Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Resistant Clinical Isolates of *Enterobacterales* from 2018-2020 Global Surveillance

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

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

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

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, under Contract No. HHSN272201300019C, 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.

01652

Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Resistant Clinical Isolates of *Enterobacterales, Pseudomonas aeruginosa,* and *Stenotrophomonas maltophilia* from 2018-2020 Global Surveillance

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

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

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

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 2018-2020 global surveillance study.

MATERIALS & 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=13,731) and *P. aeruginosa* (n=4,619) collected in 2018-2020. 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 2020. Isolates were sourced from (n/percent of total): respiratory tract infections (7,455/40.0%), urinary tract infections (3,839/ 20.6%), bloodstream infections (2,880/15.4%), intraabdominal infections (2,667/14.3%), skin/soft tissue infections (1,803/9.7%), and unknown (4/<0.1%). 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. Resistant phenotypes were based on 2021 EUCAST breakpoints [5]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤8 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 2021 breakpoints.

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	**13731 (100%)**	**0.25/99.5**	**>16/75.5**	**0.5/97.8**	**8/87.1**	**0.12/97.8**	**128/80.1**
FEP NS	2782 (20.3%)	2/97.8	>16/0	4/91.2	>8/56.7	8/91.0	>128/43.7
TZP NS	2737 (19.9%)	2/97.4	>16/30.7	>16/89.4	>8/40.0	16/88.9	>128/0
MEM NS	637 (4.6%)	16/90.0	>16/1.7	>16/59.0	>8/1.1	>16/52.1	>128/0.2
MEV NS	305 (2.2%)	16/81.6	>16/0.3	>16/32.8	>8/0.3	>16/0	>128/0
CZA NS	299 (2.2%)	>16/79.9	>16/1.0	>16/0	>8/0.3	>16/31.4	>128/3.0
MDR	2660 (19.4%)	2/97.2	>16/17.1	>16/89.2	>8/50.8	16/88.6	>128/32.0

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 2021 breakpoints; NS, nonsusceptible based on 2021 EUCAST breakpoints.
[a]Corresponds to a provisional susceptible breakpoint of ≤8 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	**4619 (100%)**	**8/94.2**	**32/79.4**	**8/90.5**	**8/88.8**	**16/86.6**	**>128/70.8**
FEP R	953 (20.6%)	32/72.1	>32/0	>16/55.3	>16/50.0	>16/51.5	>128/5.3
TZP R	1347 (29.2%)	16/82.3	>32/33.0	>16/68.6	>16/63.8	>16/58.5	>128/0
MEM NS	1222 (26.5%)	16/80.9	>32/43.5	>16/66.8	>16/62.7	>16/49.4	>128/29.7
MEV NS	619 (13.4%)	>32/70.9	>32/25.4	>16/45.6	>16/43.3	>16/0	>128/9.7
CZA NS	441 (9.5%)	>32/64.2	>32/3.4	>16/0	>16/14.3	>16/23.6	>128/4.1
CT NS	366 (7.9%)	>32/58.7	>32/0	>16/14.5	>16/0	>16/18.6	>16/0.8
MDR	1062 (23.0%)	32/75.1	>32/16.3	>16/58.9	>16/52.0	>16/49.4	>128/5.4

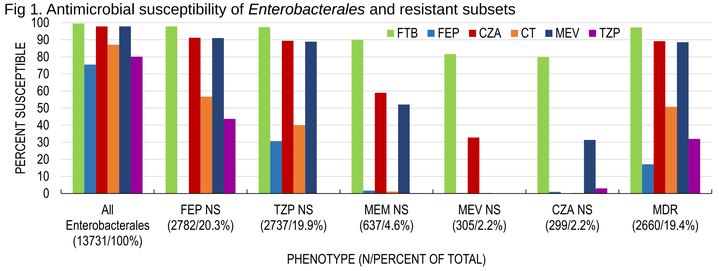
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2021 breakpoints; NS, nonsusceptible based on 2021 EUCAST breakpoints.
[a]Corresponds to a provisional susceptible breakpoint of ≤8 mg/L for comparative purposes only
[b]For FEP and TZP against *P. aeruginosa*, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure"

Table 3. Activity of cefepime-taniborbactam and comparators against *Stenotrophomonas maltophilia*

Resistance Phenotype	N (%)	MIC$_{90}$ (mg/L)/Percent susceptible[a]				
		FTB[b]	FEP[b]	CAZ	LVX	SXT
All *S. maltophilia*	**298 (100%)**	**16/85.2**	**64/8.7**	**128/36.2**	**8/82.6**	**4/87.9**
CAZ R	156 (52.3%)	16/73.1	128/0.6	>128/0	8/80.8	8/85.9
FEP MIC ≥16 mg/L	272 (91.3%)	16/83.8	64/0	128/30.5	8/82.7	4/86.8
SXT R	36 (12.1%)	16/75.0	128/0	>128/22.2	>16/55.6	16/0

