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In Vitro Activity of Cefepime-taniborbactam and Comparators Against Enterobacterales and *Pseudomonas aeruginosa* Collected in Europe (2018-2023) Stratified by β-lactamase Carriage

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INTRODUCTION

Cefepime-taniborbactam (FTB) is a combination of a 4th generation cephalosporin with a novel β-lactamase inhibitor with inhibitory activity against serine-β-lactamases, as well as NDM and VIM metallo-β-lactamases [1]. This combination is in development for use against multidrug-resistant Enterobacterales and *Pseudomonas aeruginosa*. We report on the activity of FTB and comparators against European clinical isolates of Enterobacterales and *P. aeruginosa* collected from 2018-2023, stratified by their β-lactamase content.

METHODS

- In total, 9984 Enterobacterales and 4134 *P. aeruginosa* isolates collected in 26 European countries from 2018-2023 were evaluated.
- MICs of cefepime with taniborbactam fixed at 4 mg/L and comparators were determined using the ISO 20776-1:2019 reference method [2] and interpreted using 2024 EUCAST breakpoints [3].
- For FTB, a provisional susceptible MIC breakpoint of ≤16 mg/L was used for comparison purposes [4].
- Organisms with FTB MIC >8 mg/L, those resistant to meropenem by CLSI 2024 criteria [5], and approximately 20% of Enterobacterales susceptible to meropenem but with ceftazidime or cefepime MIC ≥2 mg/L (i.e., a presumptive ESBL phenotype), were screened for acquired β-lactamases by PCR or WGS, as previously described [6,7]. β-lactamase content is presented in a "hierarchical" manner with the order MBL > KPC > OXA-48-like > ESBL > AmpC. The first category included all isolates carrying an MBL and any other β-lactamases. The second category shows isolates carrying KPC, excluding those that also carried an MBL, and so forth.
- To examine geographic variation in carbapenemase production, countries were divided into two European regions: North/Western Europe (Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom) and Central/Eastern Europe (Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, and Ukraine).

RESULTS SUMMARY

- In total, 987 Enterobacterales and 1073 *P. aeruginosa* were subjected to molecular testing. Countries contributing the most isolates included Ukraine (10.7%; n=220), Russia (10.3%; n=213), and Italy (10.3%; n=212) (Figure 1). *P. aeruginosa* and *K. pneumoniae* accounted for >83% of the molecularly-characterized isolates (Figure 2).
- Overall, 497/524 (94.8%) of the characterized meropenem-resistant (MIC ≥ 4 mg/L; CLSI 2024 [5]) Enterobacterales isolates carried one or more carbapenemase genes, of which 185/497 (37.2%) harbored at least one metallo-β-lactamase while the remainder carried serine carbapenemases (38 isolates possessed both serine and metallo-type carbapenemases). Isolates from North/Western European countries were more likely to carry KPC and less likely to carry NDM or OXA-48-like enzymes than those from Central/Eastern Europe (Figure 3A).
- Overall, 313/1000 (31.2%) of the characterized meropenem-resistant (MIC ≥ 8 mg/L; CLSI 2024 [5]) *P. aeruginosa* isolates carried one or more carbapenemase genes, of which 265/313 (84.7%) were metallo-β-lactamase carriers while the remainder harbored serine carbapenemases. Meropenem-resistant isolates in Central/Eastern Europe were more likely to possess a carbapenemase (~42%) than those originating from North/Western Europe (~15%). VIM was the most frequently encountered carbapenemase in both geographies (Figure 3B).
- FTB was the only tested agent with activity against NDM-carrying Enterobacterales, with 76.0% of the isolates inhibited at ≤16 mg/L (Table 1, Figure 4A).
- FTB at ≤16 mg/L inhibited 93.8% of VIM-carrying Enterobacterales, approximately 40 percentage points higher than the most active comparator, meropenem-vaborbactam.
- FTB also demonstrated potent antimicrobial activity against Enterobacterales harboring KPC, OXA-48-group, ESBL and acquired AmpC-type enzymes, with 100%, 98.6%, 99.4%, and 100% of the isolates inhibited at ≤16 mg/L, respectively.
- FTB was the sole agent among comparators exhibiting antimicrobial activity versus VIM-carrying *P. aeruginosa*, inhibiting 84.5% of these isolates at ≤16 mg/L (Table 1, Figure 4B).
- Against *P. aeruginosa* harboring GES-, VEB-, and PER-type enzymes, FTB was also the most active agent, with 100%, 93.5% and 100% of the isolates in the respective groups inhibited at ≤16 mg/L.

