Susceptibility Profiles of Baseline Gram-negative Pathogens from CERTAIN-1, a Phase 3 Study comparing Cefepime-taniborbactam to Meropenem in Adults with Complicated Urinary Tract Infection (cUTI)

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Introduction

- Carbapenem-resistant Enterobacterales (CRE) and carbapenem-resistant *P. aeruginosa* (CRPA) are WHO Critical, Priority 1 pathogens (WHO 2017); furthermore, CRE and multidrug-resistant (MDR) *P. aeruginosa* are CDC Urgent and Serious Threats, respectively (CDC 2021).
- While carbapenem resistance is often mediated by serine carbapenemases in Enterobacterales and by non-carbapenemase mechanisms in *P. aeruginosa* (Simner 2017), metallo-carbapenemase (NDM, VIM)-producing CRE and CRPA are emerging (Tenover 2022; Estabrook 2023).
- Troublingly, metallo-β-lactamases were the most frequent carbapenem resistance mechanism identified among CRE isolates globally (Estabrook 2023) and are estimated to contribute to approximately 1 of every 6 to 7 CRE isolates in the US and Canada (Castanheira 2022; Estabrook 2023).
- Taniborbactam is an investigational β-lactamase inhibitor that restores cefepime activity against cefepime-, carbapenem-, and multidrug-resistant Enterobacterales and *P. aeruginosa* producing serine- and metallo-β-lactamases (Hamrick 2020; Karlowsky 2022).
- In the Phase 3 CERTAIN-1 study (ClinicalTrials.gov identifier NCT03840148), cefepime-taniborbactam was superior to meropenem for the primary composite endpoint at Test of Cure in adults with cUTI, including acute pyelonephritis.
- We assessed the in vitro activity of cefepime-taniborbactam and comparators against baseline isolates of Enterobacterales and *P. aeruginosa* from patients in the CERTAIN-1 study.

Methods

- Isolates were from patients in the extended microbiologic Intent-to-Treat (extended microITT) population and were confirmed baseline uropathogens or bloodstream pathogens against which ≥1 study drug had activity: cefepime-taniborbactam MIC ≤16 µg/mL; meropenem MIC ≤2 µg/mL (Enterobacterales) or ≤4 µg/mL (*P. aeruginosa*).
- MICs were determined by broth microdilution (CLSI M07 Ed. 11; ISO 20776-1:2019) with concurrent QC (CLSI M100 Ed. 29) at the central microbiology laboratory (LabCorp; Indianapolis, USA and Shanghai, China).
- Resistant phenotypes were based on CLSI breakpoints (CLSI M100 Ed. 29). Carbapenem resistance was defined for Enterobacterales as a meropenem MIC ≥4 µg/mL, and for *P. aeruginosa* as a meropenem and/or imipenem MIC ≥8 µg/mL. For cefepime-taniborbactam, a provisional susceptible breakpoint of ≤16 µg/mL (Karlowsky 2022) was considered for comparative purposes.

References

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Results- Enterobacterales

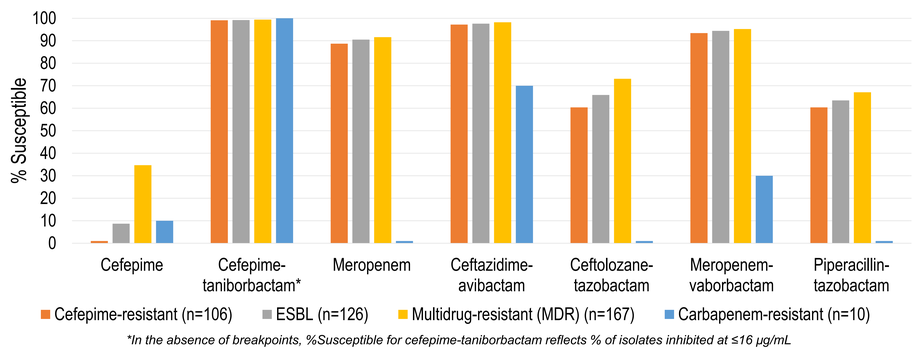
- Among Enterobacterales, 24.3%, 28.8%, 38.2%, and 2.3% of isolates were cefepime resistant, extended spectrum β-lactamase (ESBL) expressing, MDR, and carbapenem resistant, respectively (Table 1). Taniborbactam decreased the cefepime MIC_{90} by ≥1,024-fold (to 1 µg/mL) vs. cefepime-resistant, ESBL, and MDR Enterobacterales and by ≥128-fold (to 8 µg/mL) vs. CRE.

