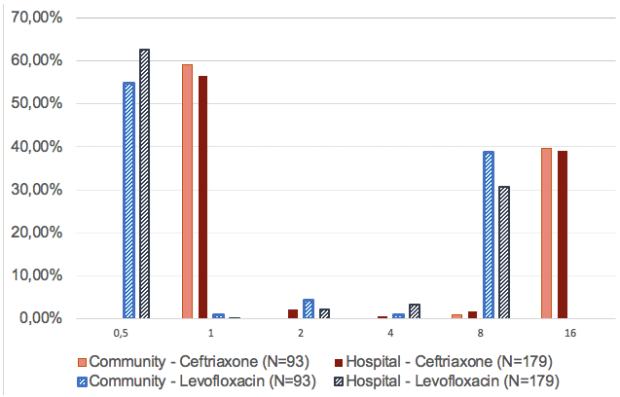

Figure 1. Enterobacterales ceftriaxone and levofloxacin minimum inhibitory concentrations (mg/L) distribution from community- and hospital-settings.

Conclusion. Similar antimicrobials resistances were found in Enterobacterales 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 regimen. Additionally, community antimicrobial stewardship programs are required.

Disclosures. **All Authors**: No reported disclosures

1290. Ceftazidime-Avibactam Resistance Report in a Third Level Hospital in Mexico City

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Session: P-72. Resistance Mechanisms

Background. The surge of resistant Gram-negative organisms has been worrying infectious disease physicians and physicians in general because of the lack of a large number of antibiotics to which these organisms remain susceptible. Ceftazidime-Avibactam (CAZ-AVI) is a drug approved by the FDA to treat complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAIs) in combination with metronidazole, and recently for the treatment of nosocomial pneumonia. Worldwide resistance rates of Enterobacteriaceae to CAZ-AVI have been reported below 2.6%, and 4-8% for *Pseudomonas aeruginosa*. The FDA, CLSI, and EUCAST assigned the clinical breakpoints of susceptibility: MIC < /=8 mg/liter susceptible, and >/=8mg/liter, resistant. In Mexico, CAZ-AVI was approved in 2018, and its cost is very high compared to other antimicrobials, so its use is limited in very specific cases. The resistance rates to this antibiotic in the Mexican population remain largely unknown.

Methods. We tested 106 specimens for susceptibility to ceftazidime-avibactam using the disk Kirby-Bauer method. The inhibition zone diameter was determined in all cases and we considered the organism susceptible when the inhibition zone diameter was >=21 mm, and resistant with an inhibition zone diameter < = 20 mm.

Results. We found 5 specimens (4.71%) resistant to ceftazidime-avibactam, corresponding to *E. coli* (3) and *P. aeruginosa* (2). Two of these were also resistant to colistin, and 4 to meropenem. All carbapenem-resistant isolates harbored Metallo-beta-lactamases genes, for *E. coli* was NDM gen, and for *P. aeruginosa* the VIM gene(GeneXpert® Cepheid).

Conclusion. The ceftazidime-avibactam resistance among Gram-negative bacteria in our study is similar to the one reported in other international studies. We need more studies in our population to know the nationwide resistance to this antibiotic.

Disclosures. **All Authors**: No reported disclosures

1291. PROVE (Retrospective Cefiderocol Chart Review) Study of Real-World Outcomes and Safety in the Treatment of Patients with Gram-negative Bacterial Infections in the US and Europe

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Session: P-72. Resistance Mechanisms

Background. Gram-negative bacterial resistance is a global health problem. Limited treatment options exist, especially for carbapenem resistant (CR) pathogens containing metallo-β-lactamases (MBLs) and multidrug resistant non-lactose fermenting bacteria. Cefiderocol (CFDC) retains activity against resistant strains. We describe the objectives, design, and early results of PROVE, a real world retrospective study of CFDC use.

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).