CONCLUSIONS

Taniborbactam strongly potentiated cefepime against most isolates of Enterobacterales carrying NDM and VIM metallo-β-lactamases, as well as isolates carrying serine β-lactamases. Against *P. aeruginosa* producing VIM, as well as GES-, PER- and VEB-type serine β-lactamases, FTB at ≤16 mg/L inhibited a greater percentage of isolates than comparators. FTB could represent an important addition to the antimicrobial armamentarium.

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DISCLOSURES

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RESULTS

Figure 1. Number of molecularly characterized isolates of *P. aeruginosa* (n=1073) and Enterobacterales (n=987), by country of collection

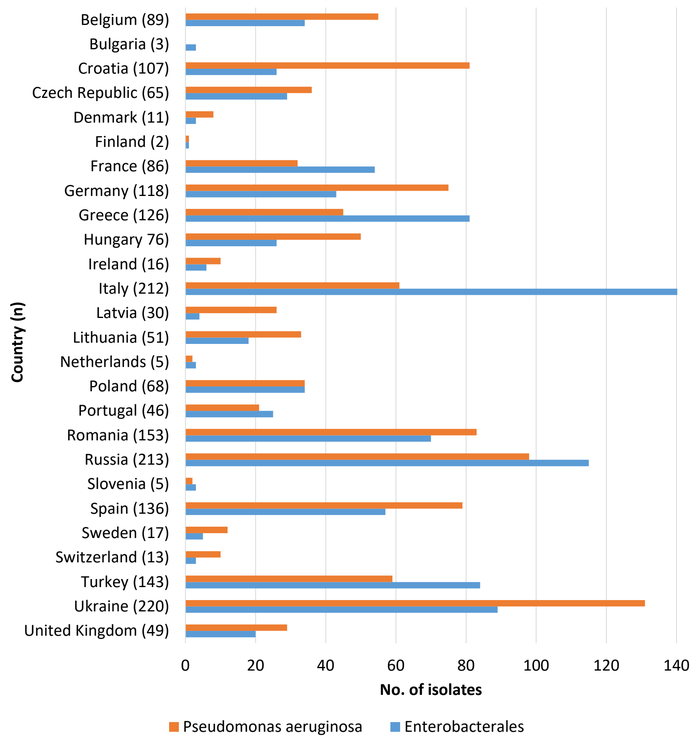


Figure 2. Taxon distribution of molecularly characterized isolates included in this study

