

30.5% susceptible to CAZ-AVI) and (2) NS to all drugs except colistin and amikacin ($n = 97$, 21% of all MDR isolates; 70.1% susceptible to CAZ-AVI).

Conclusion. These *in vitro* data suggest that CAZ-AVI can be an effective treatment option for infections caused by MDR *Enterobacteriaceae* and *P. aeruginosa* collected in Latin America.

Species/phenotype (n)	Drug (% susceptible)					
	CAZ-AVI	CAZ	MEM	AMK	CST	TGC
All <i>Enterobacteriaceae</i> (5381)	99.3	70.5	94.4	96.7	82.7	97.3
MDR (1426)	97.3	11.4	79.1	88.3	88.1	97.3
All <i>E. coli</i> (1848)	99.95	71.2	99.2	98.4	99.1	99.9
MDR (547)	99.8	13.5	97.4	95.2	98.5	100
All <i>K. pneumoniae</i> (1499)	98.7	54.2	84.7	93.1	94.7	97.5
MDR (622)	97.1	4.8	63.3	84.6	88.9	96.1
All <i>E. cloacae</i> (356)	97.8	61.8	93.8	95.5	94.4	97.8
MDR (101)	92.1	2.0	79.2	84.2	95.0	96.0
All <i>P. aeruginosa</i> (1347)	87.2	69.9	66.1	82.4	99.6	NA
MDR (462)	62.8	22.3	17.1	51.9	99.6	NA

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; AMK, amikacin; CST, colistin; TGC, teicoplanin; NA, not applicable

Disclosures. All authors: No reported disclosures.

707. QPX9003: Pharmacology of a Novel Polymyxin in Mice and Rats

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Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
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Background. Currently available polymyxins are limited by toxicity and poor efficacy at tolerated doses. We have developed a new series of polymyxin derivatives with improved safety profiles and *in vitro* potency against major MDR bacteria. The following describes studies on the *in vivo* antimicrobial activity and toxicity of QPX9003 in mice and rats.

Methods. Mouse studies. The minimum lethal dose (MLD by IV bolus) and nephrotoxicity (6 IP doses administered 2 hours apart) of QPX9003 and polymyxin B (PMB) were determined in Swiss mice. For the neutropenic mouse thigh infection using *A. baumannii*, Swiss mice were infected with $\sim 10^6$ CFU/thigh. Doses were administered IP at various intervals starting 2-hour post-infection and continued over 24 hours. **Rat studies.** For the rat lung infection model, Sprague-Dawley rats were infected with $\sim 10^7$ CFU/lung. QPX9003 and PMB were administered IV every 4 hours starting 2 hours post-infection and continued over 24 hours. **Bacteria.** For both infection models, animals were infected with *A. baumannii* AB1016 (QPX9003 MIC of 0.5 mg/L and PMB MIC of 1.0 mg/L). Untreated control groups were sacrificed at the start of treatment and both untreated and treated groups were sacrificed 24 hours after the start of treatment, infected tissues harvested, homogenized, and plated to determine colony counts.

Results. QPX9003 had reduced acute toxicity and nephrotoxicity compared with PMB in mice. QPX9003 showed better bacterial killing of *A. baumannii* than PMB at similar plasma exposures in both the mouse thigh model (-0.41 vs. $+0.83$ log CFU/thigh) and rat lung infection model (-1.10 vs. $+1.44$ log CFU/lung).

Conclusion. QPX9003 was less acutely toxic, less nephrotoxic, and was more efficacious in mouse and rat infection models compared with PMB. QPX9003 is a promising new polymyxin. (This work was supported in part by federal funds from the National Institutes of Allergy and Infectious Diseases [R01AI098771], and the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under OTA number HHSO100201600026C).

Compounds	Mouse: Single Dose MLD IV (mg/kg)	Mouse: Kidney Changes (10 mg/kg IP x 6 doses)	Rat Lung Model: 24h AUC for 1-log bacterial killing vs. <i>A. baumannii</i>
PMB	7.5	Minimal to Severe Nephrosis	>160
QPX9003	20	No change	46

Disclosures. All authors: No reported disclosures.

