Cefepime-taniborbactam and comparator activity in vitro against carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and multidrug-resistant (MDR) Enterobacterales and *P. aeruginosa* from 2018-2020 surveillance

Poster EA03
ESCMID/ASM Conference
Dublin, IE October 4-7, 2022

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Background

- CRE and CRPA are WHO Critical, Priority 1 pathogens (WHO 2017); CRE and MDR *P. aeruginosa* are CDC Urgent and Serious Threats, respectively (CDC 2021)
- Carbapenem resistance is most often mediated by carbapenemases (e.g. KPC, OXA-48) in Enterobacterales and by non-carbapenemase mechanisms (e.g. OprD porin loss; efflux upregulation) in *P. aeruginosa* (Simner 2017). However, metallo-carbapenemase (NDM, VIM)-producing CRE and CRPA are emerging (Tamma 2022; Tenover 2022)
- Since limited screening may underestimate carbapenemase gene carriage, and since CRE, CRPA and MDR infections may have poor outcomes, resistance epidemiology should guide development of new agents to ensure activity against CRE, CRPA and MDR organisms, regardless of mechanism
- Approved BL/BLIs lack activity against metallo-β-lactamase (MBL)-producing organisms, and characterization of their activity against non-carbapenemase-producing CRE (e.g. Castanheira 2021) and CRPA remains a work in progress
- Taniborbactam is a boronate inhibitor of serine and metallo-β-lactamases (Hamrick 2020). Cefepime-taniborbactam was statistically superior to meropenem in a Phase 3 study of adults with cUTI (NCT03840148)
- Here, we evaluated the in vitro activity of cefepime-taniborbactam and comparators against CRE, CRPA, and MDR isolates from the Global Evaluation of Antimicrobial Resistance via Surveillance (GEARS) program, 2018-2020

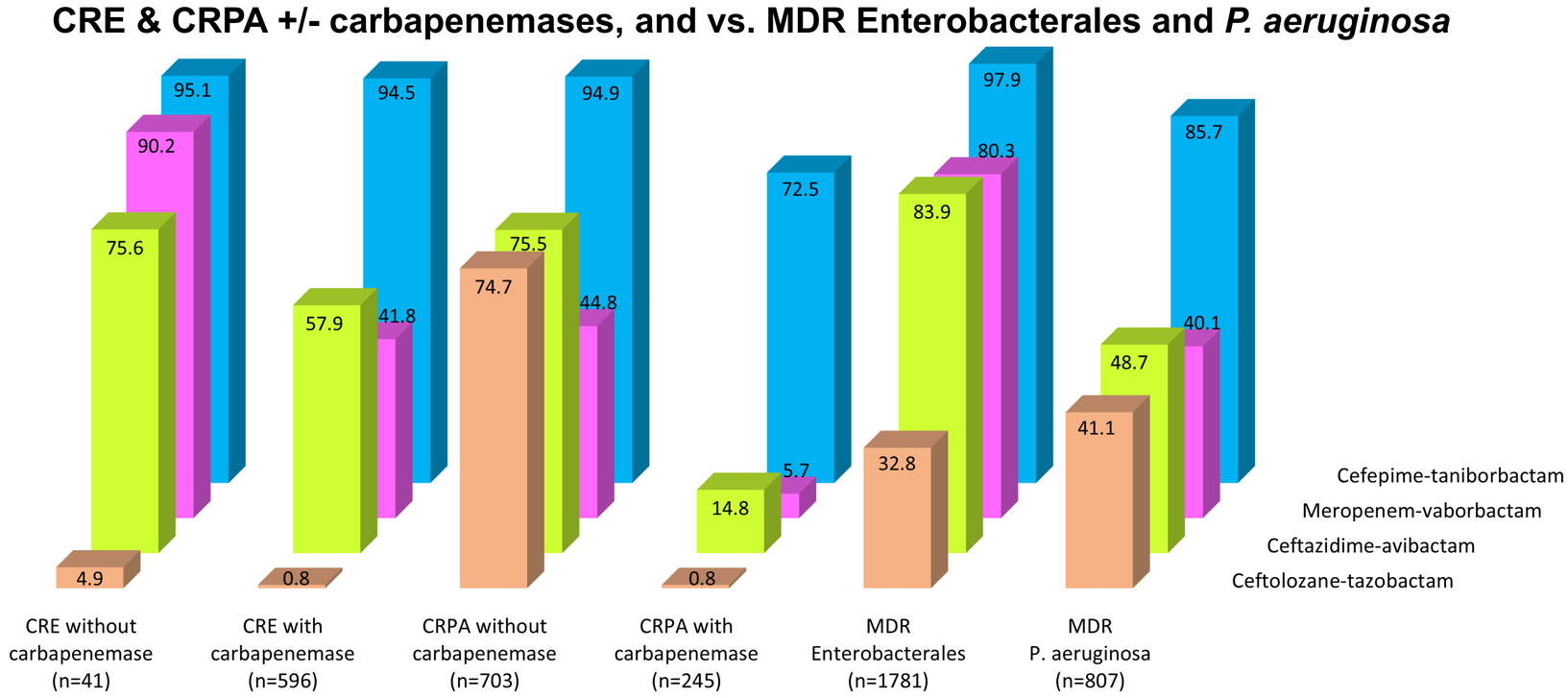
Results- CRPA with and without carbapenemases

