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In vitro activity of ceftibuten-ledaborbactam and comparators against Enterobacterales from a Phase 3 study of adults with complicated urinary tract infection (cUTI)

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Background

- Enterobacterales infections are an emerging threat, as more strains now produce serine-carbapenemases and extended-spectrum β-lactamases (ESBLs) that can cause formerly effective β-lactam-based therapies to fail. Many complicated urinary tract infections (cUTIs) are the result of antibiotic resistant Enterobacterales. There is a pressing need for novel oral agents to treat cUTIs so patients with these infections can be managed on an outpatient basis, reducing healthcare resource utilization.
- Ledaborbactam is an investigational cyclic boronate β-lactamase inhibitor (BLI) in development as the orally bioavailable prodrug ledaborbactam-etzadroxil for use in combination with the oral third-generation cephalosporin ceftibuten[1, 2, 3]. Ledaborbactam has potent activity against ESBLs, serine carbapenemases, and AmpC enzymes which restores ceftibuten activity[1, 2, 3]. Here, we evaluate ceftibuten-ledaborbactam along with relevant oral comparators in vitro against 406 Enterobacterales strains from a recent Phase 3 cUTI study (CERTAIN-1; Wagenlehner 2024)[4].

Methods

- Broth microdilution MICs were performed in cation-adjusted Mueller Hinton broth (CAMHB) and interpreted according to CLSI standards.[5,6] Amoxicillin-clavulanate (AMC), cefazolin (CFZ) and cefotaxime (CTX) were tested from 0.03 µg/mL to 64 µg/mL, cefibuten-ledaborbactam (CLB) and ceftibuten (CTB) were tested from 0.016 µg/mL to 32 µg/mL, ertapenem (ETP) was tested from 0.002 µg/mL to 4 µg/mL and tebipenem (TBP) was tested from 0.004 µg/mL to 4 µg/mL. *E. coli* NCTC 13353, *E. coli* ATCC 25922, and *S. aureus* ATCC 29213 and associated CLSI MIC ranges were used for quality control[6].
- Susceptibility was defined using CLSI breakpoints. A provisional breakpoint of 0.12 µg/mL was used for tebipenem[7]. The EUCAST ceftibuten susceptible breakpoint of 1 µg/mL was applied as a provisional breakpoint for ceftibuten-ledaborbactam.
- Four non-exclusive phenotypic resistance subsets were used for data analysis: multidrug resistant (MDR), extended-spectrum β-lactamase (ESBL), carbapenem resistant (CARB-R), and amoxicillin-clavulanate resistant (AMC-R). Resistance profiles were determined during the CERTAIN-1 study[4] and updated as needed to reflect results from the current study using M100 criteria[6].
- β-lactamases and other resistance mechanisms were genetically determined through whole genome sequencing and analysis for a subset of strains that met specific phenotypic criteria previously as part of the CERTAIN-1 study[4].

Figure 1: Enterobacterales antimicrobial susceptibility overall and by phenotypic resistance subset

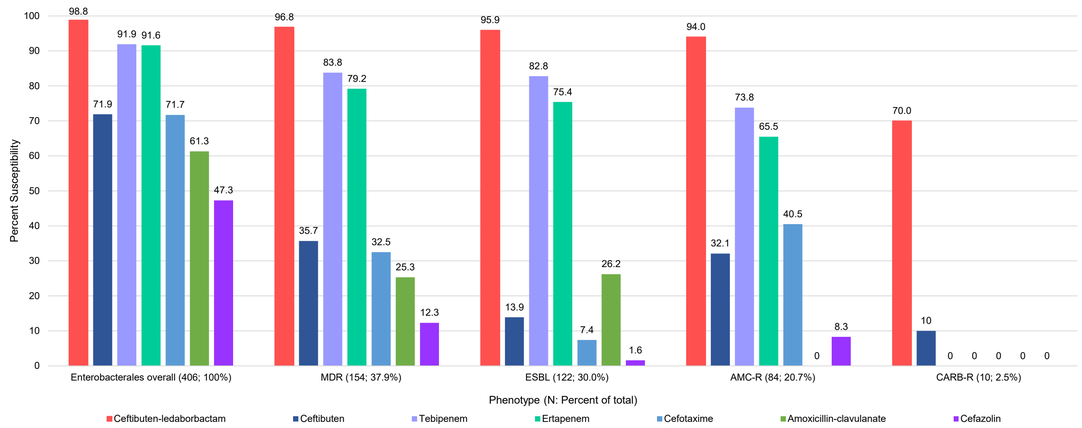
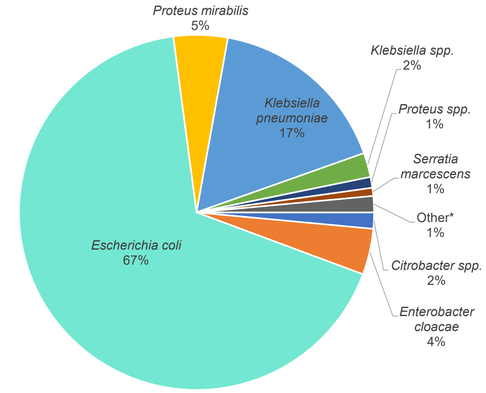