708. In Vitro Activity of Plazomicin vs. Clinical Isolates of Gram-Negative Bacilli, Including Aminoglycoside Nonsusceptible and Multidrug-Resistant Subsets, Recovered from Patients Across Canada as Part of the CANWARD study, 2011–2018

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Background. Plazomicin (PLZ) is a next-generation aminoglycoside currently approved by the US FDA for the treatment of complicated urinary tract infections,

including pyelonephritis. The purpose of this study was to evaluate the *in vitro* activity of PLZ against a large collection of Gram-negative bacilli obtained from patients attending Canadian hospitals.

Methods. Annually from 2011 to 2018, sentinel hospitals across Canada submitted blood, respiratory, urine, and wound isolates from patients attending ERs, medical and surgical wards, hospital clinics, and ICUs (CANWARD). Susceptibility testing was performed using broth microdilution (and breakpoints) as described by CLSI (FDA breakpoints used for PLZ).

Results. See table.

S, susceptible; NS, nonsusceptible; ESBL, extended-spectrum β -lactamase; MDR, multidrug-resistant (NS to antimicrobials from three or more classes); n.d., not defined.

Conclusion. PLZ demonstrated excellent *in vitro* activity vs. *E. coli* and *K. pneumoniae* clinical isolates, including aminoglycoside NS, ESBL-positive, and MDR subsets.

Organism/Phenotype (Number tested)	PLZ		Gentamicin		Meropenem	
	MIC _{50/90}	%S	MIC _{50/90}	%S	MIC _{50/90}	%S
<i>Escherichia coli</i> ALL (4793)	0.5/1	99.4	$\leq 0.5/2$	90.4	$\leq 0.03/\leq 0.03$	99.9
Gentamicin NS (458)	0.5/1	98.9	32/>32	0.0	$\leq 0.03/\leq 0.03$	99.6
Tobramycin NS (405)	0.5/1	98.8	32/>32	31.6	$\leq 0.03/\leq 0.03$	99.5
ESBL-positive (489)	0.5/1	99.8	1/>32	66.5	$\leq 0.03/0.06$	99.8
MDR (570)	0.5/1	99.1	2/>32	50.4	$\leq 0.03/0.06$	99.6
<i>Klebsiella pneumoniae</i> All (1627)	0.25/0.5	99.8	$\leq 0.5/\leq 0.5$	96.5	$\leq 0.03/0.06$	99.3
Gentamicin NS (57)	0.25/1	96.5	32/>32	0.0	$\leq 0.03/1$	91.2
Tobramycin NS (78)	0.25/0.5	97.4	32/>32	38.5	0.06/2	89.7
ESBL-positive (104)	0.25/0.5	98.1	$\leq 0.5/\leq 32$	53.9	$\leq 0.03/1$	91.4
MDR (116)	0.25/0.5	97.4	1/>32	53.4	$\leq 0.03/1$	90.5
<i>Klebsiella aerogenes</i> (174)	0.5/0.5	99.4	$\leq 0.5/\leq 0.5$	99.4	0.06/0.12	98.9
<i>Klebsiella oxytoca</i> (447)	0.25/0.5	99.8	$\leq 0.5/\leq 0.5$	98.2	$\leq 0.03/0.06$	100.0
<i>Enterobacter cloacae</i> (736)	0.25/0.5	99.6	$\leq 0.5/\leq 0.5$	97.2	$\leq 0.03/0.12$	99.2
<i>Morganella morganii</i> (90)	2/4	73.3	$\leq 0.5/2$	92.2	0.06/0.25	100.0
<i>Proteus mirabilis</i> (357)	4/8	43.1	$\leq 0.5/2$	93.3	0.06/0.12	100.0
<i>Serratia marscesens</i> (419)	0.5/1	97.9	$\leq 0.5/1$	99.3	0.06/0.06	99.5
<i>Pseudomonas aeruginosa</i> (2665)	4/16	n.d.	1/8	88.7	0.5/8	79.4

Disclosures. All authors: No reported disclosures.

