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Antimicrobial Activity of Cefepime in Combination with Taniborbactam Against Resistant Clinical Isolates of Enterobacterales and *Pseudomonas aeruginosa* Collected in Europe, 2018-2022

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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* [2]. In this study we evaluated the activity of cefepime-taniborbactam and comparator agents against resistant clinical isolates of Enterobacterales and *P. aeruginosa* isolated in Europe from a 2018-2022 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 [3] against Enterobacterales (n=8,760) and *P. aeruginosa* (n=3,480) collected in 2018-2022. Quality control (QC) testing was performed each day of testing as specified by the CLSI [4, 5]. Isolates were collected from community and hospital infections from 140 sites in 25 countries in Europe (Figure 1). Isolates were sourced primarily from (n/percent of total): respiratory tract (5,616/45.9%), urinary tract (2,611/21.3%), intraabdominal (1,931/15.8%), blood (1,373/11.2%), and skin and soft tissue (712/5.8%). 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 [5]. Resistant phenotypes were based on 2023 EUCAST breakpoints [6]. As cefepime-taniborbactam breakpoints have not yet been established, a provisional non-resistant breakpoint of ≤16 mg/L was considered for comparative purposes [2]. Multidrug resistant (MDR) was defined as resistance to at least one agent from ≥3 drug classes based on EUCAST 2023 breakpoints. To examine geographic variation in antimicrobial resistance, countries were divided into two European regions: North/West (NW) Europe (Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom) and Central/East (CE) Europe (Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, and Ukraine).

RESULTS SUMMARY

- Among Enterobacterales isolates from NW Europe, 15.4% and 17.6% were nonsusceptible to cefepime and piperacillin-tazobactam, respectively (Table 1). Corresponding percentages for isolates from CE Europe were 37.9% and 29.4%, respectively (Table 2).
- Cefepime-taniborbactam had potent activity against all Enterobacterales, with $MIC_{50/90}$ values of 0.06/0.12 mg/L and 99.9% inhibited at ≤16 mg/L (NW Europe) and $MIC_{50/90}$ values of 0.06/1 mg/L and 98.9% inhibited at ≤16 mg/L (CE Europe).
- Cefepime-taniborbactam maintained activity against all resistant subsets of Enterobacterales (MIC_{90} range, 1 to 32 mg/L; 80.9% to 99.5% inhibited at ≤16 mg/L) including MDR isolates (MIC_{90}, 2 µg/mL; 98.9% inhibited at ≤16 mg/L [NW Europe]; MIC_{90}, 8 µg/mL; 94.5% inhibited at ≤16 mg/L [CE Europe]) (Table 1, Table 2).
- From 17.4% to 25.5% of *P. aeruginosa* isolates from NW Europe were nonsusceptible/resistant to cefepime, piperacillin-tazobactam and/or meropenem (Table 3). Among isolates from CE Europe, 31.4% to 45.8% were nonsusceptible/resistant to these agents (Table 4).
- Cefepime-taniborbactam was active against *P. aeruginosa* overall, with $MIC_{50/90}$ values of 2/8 mg/L and 99.2% inhibited at ≤16 mg/L for isolates from NW Europe, and $MIC_{50/90}$ values of 4/16 mg/L and 93.8% inhibited at ≤16 mg/L for isolates from CE Europe (Table 3, Table 4).
- Percentages of *P. aeruginosa* isolates in the nonsusceptible subsets that were inhibited by ≤16 mg/L cefepime-taniborbactam ranged from 90.2% for ceftazidime-avibactam resistant isolates to 97.3% for piperacillin-tazobactam resistant isolates among isolates from NW Europe, and from 71.4% for ceftazidime-avibactam resistant isolates to 86.6% for meropenem resistant isolates from CE Europe.
- Against MDR *P. aeruginosa* (14.9% and 35.1% of total in NW Europe and CE Europe, respectively), cefepime-taniborbactam maintained substantial activity, with $MIC_{50/90}$ values of 8/16 mg/L and 8/128 mg/L, and 94.8% and 84.0% inhibited at ≤16 mg/L for isolates from NW Europe and CE Europe, respectively (Table 3, Table 4).

CONCLUSIONS

- Activity of all antimicrobials tested was reduced in CE compared to NW Europe.
- The addition of taniborbactam to cefepime greatly enhanced its *in vitro* activity against Enterobacterales and *P. aeruginosa* from European sites, including most isolates nonsusceptible or resistant to cefepime, meropenem, piperacillin/tazobactam, ceftazidime-avibactam, ceftolozane-tazobactam, and/or meropenem-vaborbactam.
- Continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram-negative pathogens is warranted.

