Methods. PROVE is a multi-center, chart review study of CFDC use for resistant Gram-negative infections (GNI). Cases were eligible if they received ≥ 72 hrs of CFDC. Demographics, comorbidity, pathogen, infection site, and treatment course were assessed. Outcomes included all-cause 14-day and inpatient mortality and length of stay (LOS). Clinical resolution was defined by documentation that clinical signs and/or symptoms had resolved or improved without relapse.

Results. 24 patients who were treated with CFDC at 2 sites were included to date. Median age was 48 years (Range: 19 - 69 years); 33% were female. The most common comorbidity was diabetes (n=7, 29%). Median total ICU LOS was 36 days. Targeted treatment of documented GNI without preceding failure of prior therapy accounted for 71% of CFDC use. Empirical and salvage treatments accounted for 4% and 25% respectively (Table 1). Median time from admission to 1st CFDC dose was 21 days. Acinetobacter baumannii and Pseudomonas aeruginosa accounted for > 75% of isolates (Fig 1). 92% of patients had CR isolates; > 50% were respiratory. Sensitivity to CFDC was tested in 58% of which 71% were sensitive. All-cause 14-day post-CFDC mortality was 13% (95% CI: 2, 27) and overall hospital mortality 25% (95% CI: 6, 44). Clinical resolution was reached in 54% (95% CI: 33, 76). Median post-CFDC LOS was 40 days. Outcomes were stratified by key covariates (Table 2).

Figure 1. Enterobacteriales ceftaxime and levofloxacin minimum inhibitory concentration (mg/L) distribution from community- and hospital-settings.

Conclusion. Similar antimicrobials resistances were found in Enterobacteriales from community- and hospital-acquired infections. New anti-infective agents are needed urgently to treat pathogens from the community-acquired infections and hospitals that have resistance to the first line regimens. Additionally, community antimicrobial stewardship programs are required.

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Ceftobuten in combination with VNRX-7145 is under development as an oral treatment for complicated urinary tract infections caused by serine β-lactamase-producing Enterobacteriaceae, including isolates carrying ESBLs and carbapenemases. In vitro, VNRX-7145 (VNRX-5236 etzadroxil) is cleaved into the active inhibitor, VNRX-5236. This study assessed the in vitro activity of ceftobuten/VNRX-5236 against 592 isolates of Enterobacteriaceae from urinary tract infections (UTIs) from 2018-2020 global culture collection.

**Methods.** MICs of ceftobuten with VNRX-5236 fixed at 4 µg/mL and comparators were determined following CLSI M07-A11 guidelines against 592 Enterobacteriaceae. Isolates were from community and hospital UTI infections collected from 133 sites in 31 countries in 2018-2020. Resistant phenotypes were based on 2021 CLSI breakpoints. **Results.** A substantial percentage of isolates were non-susceptible to extended-spectrum β-lactams, levofloxacin (LVX), trimethoprim-sulfamethoxazole (SXT), and amoxicillin-clavulanate (AMC) (Table). The addition of VNRX-5236 reduced ceftobuten MIC values by ≥ 8-fold to ≥ 128-fold, depending on the resistant subset. Ceftobuten/VNRX-5236 had potenti activity against all Enterobacteriaceae, with MIC<sub>50</sub> values of 0.06/0.25 µg/mL and 98.3% inhibited at ≤ 2 µg/mL. Ceftobuten/VNRX-5236 maintained activity against resistant subsets (MIC<sub>50</sub> range, 0.5 to 2 µg/mL; 91.5% to 97.1% inhibited at ≤ 2 µg/mL), including serine carbapenemase-positive isolates (MIC<sub>50</sub> 0.5 µg/mL; 100% inhibited at ≤ 1 µg/mL). Ceftobuten/VNRX-5236 in vitro potency was similar to that of newer parenteral and investigational oral therapies.