709. In Vitro Antibacterial Activity and In Vivo Efficacy of Sulbactam–Durlobactam (ETX2514SUL) Against Pathogenic Burkholderia Species

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Background. The genus *Burkholderia* contains several pathogenic species with distinct etiologies, including *Burkholderia pseudomallei* the biothreat pathogen responsible for melioidosis and *Burkholderia mallei* which causes glanders. β -Lactams, such as ceftazidime and meropenem, are important therapeutic options for these infections. However, clinical resistance to β -lactams, which is primarily mediated by multiple types of β -lactamases in these species, is a growing concern. Durlobactam (ETX2514, DUR) is a novel β -lactamase inhibitor with broad-spectrum activity against Ambler class A, C, and D β -lactamases. Sulbactam (SUL) is an Ambler Class A β -lactamase inhibitor with intrinsic antibacterial activity against a limited number of species, including *Acinetobacter* spp. SUL-DUR is currently in Phase 3 clinical testing for the treatment of carbapenem-resistant infections caused by *Acinetobacter* spp. In this study, SUL-DUR was tested for *in vitro* antibacterial activity against *B. pseudomallei* and *B. mallei* as well as for *in vivo* efficacy in a preclinical model of melioidosis.

Methods. The antibacterial activity of SUL alone or in combination with DUR (fixed at 4 mg/L) against *B. pseudomallei* ($n = 30$) and *B. mallei* ($N = 28$) was determined following CLSI guidelines. *In vivo* efficacy was tested in an acute murine model of melioidosis in which 4×10^4 cfu *Bp* K96423 (SUL-DUR MIC = 1 mg/L) was administered intranasally to BalbC mice. SUL-DUR (100/200 or 400/200 mg/kg) was administered q4h subcutaneously 6 hours post-challenge for 6 days and murine survival was monitored for 45 days. Doxycycline (DOX) and ciprofloxacin (CIP) were dosed as positive controls at 40 mg/kg q12 h for 6 days.

Results. The addition of DUR effectively lowered the SUL MIC_{50/90} from 8/16 to 0.25/0.5 mg/L vs. *B. pseudomallei* and from 8/8 to 1/2 mg/L for *B. mallei*. All untreated mice in the melioidosis model succumbed to infection within 3 days of challenge. 60% survival was observed for both dose arms of SUL-DUR as compared with 40% survival observed for both CIP and DOX.

Conclusion. Preliminary preclinical data demonstrating robust *in vitro* and *in vivo* antibacterial activity of SUL-DUR against *Burkholderia* spp. suggests this combination may be an effective new therapy for the treatment of these challenging pathogens.

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710. In Vitro Activity and Performance of Available Susceptibility Testing Methods for Eravacycline Against Carbapenem-Resistant Enterobacteriaceae (CRE)

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Background. Eravacycline (ERV) is a recently-approved, fully synthetic fluorocycline agent that demonstrates broad *in vitro* activity against multidrug-resistant pathogens. We sought to compare the activity of ERV with minocycline (MIN) and tigecycline (TGC) against diverse CRE clinical isolates, and to evaluate the performance of commercially-available susceptibility testing methods.

Methods. ERV, MIN, and TGC minimum inhibitory concentrations (MICs) were determined in triplicate by broth microdilution against previously characterized CRE isolates. ERV susceptibility was also measured by disk diffusion (20 µg disk; Mast Group) and MIC test strips (MTS; Liofilchem) according to manufacturer instructions.

