1672

Antimicrobial Activity of Cefepime-Taniborbactam and Comparators Against Clinical Isolates from ICU and Non-ICU Patients; 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

INTRODUCTION

Taniborbactam is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with selective direct inhibitory activity against both serine- and metallo-β-lactamases. Taniborbactam restores the activity of cefepime against many difficult to treat organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. Antimicrobial resistance is typically higher in isolates collected from ICUs, leaving clinicians with limited treatment options. In this study, we evaluated the *in vitro* activity of cefepime-taniborbactam and comparator agents against clinical isolates of Enterobacterales and *P. aeruginosa* collected from ICUs and non-ICUs in a 2018-2020 global surveillance study.

METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined using the CLSI reference method [1] against Enterobacterales (n=12,428) and *P. aeruginosa* (n=4,314) collected in 2018-2020. Quality control (QC) testing was performed each day of testing as specified by the CLSI [1, 2]. Isolates were collected from community and hospital infections from 266 sites in 56 countries. Only isolates collected from patients in wards designated ICU (n= 5,225 Enterobacterales/1,947 *P. aeruginosa*) and non-ICU (n= 7,243 Enterobacterales/2,367 *P. aeruginosa*) were included in this analysis. Isolates were sourced from (n/percent of total): respiratory tract infections (6,911/41.3%), urinary tract infections (3,245/ 19.4%), intraabdominal infections (2,537/15.2%), bloodstream infections (2,431/14.5%), skin/soft tissue infections (1,616/9.7%), and unknown (2/<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 2022 CLSI breakpoints [2]. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2022 breakpoints [2]. As there is no CLSI breakpoint for meropenem-vaborbactam for *P. aeruginosa*, the EUCAST 2022 susceptible breakpoint of ≤8 mg/L has been applied [3]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional susceptible (S) breakpoint of ≤16 mg/L was applied for cefepime-taniborbactam for comparative purposes.

RESULTS

Table 1. Activity of cefepime-taniborbactam and comparators against Enterobacterales isolates from ICU and non-ICU wards

Phenotype (N[a]/% of total)	Ward	N (%)[b]	MIC$_{90}$/%S (mg/L) FTB[c]	CZA	C/T	MEV
Enterobacterales						
All (12,428/100)	Non-ICU	7,203 (58.0)	0.25/99.8	0.5/98.5	4/89.8	≤0.06/98.5
	ICU	5,225 (42.0)	0.5/99.6	1/96.6	>8/82.4	0.12/95.7
FEP NS (2,913/23.5)	Non-ICU	1,399 (19.4)	2/99.8	4/92.6	>8/64.0	2/92.2
	ICU	1,514 (29.0)	2/98.5	>16/88.4	>8/50.7	16/85.3
MEM NS (675/5.4)	Non-ICU	248 (3.4)	8/94.8	>16/62.1	>8/4.0	>16/55.6
	ICU	427 (8.2)	8/95.6	>16/61.4	>8/1.6	>16/47.1
TZP NS (2,030/16.3)	Non-ICU	907 (12.6)	2/98.5	>16/89.0	>8/30.2	16/87.9
	ICU	1,123 (21.5)	4/98.0	>16/84.6	>8/25.9	>16/79.9
MDR (1,669/13.4)	Non-ICU	758 (10.5)	4/98.2	>16/86.9	>8/40.0	16/85.5
	ICU	911 (17.4)	4/97.7	>16/80.9	>8/26.8	>16/75.3

FTB, cefepime with taniborbactam fixed at 4 µg/mL; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2022 breakpoints; NS, nonsusceptible based on CLSI 2022 breakpoints; na, CLSI breakpoints not available.
[a]N=number of isolates with ICU or non-ICU patient location provided.
[b]Percent indicates percentage of isolates from total non-ICU or total ICU isolates.
[c]%S corresponds to FTB provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only.