TABLE 1. CFDC Use Patterns

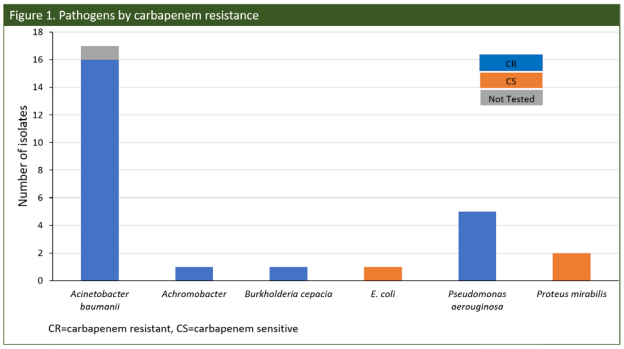
Characteristic	N	%
Number of Patients	24	100%
Reason for starting cefiderocol		
Documented infection	17	71%
Empirical for suspected CR GNBI	1	4%
Salvage treatment, prior antibiotics failed	6	25%
Reason for stopping cefiderocol		
Adverse drug reactions	1	4%
Clinical failure/infection not resolved	2	8%
Clinical sign-symptoms resolved	15	62%
Patient died	4	17%
Switched to alternative susceptible drug(s)	1	4%
Days on CFDC		
Median (Q1–Q3)	12.5	(10.5–17)
Min-Max	7	52
Admission to pos. culture		
Median (Q1–Q3)	12	(2.5–36)
Min-Max	-9	256
Positive culture to 1st CFDC dose		
Median (Q1–Q3)	4.5	(2–8)
Min-Max	-5	28
Antibiotics in use before CFDC [1]	N	%
CEFAZOLIN	2	10%
CEFEPIME	1	5%
CEFTAZIDIME/AVIBACTAM	1	5%
CEFTRIAXONE	1	5%
COLISTIN	1	5%
MEROPENEM	5	25%
MINOCYCLINE	1	5%
PIPERACILLIN/TAZOBACTAM	5	25%
TIGECYCLINE	2	10%
Antibiotics added onto CFDC (concurrent, combo therapy)[2]		
AMPICILLIN	1	3%
AMPICILLIN/SULBACTAM	1	3%
CEFTAZIDIME-AVIBACTAM	1	3%
IMIPENEM	1	3%
IMIPENEM-RELEBACTAM	1	3%
LEVOFLOXACIN	2	7%
MEROPENEM	1	3%
MINOCYCLINE	4	13%
POLYMYXIN B	5	17%
TIGECYCLINE	1	3%
TRIMETHOPRIM-SULFAMETHOXAZOLE	2	7%

[1] Antibiotics used for at least 2 days with stop date on or before cefiderocol initiation date.
[2] Antibiotics used for at least 2 days with start date on or after cefiderocol initiation date but not after last dose of CFDC.

TABLE 2. Outcomes by Key Covariates

Characteristic	Overall		All-Cause Hospital Mortality		14-Day Post-CFDC Mortality[1]		Clinical Cure[2]	
	N	%	n Deaths	n/N %	n Deaths	n/N %	n Cured	n/N %
Number of Patients	24	100%	6	25%	3	13%	13	54%
Pathogen at Primary Site								
Achromobacter	1	4%	0	0%	0	0%	1	100%
Acinetobacter baumannii	15	62%	2	13%	1	7%	8	53%
Burkholderia	1	4%	1	100%	0	0%	0	0%
Pseudomonas aeruginosa	4	17%	2	50%	2	50%	2	50%
2 pathogens[3]	3	12%	1	33%	0	0%	2	67%
CR pathogen status								
CR	22	92%	5	23%	3	14%	12	55%
CS	1	4%	1	100%	0	0%	0	0%
Not Tested	1	4%	0	0%	0	0%	1	100%
CFDC R pathogen status								
CFDC R	4	17%	1	25%	1	25%	0	0%
CFDC S	10	42%	3	30%	2	20%	6	60%
Not Tested	10	42%	2	20%	0	0%	7	70%

Abbreviations: CFDC=cefiderocol, CR=carbapenem resistant, CS=carbapenem sensitive, R=resistant; S=sensitive, AB=*Acinetobacter baumannii*, PA=*Pseudomonas aeruginosa*, PM=*Proteus mirabilis*.
[1] 14-day mortality is defined as deaths among those within 14 days from the first dose of CFDC.
[2] Clinical cure indicates whether CFDC was clinically successful and is based on answer to the Clinical Assessment of CFDC question. Resolved, Improved=Cured; Once resolved then relapse, Failure=Failure, Unknown=Unknown.
[3] Combination of pathogens are PM + AB, *E. coli* + PM, and PA + AB.



Conclusion. We present initial data for real world use of CFDC for resistant GNI. Patients were complex with multiple comorbidities, some hospitalized for long periods before their index GNI. Outcomes largely reflect this patient population. Additional data are needed to determine the optimal role of CFDC. PROVE offers an opportunity to see how CFDC is being utilized in various settings as well as a first look at key, real world outcomes.

Disclosures. **Stephen Marcella, MD, MPH**, **Shionogi, Inc** (Employee) **Steven Smoke, PharmD**, **Karius** (Advisor or Review Panel member)**Shionogi** (Scientific Research Study Investigator, Advisor or Review Panel member) **Ryan K. Shields, PharmD, MS**, **Shionogi** (Consultant, Research Grant or Support) **David van Duin, MD, PhD**, **Entasis** (Advisor or Review Panel member)**genentech** (Advisor or Review Panel member)**Karius** (Advisor or Review Panel member)**Merck** (Grant/Research Support, Advisor or Review Panel member)**Pfizer** (Consultant, Advisor or Review Panel member)**Qpex** (Advisor or Review Panel member)**Shionogi** (Grant/Research Support, Scientific Research Study Investigator, Advisor or Review Panel member)**Utility** (Advisor or Review Panel member)

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 *Enterobacterales* 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 carbapenemase-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 (all 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 Ceftibuten in Combination with VNRX-5236 against Clinical Isolates of Enterobacterales 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. Ceftibuten in combination with VNRX-7145 is under development as an oral treatment for complicated urinary tract infections caused by serine β-lactamase-producing Enterobacterales, including isolates carrying ESBLs and carbapenemases. *In vivo*, VNRX-7145 (VNRX-5236 etzadroxil) is cleaved into to the active inhibitor, VNRX-5236. This study assessed the *in vitro* activity of ceftibuten/VNRX-5236 against 592 isolates of Enterobacterales from urinary tract infections (UTIs) from a 2018-2020 global culture collection.