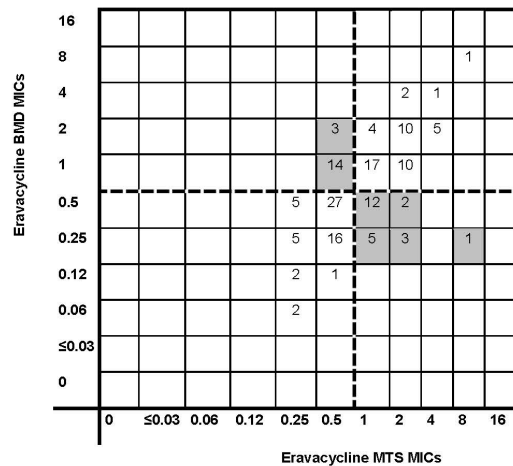
Results. 148 CRE were tested, including 92 *K. pneumoniae*, 32 *Enterobacter spp.*, 11 *E. coli*, 5 *C. freundii*, 4 *K. oxytoca*, and 4 *S. marcescens*. 72% of isolates harbored *bla_{KPC}*, which encoded KPC-2 (*n* = 33), KPC-3 (*n* = 48), and other KPC variants (*n* = 22). 77% and 19% of isolates were resistant to meropenem and ceftazidime-avibactam, respectively. By BMD, the ERV, MIN, and TGC MIC range, MIC₅₀ and MIC₉₀ for shown in the Table. ERV MICs were ≥2-fold lower than MIN and TGC against 99% and 43% of isolates, respectively. ERV MICs did not vary by species or KPC-subtype. ERV MICs determined by BMD and MTS were well-correlated showing 89% essential agreement (MIC within one 2-fold dilution; Figure). The rate of categorical agreement (CA) was 73%. By comparison, the CA rate between BMD and disk diffusion was 78%. By both MTS and disk diffusion methods, susceptibility results clustered on either side of the susceptibility breakpoint. 50% of disk diffusion zones clustered between 14 and 16 millimeters (mm), which is 1 mm on either side of the susceptibility breakpoint (≥15 mm).

Conclusion. This study confirms the *in vitro* activity of ERV against CRE clinical isolates, which is comparable to TGC. ERV MTS demonstrated high rates of EA, but lower rates of CA. Clinicians should be aware of the nuances of ERV susceptibility testing and recognize that the modal distribution of ERV MICs against CRE lies on either side of the susceptibility breakpoint.

Table. Comparison of MICs for ERV, MIN, and TGC against CRE clinical isolates.

Agent	MIC range	MIC ₅₀	MIC ₉₀
Ceftazidime-avibactam	≤0.25 - >256	1	64
Meropenem	≤0.06 - >64	8	>64
Eravacycline (ERV)	0.06 – 8	0.5	2
Minocycline (MIN)	0.25 – 32	4	16
Tigecycline (TGC)	0.06 – 8	1	2

Figure. Correlation of ERV MICs determined by BMD and MTS



Note. ERV susceptibility breakpoint is identified by the dotted horizontal and vertical lines. Isolates with discrepant categorical interpretations are shaded in grey.

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711. Exebacase (Lysin CF-301) Activity Against *Staphylococcus aureus* (*S. aureus*) Isolates From Bacteremic Patients Enrolled in a Phase 2 Study (CF-301-102)
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Background. Exebacase (CF-301) is a novel, recombinantly-produced, bacteriophage-derived lysin (cell wall hydrolase) which is the first lysin to report Phase 2 (Ph2) results which demonstrated 42.8% higher clinical responder rates with a single dose of exebacase used in addition to standard of care antibiotics (SOC) vs. SOC alone for

the treatment of methicillin-resistant *S. aureus* (MRSA) bacteremia including endocarditis. We examined exebacase activity by broth microdilution (BMD) against baseline methicillin-sensitive *S. aureus* (MSSA) and MRSA isolates from each of the 116 participants in the recently complete exebacase[®] first-in-patient[®] Ph2 study (NCT03163446).

Methods. Patients with complicated bacteremia or endocarditis caused by *S. aureus* were enrolled into Study CF-301-102 at study centers in the United States, EU, Latin America, Israel, and Russia from 2017 and 2018. Baseline isolates from blood cultures were collected prior to administration of exebacase. Exebacase MICs against 117 isolates of MSSA (*n* = 74) and MRSA (*n* = 43) were determined at a central laboratory using a modified BMD approved by the CLSI for exebacase AST.