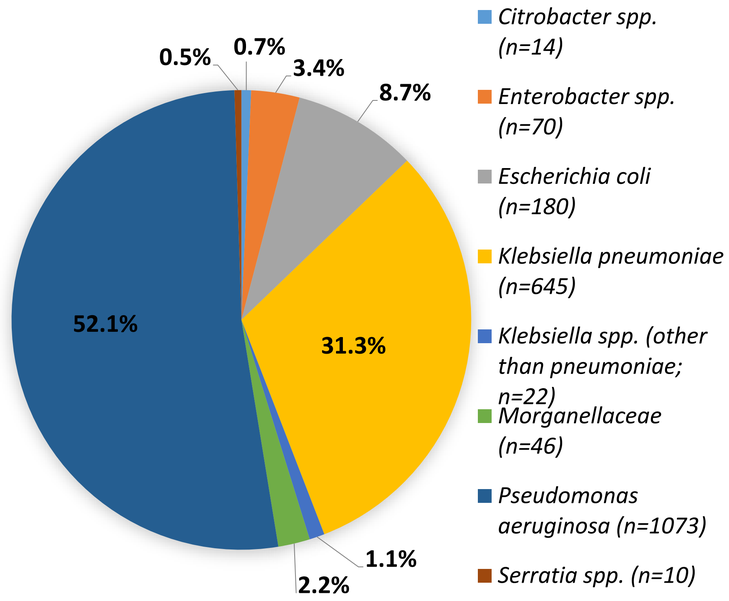
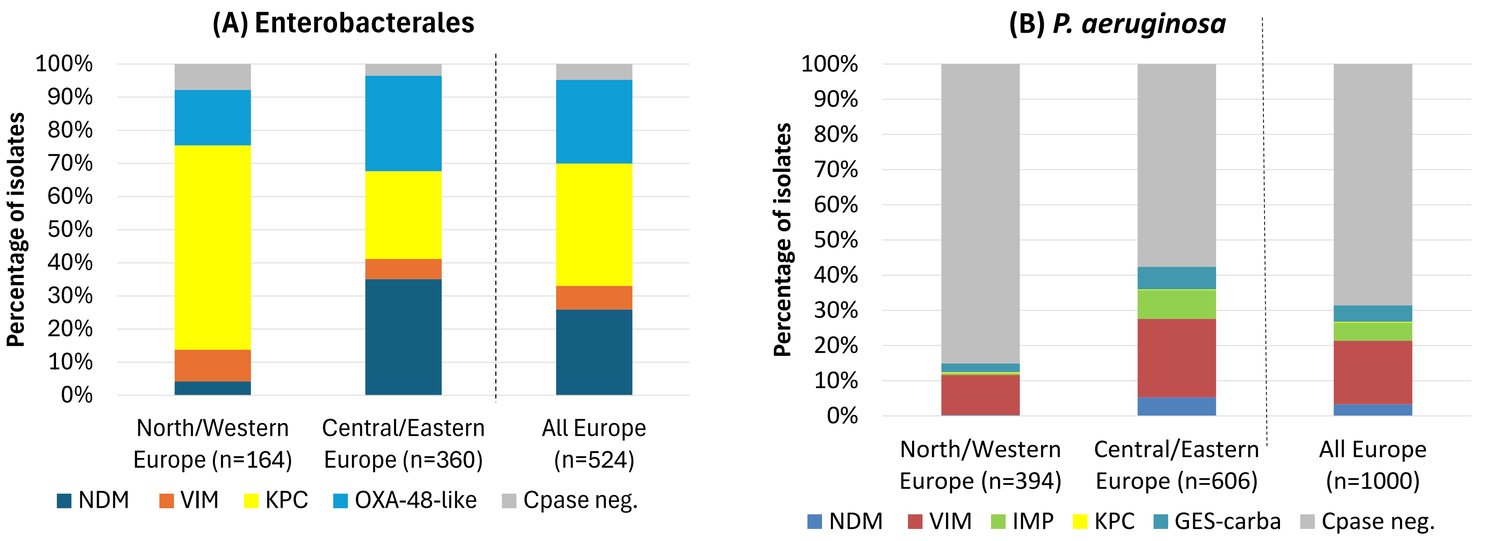


Figure 3. Diversity of carbapenemases detected among meropenem-resistant (CLSI 2024 [5]) Enterobacterales (A) and *P. aeruginosa* (B) by European region*



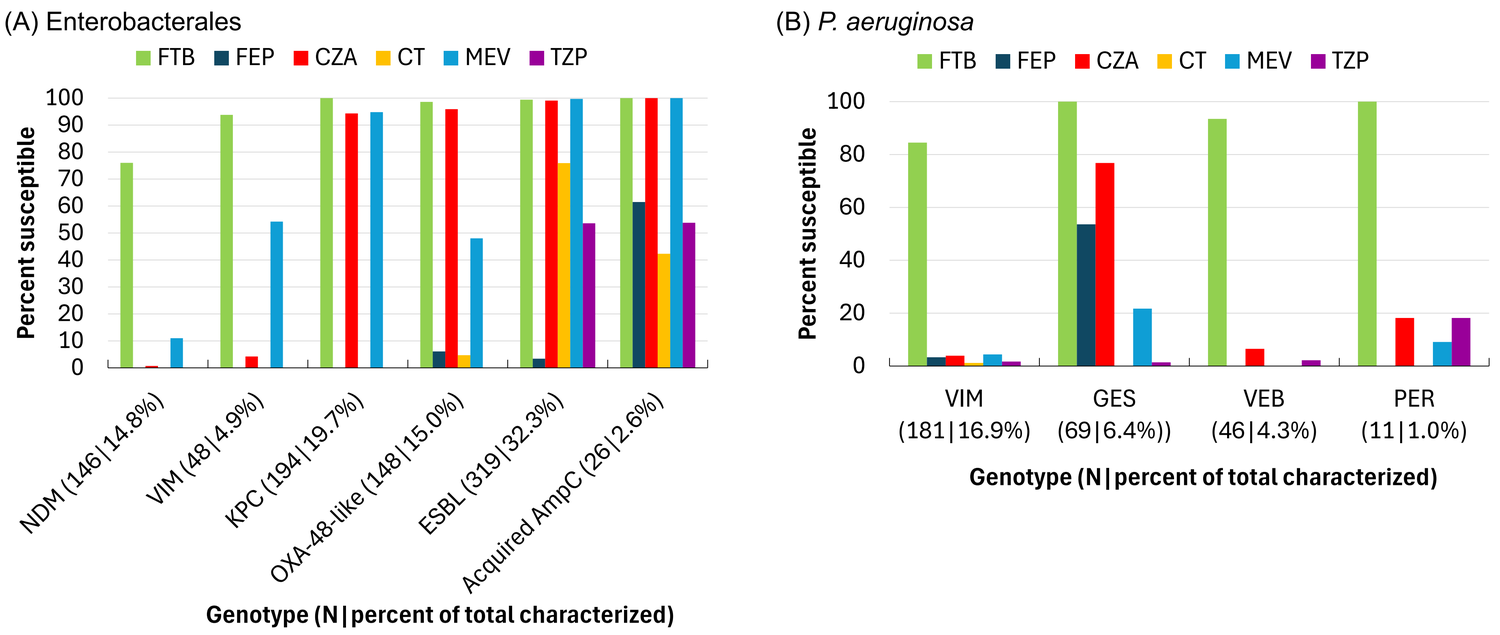
*Central/Eastern: Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, Ukraine. North/Western: Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom. Isolates that carried multiple carbapenemases were counted for each carbapenemase type. "GES-carba" only tallies GES variants with reported carbapenemase activity. "Cpase neg" = no carbapenemases were detected.