- Of 4,619 *P. aeruginosa* isolates, 948 (20.5%) were CRPA, 703/948 (74.2%) of which lacked a carbapenemase (Fig. 1)
- CRPA isolates without carbapenemases were widely distributed: 25 countries contributed at least 10 isolates to this subset (Fig. 2). In contrast, carbapenemase-producing CRPA were largely from Russia and Latin America. Most CRPA isolates with carbapenemases produced VIM (n=161); smaller numbers of isolates produced GES (n=33), IMP (n=30), NDM (n=17) and/or KPC (n=13)
- Cefepime-taniborbactam inhibited 94.9% of CRPA isolates without carbapenemases at ≤16 µg/mL whereas 75.5% were ceftazidime-avibactam-S and 74.7% were ceftolozane-tazobactam-S (Fig. 1). Against carbapenemase-producing CRPA, cefepime-taniborbactam was the most active agent (72.5% inhibited vs. 14.8% ceftazidime-avibactam-S)
- Cefepime-taniborbactam inhibited 86.3% of VIM-positive CRPA isolates and 100% of GES carbapenemase-positive CRPA isolates at ≤16 mg/L. No approved BL/BLI inhibited more than 6.2% of VIM-producing isolates, highlighting the need for novel agents against MBL-producing *P. aeruginosa*

Results- CRE with and without carbapenemases

- Of 13,731 Enterobacterales isolates, 637 (4.6%) were CRE. 596/637 (93.6%) isolates of CRE produced a carbapenemase (Fig. 1), most frequently KPC (n=232), NDM (n=208) and OXA-48 group (n=188). Several isolates produced multiple carbapenemases
- CRE were widely distributed: 16 countries contributed at least 10 isolates each to the total CRE subset from surveillance (Fig. 2)
- Cefepime-taniborbactam inhibited 94.5% of carbapenemase-producing CRE and 95.1% of non-carbapenemase-producing CRE at ≤16 µg/mL (Fig. 1). The most active BL/BLI comparators against carbapenemase-producing CRE were ceftazidime-avibactam (57.9% susceptible [S]) and meropenem-vaborbactam (41.8% S)
- Cefepime-taniborbactam inhibited 84.6% of NDM-positive CRE (not including one isolate co-carrying IMP) and 100% of VIM-positive CRE. No approved BL/BLI inhibited more than 3.4% of NDM-positive CRE isolates or 45.0% of VIM-positive CRE isolates

Figure 1. Comparative activity (% Susceptible) of β-lactam/β-lactamase inhibitors vs. CRE & CRPA +/- carbapenemases, and vs. MDR Enterobacterales and *P. aeruginosa*