Figure 2: Enterobacterales species distribution (n=406)



*Comprised of *Kluyvera ascorbata* (n=1), *Morganella morganii* (n=4), and *Providencia rettgeri* (n=1)

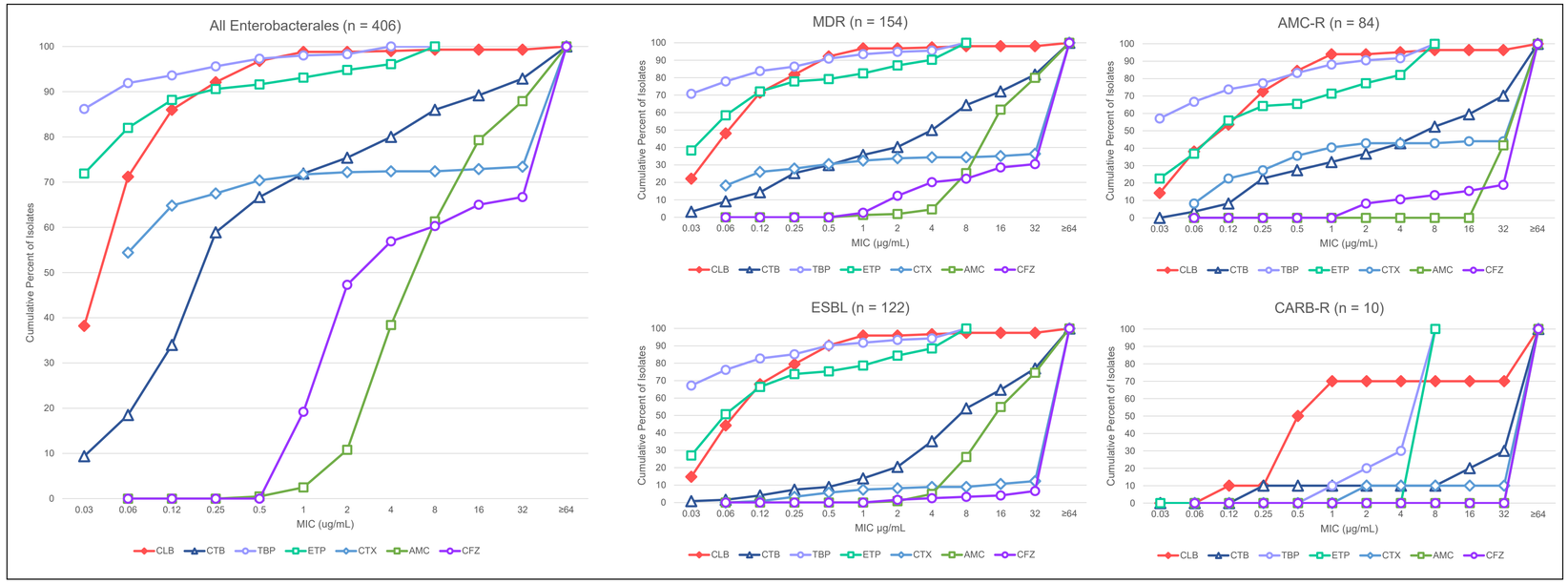
Table 1: Susceptibility percentages and MIC_{90} overall and by phenotypic resistance subset