Table 1. *In vitro* activity of FTB and comparators against molecularly characterized Enterobacterales and *P. aeruginosa*, by genotypic subset

Organism / Genotype	N (% of total) characterized	Percent susceptible/MIC$_{90}$ (mg/L)					
		FTB[a]	FEP[b]	CZA	CT	MEV	TZP[b]
Enterobacterales							
NDM	146 (14.8%)	76.0/64	0/>16	0.7/>16	0/>8	11.0/>16	0/>128
VIM	48 (4.9%)	93.8/16	0/>16	4.2/>16	0/>8	54.2/>16	0/>128
KPC[c]	194 (19.7%)	100/4	0/>16	94.3/8	0/>8	94.8/4	0/>128
OXA-48-like[d]	148 (15.0%)	98.6/4	6.1/>16	95.9/4	4.7/>8	48.0/>16	0/>128
ESBL[e]	319 (32.3%)	99.4/1	3.4/>16	99.1/1	75.9/>8	99.7/0.12	53.6/>128
Acquired AmpC[f]	26 (2.6%)	100/0.25	61.5/4	100/1	42.3/>8	100/0.12	53.8/>128
P. aeruginosa							
VIM	181 (16.9%)	84.5/128	3.3/>32	3.9/>16	1.1/>16	4.4/>16	1.7/>128
GES[e]	69 (6.4%)	100/16	53.6/32	76.8/16	0/>16	21.7/>16	1.4/>128
VEB[e]	46 (4.3%)	93.5/16	0/>32	6.5/>16	0/>16	0/>16	2.2/>128
PER[e]	11 (1.0%)	100/8	0/>32	18.2/>16	0/>16	9.1/>16	18.2/>128

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]"Percent susceptible" corresponds to percentage of isolates inhibited by ≤16 mg/L FTB (for comparative purposes).
[b]For FEP and TZP against P. aeruginosa, "Percent Susceptible" corresponds to "Percent Susceptible, Increased Exposure"
[c]Excludes isolates co-producing NDM (n=4) or VIM (n=12). These isolates included in the rows above.
[d]Excludes isolates co-producing NDM (n=22). These isolates included in the "NDM" row above.
[e]Excludes isolates co-producing carbapenemases. These isolates are included in respective carbapenemase rows above.
[f]Excludes isolates co-producing carbapenemases and ESBLs. These isolate are included in respective carbapenemase or ESBL rows above.

Figure 4. Antimicrobial susceptibility of Enterobacterales (A) and *P. aeruginosa* (B) to FTB and comparators, by β-lactamase carriage



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 = 987; total n of P. aeruginosa = 1073. For FTB, percent susceptible corresponds to percentage of isolates inhibited by ≤16 mg/L (for comparative purposes only). KPC-, and OXA-48-like-carrying groups exclude any isolates co-producing MBLs. ESBL-, GES-, VEB- and PER-carrying groups excludes isolates co-producing carbapenemases. Acquired AmpC-carrying group excludes isolates co-producing carbapenemases and/or ESBLs.

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