Table 2. Activity of cefepime-taniborbactam and comparators against *P. aeruginosa* isolates from ICU and non-ICU wards

Phenotype (N[a]/% of total)	Ward	N (%)[b]	MIC$_{90}$/%S (mg/L) FTB[c]	CZA	C/T	MEV[d]
P. aeruginosa						
All (4,314/100)	Non-ICU	2,367 (54.9)	8/97.9	8/92.5	4/91.1	16/89.9
	ICU	1,947 (45.1)	8/96.9	16/87.9	16/86.1	16/82.0
FEP NS (899/20.8)	Non-ICU	441 (18.6)	32/88.7	>16/60.1	>16/55.8	>16/57.4
	ICU	458 (23.5)	>32/87.0	>16/50.4	>16/46.1	>16/45.2
MEM NS (1,162/26.9)	Non-ICU	527 (22.3)	16/90.9	>16/68.4	>16/64.8	>16/54.8
	ICU	635 (32.6)	16/91.1	>16/66.1	>16/62.7	>16/44.8
TZP NS (1,271/29.6)	Non-ICU	613 (25.9)	16/92.5	>16/71.7	>16/67.5	>16/64.7
	ICU	658 (33.8)	16/91.6	>16/66.1	>16/61.9	>16/52.6
MDR (757/17.5)	Non-ICU	365 (15.4)	32/87.1	>16/54.1	>16/48.1	>16/44.5
	ICU	392 (20.1)	>32/84.7	>16/43.1	>16/36.0	>16/35.2

FTB, cefepime with taniborbactam fixed at 4 µg/mL; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2022 breakpoints; S, susceptibility based on CLSI 2022 breakpoints.
[a]N=number of isolates with ICU or non-ICU patient location provided.
[b]Percent indicates percentage of isolates from total non-ICU or total ICU isolates.
[c]%S corresponds to FTB provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only.
[d]As no CLSI breakpoints are available for MEV, the EUCAST 2022 susceptible breakpoint of ≤8 mg/L has been applied.

Figure 1. MIC distribution of cefepime-taniborbactam for Enterobacterales by ward type

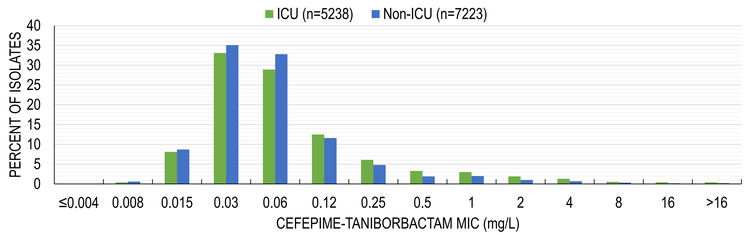


Figure 2. MIC distribution of cefepime-taniborbactam for of *Pseudomonas aeruginosa* by ward type

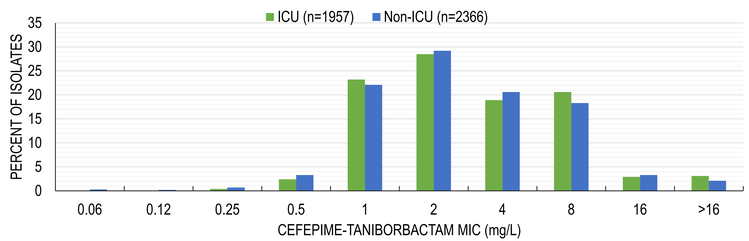
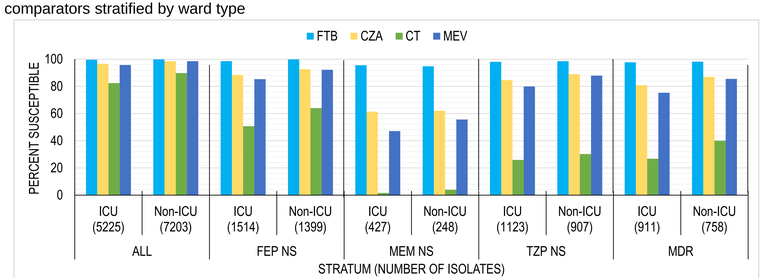
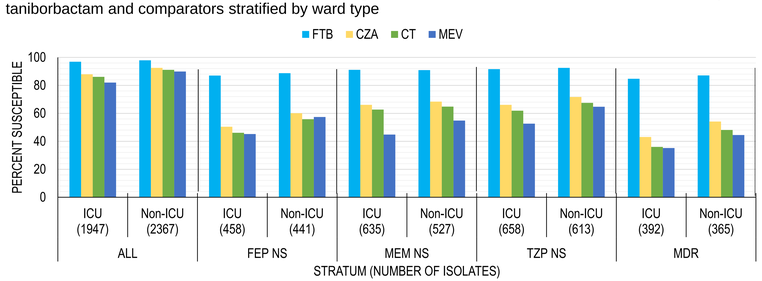