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DISCLOSURES

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RESULTS

Figure 1. Countries contributing isolates

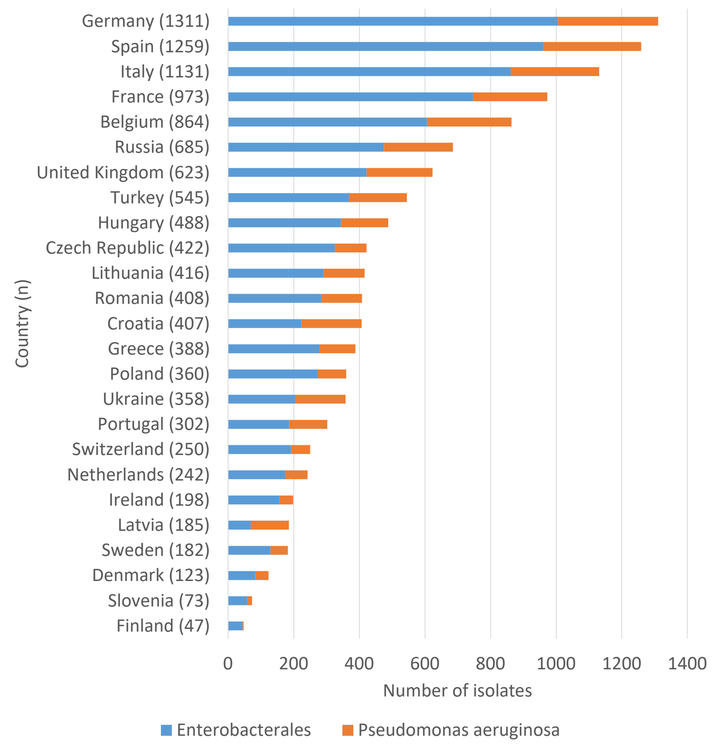

Figure 2. Enterobacterales species included in the study

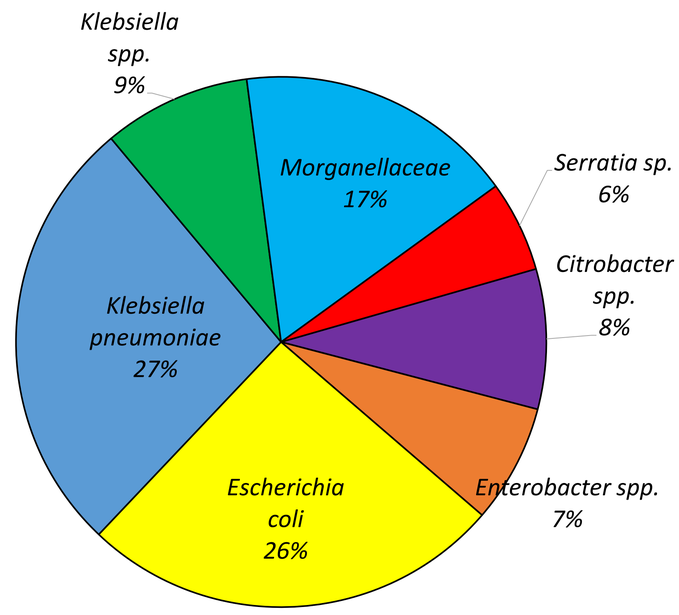

Table 1. Activity of cefepime-taniborbactam and comparators against Enterobacterales from North/West Europe[a]

Resistance Phenotype	N (%)	MIC_{90} (µg/mL)/Percent susceptible					
		FTB[b]	FEP	CZA	CT	MEV	TZP
Enterobacterales	**5926 (100)**	**0.12/99.9**	**8/86.6**	**0.5/99.4**	**2/90.6**	**0.12/99.5**	**64/82.4**
FEP NS	911 (15.4)	1/99.5	>16/0	2/95.9	>8/56.2	1/97.5	>128/40.5
TZP NS	1045 (17.6)	1/99.4	>16/48.1	2/96.5	>8/51.1	1/97.7	>128/0
MEM NS	146 (2.5)	4/97.3	>16/2.1	>16/81.5	>8/2.1	>16/83.6	>128/0.7
MEV NS	24 (0.4)	32/87.5	>16/4.2	>16/37.5	>8/4.2	>16/0	>128/0
CZA NS	37 (0.6)	16/94.6	>16/0	>16/0	>8/0	>16/59.5	>128/0
MDR	364 (6.1)	2/98.9	>16/8.5	8/92.0	>8/29.7	4/93.7	>128/0

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 2023 EUCAST breakpoints; NS, nonsusceptible based on 2023 EUCAST breakpoints
[a]Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, and United Kingdom
[b]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only