Table 1. Susceptibility summary: baseline isolates of Enterobacterales

	MIC_{90} (µg/mL)						
Pathogen Phenotype (n; % of total)	Cefepime	Cefepime-taniborbactam	Meropenem	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam	Piperacillin-tazobactam
All Enterobacterales (437; 100%)	512	0.25	0.12	0.5	4	0.06	64
Cefepime resistant (106; 24.3%)	>512	1	2	1	>64	0.5	>128
ESBL (126; 28.8%)	>512	1	1	1	>64	0.25	>128
MDR (167; 38.2%)	>512	1	0.5	1	>64	0.12	>128
Carbapenem resistant (10; 2.3%)	>512	8	64	>64	>64	64	>128

- Cefepime-taniborbactam inhibited higher percentages of Enterobacterales isolates than all tested comparators, regardless of resistance phenotype (Figure 1).

Figure 1. In vitro activity against baseline isolates of Enterobacterales, by resistance phenotype



In the absence of breakpoints, %Susceptible for cefepime-taniborbactam reflects % of isolates inhibited at ≤16 µg/mL

Results- *P. aeruginosa*

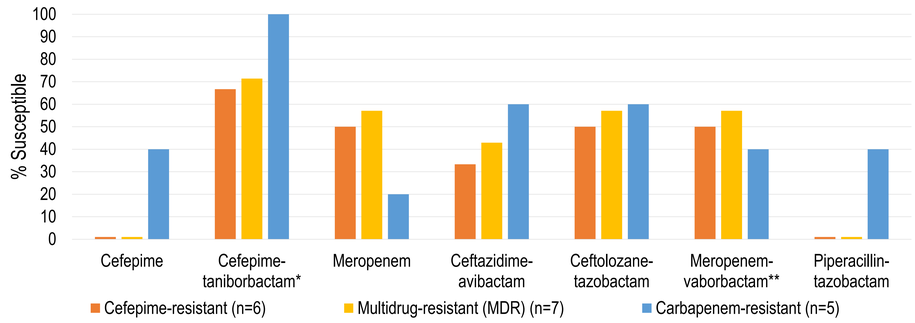
- Among *P. aeruginosa*, 26.1%, 30.4%, and 21.7% of isolates were cefepime-resistant, MDR, and carbapenem resistant, respectively (Table 2).

Table 2. Susceptibility summary: baseline isolates of *P. aeruginosa*

	MIC_{90} or MIC range (µg/mL)						
Pathogen Phenotype (n; % of total)	Cefepime	Cefepime-taniborbactam	Meropenem	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam	Piperacillin-tazobactam
All *P. aeruginosa* (23; 100%)	32	16	16	32	>64	16	>128
Cefepime resistant (6; 26.1%)	32 - 512	4 - 32	0.25 - >64	8 - 64	2 - >64	0.25 - >64	32 - >128
MDR (7; 30.4%)	16 - 512	4 - 32	0.25 - >64	4 - 64	1 - >64	0.25 - >64	32 - >128
Carbapenem resistant (5; 21.7%)	4 - 512	4 - 16	0.5 - >64	1 - 64	0.5 - >64	0.25 - >64	1 - 128

- Cefepime-taniborbactam at ≤16 µg/mL inhibited 66.7%, 71.4% and 100% of cefepime-, MDR-, and carbapenem-resistant *P. aeruginosa* isolates, respectively (Figure 2). These percentages were higher than those of all tested comparators, regardless of resistance phenotype.

Figure 2. In vitro activity against baseline isolates of *P. aeruginosa*, by resistance phenotype



In the absence of breakpoints, %Susceptible for cefepime-taniborbactam reflects % of isolates inhibited at ≤16 µg/mL

Conclusions

- Taniborbactam substantially potentiated cefepime activity against most isolates of Enterobacterales and *P. aeruginosa* that expressed an ESBL or were cefepime-, multidrug-, or carbapenem-resistant in the Phase 3 CERTAIN-1 cUTI study.
- Concordantly, taniborbactam restores cefepime activity in nonclinical studies against gram-negative pathogens producing serine- and metallo-β-lactamases.
- Continued development of cefepime-taniborbactam is warranted as a potential new therapeutic agent for adult patients with cUTI due to susceptible isolates of Enterobacterales and *P. aeruginosa,* including most pathogens resistant to cefepime or carbapenems, and pathogens with ESBL or MDR phenotypes.

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