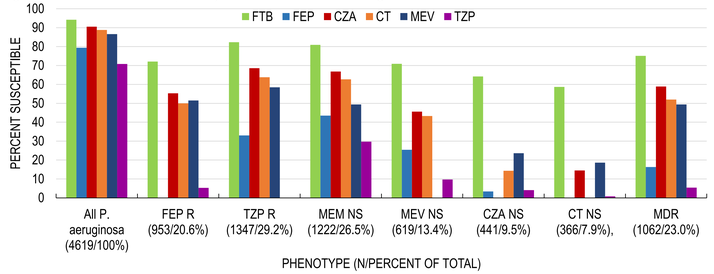
FTB, cefepime with taniborbactam fixed at 4 mg/L; CAZ, ceftazidime; FEP, cefepime; LVX, levofloxacin; SXT, trimethoprim sulfamethoxazole; R, resistant based on 2021 CLSI breakpoints
[a]Susceptibility based on CLSI 2021 breakpoints
[b]Corresponds to a provisional susceptible breakpoint of ≤8 mg/L for comparative purposes only

Fig 1. Antimicrobial susceptibility of *Enterobacterales* and resistant subsets



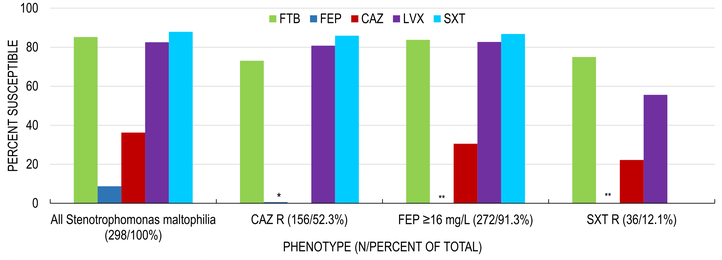
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2021 breakpoints; R, resistant based on EUCAST 2021 breakpoints; NS, non-susceptible based on EUCAST 2021 breakpoints; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤8 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 2021 breakpoints; R, resistant based on EUCAST 2021 breakpoints; NS, non-susceptible based on EUCAST 2021 breakpoints; FTB susceptibility corresponds to a provisional susceptible breakpoint of ≤8 mg/L for comparative purposes

Fig 3. Antimicrobial susceptibility of *Stenotrophomonas maltophilia* isolates and resistant subsets



FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CAZ, ceftazidime; FEP, cefepime; SXT, trimethoprim sulfamethoxazole; susceptibility based on 2021 CLSI breakpoints; FTB and FEP susceptibility correspond to a provisional susceptible breakpoint of ≤8 mg/L for comparative purposes
*indicates 0.6% of isolates susceptible to FEP; **indicates 0% of isolates provisionally susceptible to FEP

RESULTS SUMMARY

- Overall, 20.3% and 19.9% of *Enterobacterales* isolates were nonsusceptible to cefepime and piperacillin-tazobactam, respectively (Table 1). Cefepime-taniborbactam had potent activity against all *Enterobacterales*, with MIC$_{50/90}$ values of 0.06/0.25 mg/L and 99.5% inhibited at ≤8 mg/L (Figure 1).
- Cefepime-taniborbactam maintained activity against resistant subsets of *Enterobacterales* (MIC$_{90}$ range, 2 to >16 mg/L; 79.9% to 97.8% inhibited at ≤8 mg/L) including MDR isolates (MIC$_{90}$, 2 µg/mL; 97.2% inhibited at ≤8 mg/L) (Table 1, Figure 1).
- From 20.6% to 29.2% of *P. aeruginosa* isolates were NS/R to cefepime, piperacillin-tazobactam and/or meropenem (Table 2). Cefepime-taniborbactam was the most active tested agent against *P. aeruginosa* overall, with an MIC$_{90}$ value of 8 mg/L and 94.2% inhibited at ≤8 mg/L (Figure 2).
- Percentages of *P. aeruginosa* isolates in the nonsusceptible subsets that were inhibited by ≤8 mg/L cefepime-taniborbactam ranged from 58.7% for ceftolozane-tazobactam nonsusceptible isolates to 82.3% for piperacillin-tazobactam resistant isolates. Percentages that were inhibited by ≤16 mg/L cefepime-taniborbactam ranged from 78.1% for ceftolozane-tazobactam nonsusceptible isolates to 90.8% for meropenem nonsusceptible isolates. These compared to 0% to 68.6% susceptible to comparators (Table 2, Figure 2).
- Against MDR *P. aeruginosa* (23.0% of total), cefepime-taniborbactam maintained activity, with an MIC$_{90}$ value of 32 mg/L, 75.1% inhibited at ≤8 mg/L, and 88.9% inhibited at ≤16 mg/L, a substantially greater percentage than the most active comparators, CZA (58.9% S) and CT (52.0% S) (Table 2, Figure 2).
- Cefepime-taniborbactam was active against *Stenotrophomonas maltophilia* isolates with an MIC$_{90}$ value of 16 mg/L and 85.2% inhibited at ≤8 mg/L (Table 3, Figure 3).

CONCLUSIONS

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

REFERENCES

1. Hamrick,2020.https://journals.asm.org/doi/epub/10.1128/AAC.01963-19.
2. International Standard ISO 20776-1:2019(E). 2019.
3. 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.
4. Clinical and Laboratory Standards Institute. 2021. *Performance Standards for Antimicrobial Susceptibility Testing; Thirty-first Informational Supplement*. CLSI Document M100S 2020. Wayne, PA.
5. The European Committee on Antimicrobial Susceptibility Testing – *EUCAST Clinical Breakpoints* 2021; http://www.eucast.org/clinical_breakpoints/

Presented at ECCMID 2022, April 23-26, 2022 Virtual