Table 2. Activity of cefepime-taniborbactam and comparators against Enterobacterales from Central/East Europe[a]

Resistance Phenotype	N (%)	MIC_{90} (µg/mL)/Percent susceptible					
		FTB[b]	FEP	CZA	CT	MEV	TZP
Enterobacterales	**2834 (100)**	**1/98.9**	**>16/62.1**	**2/94.6**	**>8/77.5**	**1/93.4**	**>128/70.6**
FEP NS	1075 (37.9)	4/97.0	>16/0	>16/86.0	>8/46.2	>16/82.7	>128/35.3
TZP NS	832 (29.4)	4/96.2	>16/16.3	>16/81.7	>8/29.6	>16/77.5	>128/0
MEM NS	313 (11.0	32/89.8	>16/2.2	>16/54.6	>8/1.6	>16/40.3	>128/0
MEV NS	187 (6.6)	32/84.0	>16/0.5	>16/35.8	>8/1.6	>16/0	>128/0
CZA NS	152 (5.4)	32/80.9	>16/0.7	>16/0	>8/0	>16/21.1	>128/0
MDR	583 (20.6)	8/94.5	>16/1.4	>16/75.0	>8/17.2	>16/68.1	>128/0

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 2023 EUCAST breakpoints; NS, nonsusceptible based on 2023 EUCAST breakpoints
[a]Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, Ukraine
[b]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only

Table 3. Activity of cefepime-taniborbactam and comparators against *Pseudomonas aeruginosa* from North/West Europe[a]

Resistance Phenotype	N (%)	MIC_{90} (µg/mL)/Percent susceptible					
		FTB[b]	FEP[c]	CZA	CT	MEV	TZP[c]
P. aeruginosa	**2180 (100)**	**8/99.2**	**16/82.6**	**8/93.9**	**4/92.6**	**8/90.5**	**128/74.5**
FEP R	380 (17.4)	16/95.5	>32/0	>16/67.1	>16/61.3	>16/62.9	>128/7.1
TZP R	555 (25.5)	16/97.3	32/36.4	16/77.7	>16/73.7	>16/68.3	>128/0
MEM NS	507 (23.3)	16/97.0	32/50.5	16/78.5	>16/75.1	>16/59.2	>128/37.3
MEV R	207 (9.5)	16/94.2	>32/31.9	>16/57.5	>16/57.5	>16/0	>128/15.0
CZA R	133 (6.1)	16/90.2	>32/6.0	>16/0	>16/23.3	>16/33.8	>128/6.8
CT NS	161 (7.4)	16/93.2	>32/8.7	>16/36.6	>16/0	>16/45.3	>128/9.3
MDR	324 (14.9)	16/94.8	>32/17.9	>16/67.3	>16/61.4	>16/50.9	>128/3.4

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 2023 EUCAST breakpoints; NS, nonsusceptible based on 2023 EUCAST breakpoints.
[a]Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, and United Kingdom
[b]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only
[c]For FEP and TZP against *P. aeruginosa*, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure"

Table 4. Activity of cefepime-taniborbactam and comparators against *Pseudomonas aeruginosa* from Central/East Europe[a]

Resistance Phenotype	N (%)	MIC_{90} (µg/mL)/Percent susceptible					
		FTB[a]	FEP[b]	CZA	CT	MEV	TZP[b]
P. aeruginosa	**1300 (100)**	**16/93.8**	**>32/68.6**	**>16/79.8**	**>16/74.9**	**>16/71.4**	**>128/59.6**
FEP NS	408 (31.4)	>128/80.4	>32/0	>16/37.5	>16/31.4	>16/30.4	>128/5.4
TZP NS	525 (40.4)	128/86.3	>32/26.5	>16/52.0	>16/41	>16/35.8	>128/0
MEM NS	596 (45.8)	128/86.6	>32/39.1	>16/57.2	>16/47.8	>16/37.6	>128/25.7
MEV R	372 (28.6)	>128/78.8	>32/23.7	>16/39.8	>16/29.0	>16/0	>128/9.4
CZA R	262 (20.2)	>128/71.4	>32/2.7	>16/0	>16/4.2	>16/14.5	>128/3.8
CT NS	326 (25.1)	>128/76.7	>32/14.1	>16/23.0	>16/0	>16/19.0	>128/4.9
MDR	456 (35.1)	128/84.0	>32/18.9	>16/45.4	>16/33.3	>16/28.3	>128/2.4

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 2023 EUCAST breakpoints; NS, nonsusceptible based on 2023 EUCAST breakpoints
[a]Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, Ukraine
[b]Corresponds to a provisional susceptible breakpoint of ≤16 mg/L for comparative purposes only
[c]For FEP and TZP against *P. aeruginosa*, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure"

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