**Results Table**

| Phenotype (n, % of total) | Ceftobuten | Ceftobuten/ VNRX-5236 | Telipenem | Ceftazidim/ avibactam |
|--------------------------|------------|------------------------|------------|-----------------------|
| All (592, 100%)          | 0.25/0.16  | 0.09/0.25              | 0.30/0.12  | >2/0.12               |
| ESBLs (136, 23.2%)       | 0.5/1      | 0.125/0.25             | 0.30/0.25  | >0.25/1               |
| AMC (20, 35.4%)          | 2/0.5      | 0.125/0.25             | 0.30/0.25  | 0.25/0.5              |
| SXT-NS (242; 40.9%)      | >0.5/0.32  | 0.09/0.25              | 0.30/0.25  | >0.12/0.5             |
| AMC (118, 19.9%)         | 0.12/0.5   | 0.122/0.6              | 0.5/0.5    |                       |
| Sulfone-carbapenemase (10, 1.7%) | 0.5/0.1     | 0.125/0.25             |            |                       |

Ceftobuten/VNRX-5236 exhibited promising in vitro activity against recent Enterobacteriaceae from UTIs, and may have potential as an oral treatment option for complicated urinary tract infections, including those caused by serine β-lactama-expression Enterobacteriaceae (ESBL, KPC, OXA-48/OXA-48-like) for which there are currently few oral treatment options available.

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1292. Evaluation of Synergy with Piperacillin/Tazobactam plus Meropenem Against Carbapenemase-Producing Klebsiella pneumoniae and Enterobacter cloacae Using ETEST

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**Session: P-72. Resistance Mechanisms**

**Background.** Carbapenem-resistant Enterobacteriaceae are considered an urgent threat for patients in healthcare facilities, causing infections with significant morbidity and mortality. Most isolates are multidrug resistant with limited treatment options, so combination therapy is an alternative. Recently, synergy with piperacillin/tazobactam (P/T) + meropenem (MP) was demonstrated against 7/10 (70%) KPC-producing Escherichia coli and 9/10 (90%) OXA-48-producing K. pneumoniae using time-kill assay (Lawandi et al, 2021). The aim of the present study was to further evaluate the combination of P/T + MP against KPC-producing Enterobacter cloacae, in addition to OXA-producing K. pneumoniae using our rapid ETEST MIC:MIC synergy method.

**Methods.** 14 carbapenem-producing isolates: 7 OXA-48-like K. pneumoniae (1 OXA-48, 4 OXA-181, 2 OXA-232) and 7 KPC-producing E. cloacae (1 KPC-2, 4 KPC-3, 1 KPC-4, 1 KPC-6) were obtained from the CDC and FDA Antibiotic Resistance Isolate Bank. ETEST MICs for P/T and MP and our ETEST synergy method were performed in triplicate for each isolate. The summation fractional inhibitory concentration was calculated, and the mean value was interpreted as: < 0.5 synergy; 0.5-1 additivity; > 1-4 indifference; and > 4 antagonism.

**Results.** MICs (µg/mL) ranged: MP: 0.5 to > 32 (14% susceptible) and P/T, 96/4 to > 256/4 (91% resistant). The combination of P/T + MP showed synergy (3) or additivity (2) against 5/7 (71%) OXA-producing K. pneumoniae and synergy (6) or additivity (1) against all 7 KPC-producing E. cloacae. No antagonism was detected.

**Conclusion.** Using our ETEST MIC:MIC method, the combination of P/T + MP demonstrated synergy or additivity in 5/7 OXA-producing K. pneumoniae and 7/7 KPC-producing E. cloacae, similar to previously published findings showing synergy in 7/10 KPC-producing E. coli and 9/10 OXA-48-producing K. pneumoniae using time-kill assay. Our ETEST synergy method is simple to use and should be evaluated more extensively. Regardless of the method used, results may or may not correlate in an in vivo setting, in vivo studies are needed.

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1293. In vitro Activity of Ceftobuten in Combination with VNRX-5236 against Clinical Isolates of Enterobacteriaceae from Urinary Tract Infections Collected in 2018-2020

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**Session: P-72. Resistance Mechanisms**

**Background.** Increasing resistance among agents commonly prescribed to treat urinary tract infections indicate that new oral agents are urgently needed.