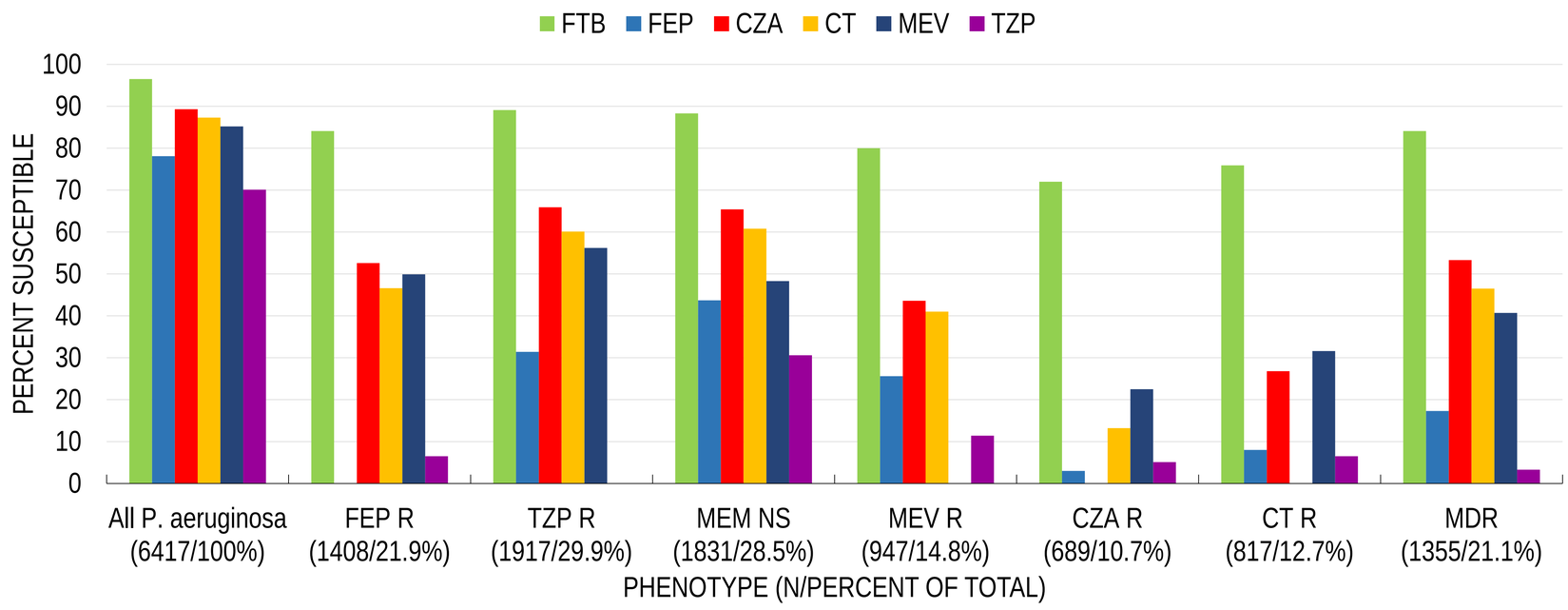
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on 2022 EUCAST breakpoints; NS, nonsusceptible based on 2022 EUCAST breakpoints
[a]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only
[b]For FEP and TZP, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure"

Fig 1. Antimicrobial susceptibility of Enterobacterales and resistant subsets



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; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2022 breakpoints; R, resistant based on EUCAST 2022 breakpoints; NS, non-susceptible based on EUCAST 2022 breakpoints; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes

Fig 2. Antimicrobial susceptibility of *Pseudomonas aeruginosa* and resistant subsets



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; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2022 breakpoints; R, resistant based on EUCAST 2022 breakpoints; NS, non-susceptible based on EUCAST 2022 breakpoints; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes

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