Methods. MICs of ceftibuten with VNRX-5236 fixed at 4 µg/mL and comparators were determined following CLSI M07-A11 guidelines against 592 Enterobacterales. 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 ceftibuten MIC_{90} values by ≥8-fold to ≥128-fold, depending on the resistant subset. Ceftibuten/VNRX-5236 had potent activity against all Enterobacterales, with $MIC_{50/90}$ values of 0.06/0.25 µg/mL and 98.3% inhibited at ≤2 µg/mL. Ceftibuten/VNRX-5236 maintained activity against resistant subsets (MIC_{90} range, 0.5 to 2 µg/mL; 91.5% to 97.1% inhibited at ≤2 µg/mL), including serine carbapenemase-positive isolates (MIC_{90} 0.5 µg/mL; 100% inhibited at ≤1 µg/mL). Ceftibuten/VNRX-5236 *in vitro* potency was similar to that of newer parenteral and investigational oral therapies.

Results Table

	MIC50/MIC90 (µg/mL)			
Phenotype (n; % of total)	Ceftibuten	Ceftibuten/ VNRX-5236	Tebipenem	Ceftazidime/ avibactam
All (592; 100%)	0.25/16	0.06/0.25	0.03/0.12	≤0.12/0.5
ESBL (138; 23.3%)	8/>32	0.12/0.5	0.03/0.25	0.25/1
LVX-NS (228; 38.5%)	2/>2	0.12/0.5	0.03/0.25	0.25/0.5
SXT-NS (242; 40.9%)	≤0.06/>32	0.06/0.25	0.03/0.25	≤0.12/0.5
AMC-NS (118; 19.9%)	8/>32	0.12/2	0.06/>4	0.5/2
Serine carbapenemase[a] (10; 1.7%)	8/>32	0.12/0.5	>4/>4	1/2

Ceftibuten/VNRX-5236, ceftibuten with VNRX-5236 fixed at 4 µg/mL; ESBL, extended spectrum β-lactamase positive; NS, nonsusceptible based on 2021 CLSI breakpoints; LVX, levofloxacin; SXT, trimethoprim-sulfamethoxazole; AMC, amoxicillin clavulanate
[a]Serine carbapenemases include KPC (n=6) and OXA-48-like (n=4)

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

Disclosures. **Meredith Hackel, PhD MPH**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Mark G G. Wise, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor) **Daniel F. Sahm, PhD**, **IHMA** (Employee)**Pfizer, Inc.** (Independent Contractor)

1294. Activity of Ceftolozane/Tazobactam and Comparators against Resistant *Pseudomonas aeruginosa* Isolates from Patients with Respiratory Tract or Bloodstream Infections in ICU and non-ICU settings – SMART United States 2018-2019

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Session: P-72. Resistance Mechanisms

Background. ICUs are considered hotspots of antimicrobial resistance. Treatment of ICU patients with infections caused by *P. aeruginosa* (*Pa*) is especially challenging. When patients fail to improve on therapy with first-line antipseudomonal agents such as piperacillin/tazobactam (P/T) or cefepime (FEP), clinicians often escalate to a carbapenem. Ceftolozane/tazobactam (C/T) is an antipseudomonal cephalosporin (combined with a β-lactamase inhibitor) that was specifically developed to have enhanced antibacterial activity against *Pa*. We evaluated the activity of C/T and comparators against *Pa* isolates collected from patients with respiratory tract (RTI) or bloodstream infections (BSI) in ICU and non-ICU settings. Co-resistance (*e.g.*, activity of C/T or meropenem (MEM) when *Pa* is nonsusceptible (NS) to P/T or FEP) was also evaluated to help inform common clinical scenarios.

Methods. In 2018-2019, 24 US clinical labs each collected up to 100 RTI and 50 BSI consecutive gram-negative pathogens per year as part of the global SMART surveillance program. Only the 1195 *Pa* isolates collected from patients in ICU or non-ICU hospital wards were included in this report; 1078 and 117 isolates were from patients with RTI and BSI, respectively. MICs were determined using CLSI broth microdilution and breakpoints.

Results. Susceptibility for P/T, FEP, and MEM was generally lower among isolates from patients in ICU than non-ICU wards by 5-14 percentage points, while the difference was ≤3 percentage points for C/T (Table). C/T maintained activity against 96% of ICU isolates, 17-23 percentage points higher than P/T, MEM, or FEP. MEM inhibited 40% of P/T-NS and 34% of FEP-NS ICU isolates, while C/T maintained activity against 81-88% of P/T-NS, FEP-NS, and MEM-NS isolates from ICU patients (Table, Figure).