Figure 3. Susceptibility of Enterobacterales and resistant subsets isolates to cefepime-taniborbactam and comparators stratified by ward type



FTB, cefepime with taniborbactam fixed at 4 µg/mL; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2022 breakpoints; percent susceptible and non-susceptible (NS) based on CLSI 2022 breakpoints; FTB percent susceptible corresponds to provisional susceptible breakpoint of ≤16 µg/mL..

Figure 4. Susceptibility of *Pseudomonas aeruginosa* isolates and resistant subsets to cefepime-taniborbactam and comparators stratified by ward type



FTB, cefepime with taniborbactam fixed at 4 µg/mL; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; FEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; MDR, multidrug resistant defined as resistance to at least one agent from ≥3 drug classes based on CLSI 2022 breakpoints; percent susceptible and non-susceptible (NS) based on CLSI 2022 breakpoints.. As no CLSI breakpoints are available for MEV, the EUCAST 2022 susceptible breakpoint of ≤8 mg/L has been applied; FTB percent susceptible corresponds to provisional susceptible breakpoint of ≤16 µg/mL.

RESULTS SUMMARY

- Cefepime-taniborbactam showed *in vitro* activity against Enterobacterales, with MIC$_{90}$ values of 0.25 mg/L for isolates from non-ICU patients and 0.5 µg/mL for isolates from ICU patients (Table 1, Figure 1). Greater than 99% of all Enterobacterales from both wards were inhibited by ≤16 mg/L of cefepime-taniborbactam.
- Cefepime-taniborbactam maintained activity against resistant phenotypes of Enterobacterales in both ward types, with 94.8 - 99.8% of isolates inhibited at ≤16 mg/L.
- The percent susceptible to comparator agents against the resistant subsets ranged from 1.6% to 92.6% for Enterobacterales (Table 1, Figure 3).
- Cefepime-taniborbactam showed *in vitro* activity against *P. aeruginosa*, with an MIC$_{90}$ value of 8 mg/L and inhibiting at least 96.9% of isolates at ≤16 mg/L for both ICU and non-ICU isolates (Table 2, Figure 2).
- Cefepime-taniborbactam maintained activity against resistant phenotypes of *P. aeruginosa* in both ward types, with 84.7% to 92.5% inhibited at ≤16 mg/L (Table 2).
- The percent susceptible to comparator agents against the resistant subsets *of P. aeruginosa* ranged from 35.2% to 68.4% (Table 2, Figure 4).
- Against the particularly challenging subset of MDR *P. aeruginosa* from ICU patients, cefepime-taniborbactam was the most active agent tested as it inhibited 84.7% of isolates at ≤16 mg/L compared to 43.1% susceptible to ceftazidime-avibactam, 36.0% susceptible to ceftolozane-tazobactam, 35.2% susceptible to meropenem-vaborbactam.

CONCLUSIONS

- Cefepime-taniborbactam demonstrated potent *in vitro* activity against Enterobacterales and *P. aeruginosa* from ICU and non-ICU wards, including difficult to treat resistant subsets of isolates.
- This supports the continued development of cefepime-taniborbactam as a potential new treatment option for infections due to resistant Gram-negative pathogens.

REFERENCES

1. 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.
2. Clinical and Laboratory Standards Institute. 2022. *Performance Standards for Antimicrobial Susceptibility Testing*; Thirty-second Informational Supplement. CLSI Document M100S 2022. Wayne, PA.
3. The European Committee on Antimicrobial Susceptibility Testing – *EUCAST Clinical Breakpoints 2022*; http://www.eucast.org/clinical_breakpoints/

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.

Presented at IDWeek 2022, October 19-23, 2022 in Washington, D.C.