Results. The exebacase MICs of baseline patient isolates from the Ph2 study ranged from 0.125 – 2 µg/mL and the MIC_{50/90} values for all MSSA and MRSA isolates were 0.5/1 µg/mL. Exebacase MICs reported in a recent surveillance study were similar, with MIC_{50/90} values of 0.5/1 µg/mL. Of the 6 total subjects with EXE MICs of 2, 3 were clinical responders, 2 were indeterminate (not available for assessment), and 1 was a clinical nonresponder at Day 14.

Conclusion. Exebacase was highly active against all baseline *S. aureus* isolates from blood cultures obtained from bacteremic patients enrolled in the Ph2 study. Based on data from previously presented exposure target attainment animal studies, PK/PD modeling and preliminary nonclinical breakpoint assessments, we expected that strains with MIC values of ≤2 µg/mL will have been susceptible to the Ph2 clinical exebacase dose determined based on target attainment studies under study in Ph2.

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712. Activity of Exebacase (CF-301) Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Biofilms on Orthopedic Kirschner Wires

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Background. Orthopedic foreign body-associated infection can be difficult to treat due to the formation of biofilms protecting microorganisms from both antimicrobials and the immune system. Exebacase (EXE) is a phage-derived lysin which acts as a direct lytic agent by hydrolyzing the peptidoglycan cell wall of *Staphylococcus aureus*. In this study, the activity of EXE was evaluated in comparison to daptomycin against MRSA biofilms on orthopedic Kirschner wires (K-wires).

Methods. MRSA strain IDRL-6169 was studied; it has a MIC of 0.5 µg/mL for both daptomycin (DAP) and EXE. Biofilms were formed in 1 mL of 10⁶ cfu/mL tryptic soy broth on 0.5x0.1 mm threaded stainless steel K-wires for 10 hours, after which the wires were removed from the media and placed into 0.04 mL of either DAP or EXE at 0 (vehicle only), 0.098, 0.98, or 9.8 mg/mL. DAP+EXE was also tested, each at 0.098 mg/mL. Bacteria were quantified after 0, 2, 4, 8, and 12 hours of incubation at 37°C. Testing was performed in triplicate. Results were reported as log₁₀ cfu/K-wire reduction relative to vehicle alone. A 3-log₁₀ cfu/K-wire reduction was considered bactericidal. P-values were calculated using Kruskal-Wallis.

Results. The bacterial burden of vehicle alone ranged from 5.49- to 6.33-log₁₀ cfu/K-wire at all time points. Bacterial reductions for each treatment compared with carrier solution are shown in the table. DAP showed no bactericidal activity. EXE showed bactericidal activity at all time points studied except 0.098 mg/mL at 8 hours. There was no significant difference between EXE at 0.098 and 0.98 mg/mL at any time point but EXE at 9.8 mg/mL did show superiority over the lower concentrations. DAP+EXE 0.098 mg/mL was bactericidal at all time points.

Conclusion. EXE showed a rapid effect against MRSA biofilms on orthopedic K-wires apparent within the first 2 hours of exposure and was more active than daptomycin alone at the same concentrations.

Duration of Treatment	Daptomycin			Exebacase			Daptomycin + Exebacase
	0.098 mg/ml	0.98 mg/ml	9.8 mg/ml	0.098 mg/ml	0.98 mg/ml	9.8 mg/ml	0.098 mg/ml
2 h	0.23	0.06	0.46	5.12	4.83	5.68	5.29
4 h	0.48	1.21	0.68	3.60	3.20	5.52	3.24
8 h	0.39	0.39	0.31	2.24	3.67	5.78	4.34
12 h	0.38	0.61	0.81	3.05	4.41	4.76	3.50

Bold values considered bactericidal

Disclosures. All authors: No reported disclosures.

713. Preventive Administration of MEDI6389, a Combination of Monoclonal Antibodies (mAbs) Targeting Alpha-Toxin (AT), Panton-Valentine Leukocidin (PVL), Leukocidin ED (LukED), Gamma-Hemolysin and Clumping Factor A (ClfA), in a Rabbit Model of USA300 MRSA Prosthetic Joint Infection (PJI)

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