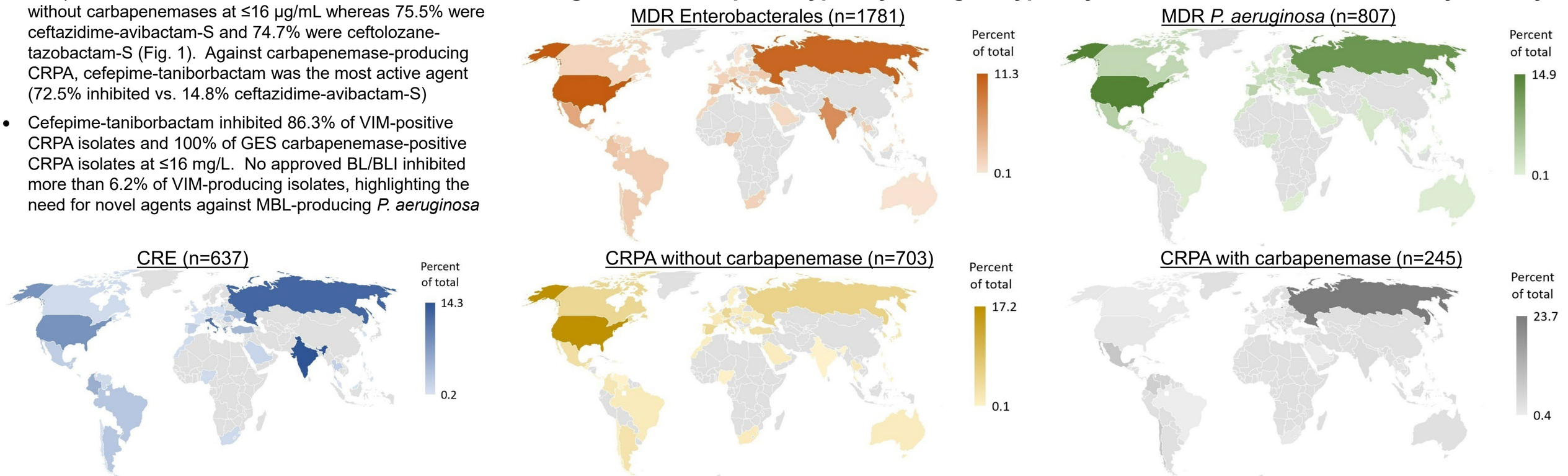


The following carbapenemases were detected in CRE: KPC (n=232), NDM (n=208), OXA-48 group (n=188), VIM (n=20), IMP (n=3) and GES (n=3); and in CRPA: VIM (n=161), GES (n=33), IMP (n=30), NDM (n=17), and KPC (n=13). The sum of isolates carrying defined carbapenemase genes may exceed the total number of CRE and CRPA with carbapenemases due to carriage of multiple carbapenemases. For cefepime-taniborbactam, % of isolates inhibited at ≤16 µg/mL is shown. EUCAST breakpoints were used for meropenem-vaborbactam against P. aeruginosa

Results- MDR Enterobacterales and MDR *P. aeruginosa*

- MDR isolates of Enterobacterales (13.0% of total) and *P. aeruginosa* (17.5% of total) were widely distributed in surveillance (Fig. 2)
- Cefepime-taniborbactam was more active against MDR Enterobacterales (97.9% of isolates inhibited at ≤16 mg/L) and MDR *P. aeruginosa* (85.7% of isolates inhibited at ≤16 mg/L) than ceftazidime-avibactam (83.9%S, 48.7%S), meropenem-vaborbactam (80.3%S, 40.1%S), and ceftolozane-tazobactam (32.8%S, 41.1%S) (Fig. 1)

Fig. 2. Source of phenotypically- and genotypically-defined isolates, in % of total, by country



Conclusions

- Cefepime-taniborbactam in vitro activity was highly differentiated from that of approved BL/BLIs against CRE and CRPA both with and without carbapenemases, against MDR Enterobacterales, and against MDR *P. aeruginosa*
- These findings support the continued development of cefepime-taniborbactam as a potential new therapeutic agent for infections due to carbapenem-resistant and MDR Enterobacterales and *P. aeruginosa*, regardless of whether their resistance to carbapenems is driven by serine or metallo-carbapenemases or by non-carbapenemase mechanisms

Methods

- Non-duplicate isolates of Enterobacterales (n=13,731) and *P. aeruginosa* (n=4,619) from documented infections were collected in prevalence mode, by species, from 266 sites in 56 countries in 2018-2020. Broth microdilution (ISO 20776-1:2019; CLSI M07 Ed. 11) was performed with concurrent quality control
- Resistant phenotypes including MDR (resistance to ≥1 agent from ≥3 drug classes) were based on CLSI 2021 breakpoints. CRE and CRPA were resistant to meropenem. For comparative purposes, a provisional nonresistant breakpoint of ≤16 mg/L for cefepime-taniborbactam (Abdelraouf 2020) was considered
- Isolates with cefepime-taniborbactam MIC ≥16 mg/L were characterized by whole genome sequencing. Meropenem-resistant isolates were screened for acquired β-lactamase genes by PCR/Sanger sequencing

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This project has been funded in part with Federal funds from the National Institute for of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201600029C