Tested isolates or subset (n; % overall)	Percent susceptible or provisionally susceptible							MIC_{90} (µg/mL)						
	Ceftibuten-ledaborbactam	Ceftibuten	Tebipenem	Ertapenem	Cefotaxime	Amoxicillin-clavulanate	Cefazolin	Ceftibuten-ledaborbactam	Ceftibuten	Tebipenem	Ertapenem	Cefotaxime	Amoxicillin-clavulanate	Cefazolin
Breakpoint (µg/mL)	(≤1/4*)	(≤1)	(≤0.12**)	(≤0.5)	(≤1)	(≤8/4)	(≤2)	(≤1/4*)	(≤1)	(≤0.12**)	(≤0.5)	(≤1)	(≤8/4)	(≤2)
Enterobacterales overall (406; 100%)	98.8	71.9	91.9	91.6	71.7	61.3	47.3	0.25/4	32	0.12	0.25	≥128	64/32	≥128
MDR (154; 37.9%)	96.8	35.7	83.8	79.2	32.5	25.3	12.3	0.5/4	≥64	0.5	4	≥128	≥128/64	≥128
ESBL (122; 30.0%)	95.9	13.9	82.8	75.4	7.4	26.2	1.6	0.5/4	≥64	0.5	≥8	≥128	≥128/64	≥128
AMC-R (84; 20.7%)	94	32.1	73.8	65.5	40.5	0	8.3	1/4	≥64	2	≥8	≥128	≥128/64	≥128
CARB-R (10; 2.5%)	70	10	0	0	0	0	0	≥64/4	≥64	≥8	≥8	≥128	≥128/64	≥128

*Provisional breakpoint corresponds to the EUCAST susceptible breakpoint for ceftibuten 400 mg PO once daily for Enterobacterales infections originating from the urinary tract.

**Provisional breakpoint[7]

Figure 3: Comparative activity against all Enterobacterales and non-exclusive resistance subsets



Summary of Results

- *E. coli* (67% of strains) and *K. pneumoniae* (17% of strains) were the two most common species in this panel of cUTI clinical isolates (Figure 2). Ceftibuten-ledaborbactam at ≤1/4 µg/mL inhibited 98.8% of Enterobacterales overall (n=406), with an MIC_{90} of 0.25/4 µg/mL (Figure 1, Table 1, Figure 3).
- Ceftibuten-ledaborbactam inhibited greater percentages of isolates in MDR, ESBL, and AMC-R resistance subsets than all comparators, with 96.8%, 95.9%, and 94.0% of isolates, respectively, inhibited at ≤1/4 µg/mL and respective MIC_{90}s of 0.5/4 µg/mL, 0.5/4 µg/mL, and 1/4 µg/mL (Figure 1, Table 1, Figure 3).
- Ledaborbactam reduced the ceftibuten MIC_{90} by 128-fold overall, and by ≥128- to ≥64-fold against MDR, ESBL, and AMC-R subsets, respectively.
- The CARB-R subset (2.5% of the overall Enterobacterales population) posed a significant challenge for all agents examined. Ceftibuten-ledaborbactam was the most active agent evaluated, with 70.0% of isolates inhibited at ≤1/4 µg/mL compared to 0 to 10% susceptible to comparators (Figure 1, Table 1, Figure 3).
- Only 5 (1.2%) out of 406 isolates had ceftibuten-ledaborbactam MICs above 1/4 µg/mL. Provisionally resistant strains had MICs ranging from 4/4 µg/mL to ≥64 µg/mL. Resistance mechanisms present among these strains which are likely responsible for elevated MICs are the presence of NDM-1[1], the co-expression of OXA, CTX-M, and Ambler class C β-lactamases in the context of porin alterations[2, 3], and YRIN amino acid insertion in PBP3[8].

Conclusions

- Ceftibuten-ledaborbactam demonstrated robust activity relative to other orally bioavailable comparators in a panel of recent cUTI isolates containing significant proportions of MDR, ESBL, and AMC-R strains.
- These data supports continued development of ceftibuten-ledaborbactam as a potential treatment option for resistant Enterobacterales infections.

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