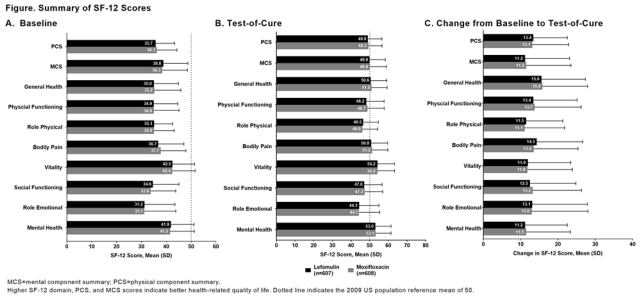
problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems, and mental health).

Methods. An exploratory analysis evaluated HRQoL in patients who received LEF or MOX in LEAP 1 (IV-PO treatment) and LEAP 2 (PO-only treatment). SF-12 was measured at baseline (BL) and test-of-cure (TOC; 5–10 days after last study drug dose). SF-12 outcomes assessed included the 8 domains, physical component summary (PCS), and mental component summary (MCS) scores. SF-12 scores were normalized to the 2009 US population reference mean (SD) of 50 (10). A 3-point change on any scale represents a clinically meaningful difference.

Results. Analysis included 1,215 patients (LEF n = 607; MOX n = 608). At BL, all mean SF-12 scores in both treatment groups were well below the US reference mean, indicating a low HRQoL level, consistent with the acute illness of the study population (figure). Clinically meaningful and significant improvements from BL to TOC were observed in all domain, PCS, and MCS scores in both groups. Mean scores were close to the reference mean, indicating an average HRQoL level. No significant differences in mean score improvements from BL to TOC were seen for LEF vs. MOX. SF-12 score improvements at TOC across predefined subgroups (age, sex, number of comorbidities, study, and PORT risk class) were comparable between treatment groups.

Conclusion. Our data indicate that adults with CABP experienced HRQoL improvements with LEF that were comparable with MOX, and treatment with either agent resulted in return to normal HRQoL. When combined with overall study results, these data suggest LEF as a potential alternative to MOX for treatment of adults with CABP.



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

677. Activity of Novel β-Lactamase Inhibitor QPX7728 Combined with β-Lactam Agents When Tested Against Carbapenem-Resistant *Enterobacteriaceae* (CRE) Isolates

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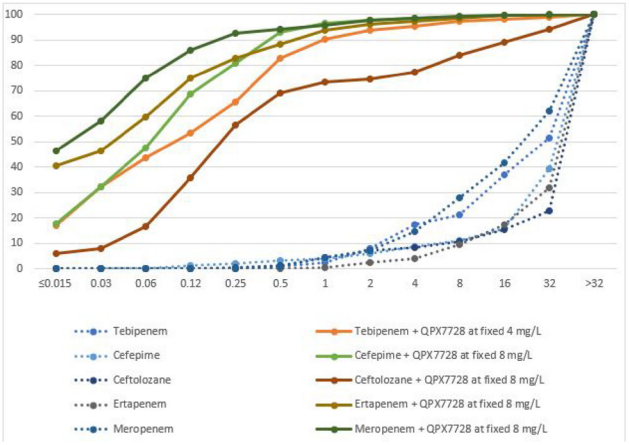
Background. CREs have been described worldwide and these isolates are often multidrug resistant with few therapeutic options remaining active against them. New β-lactam (BL)/β-lactamase inhibitor (BLI) combinations recently approved are active against KPC and some OXA-48 producers, but not against isolates producing metallo-β-lactamases (MBLs). We evaluated the activity of QPX7728 (QPX), a novel BLI paired with various BLs against a collection of CRE isolates characterized for the presence of carbapenemases.

Methods. A total of 508 CRE clinical isolates were susceptibility (S) tested by reference broth microdilution methods against meropenem (MER), tebipenem (TEB), cefepime (FEP), ceftolozane (TOL), and ertapenem (ETP), and meropenem (MEM) combined with QPX at fixed 2, 4, and 8 mg/L. Agents were provided by Qpex Biopharma except for FEP, ETP, and MEM. Carbapenemases were detected using PCR/sequencing or whole-genome sequencing.

Results. All BLs had limited activity against CRE isolates ($MIC_{50/90}$, ≥32/>32 mg/L) and QPX lowered the MIC for all agents (figure). Against 157 isolates carrying serine-carbapenemase (SCarb) genes (153 KPC-producers), MEM or ETP plus QPX at fixed 4 or 8 mg/L displayed MIC_{50} at ≤ 0.03 mg/L and MIC_{90} ranging from 0.12 to 0.5 mg/L. QPX lowered the FEP or TOL MIC_{50} to ≤ 0.25 mg/L and MIC_{90} to 0.25, 0.5 or 1 mg/L depending on the BLI concentration. Over 98.0% of the 150 isolates harboring OXA-48-like genes were inhibited by FEP, TOL, ETP or MEM plus QPX at ≤2 mg/L. Similarly, MEM, FEP, TOL and ETP + QPX inhibited >98.0% of the 51 CREs that did not carry carbapenemases at ≤2 mg/L when using a higher BLI concentration. The activity of FEP ($MIC_{50/90}$, 0.06/1 mg/L), ETP ($MIC_{50/90}$, 0.03/4 mg/L), and MEM ($MIC_{50/90}$, ≤ 0.015/2 mg/L) was mostly restored when 8 mg/L of QPX was combined with these agents and tested against 150 MBL-producing isolates.

Conclusion. QPX restored the activity of several BLs when tested against 508 CRE isolates that include 157 harboring SCarb, 150 OXA-48-like-producers, and 150 MBL-producing isolates. Further development of this BLI with inhibitory activity against all carbapenemase types seems warranted.



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

678. Galactomannan Is a Biomarker of APX001 (Fosmanogepix) Efficacy in Treating Experimental Invasive Pulmonary Aspergillosis

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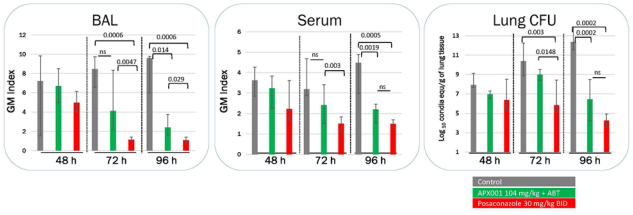
Background. Invasive pulmonary aspergillosis (IPA) is a serious fungal infection afflicting immunocompromised patients. Galactomannan (GM) detection in biological samples using the Platelia ELISA has been shown to predict therapy response by azoles, and polyenes. We previously reported on the activity of APX001 (fosmanogepix) in treating murine IPA. Here, we investigated the potential use of GM as a biomarker of APX001 efficacy in an immunosuppressed murine model of IPA.

Methods. ICR mice (n = 8/group) were immunosuppressed with cyclophosphamide and cortisone acetate on days −2, and +3, relative to infection with *Aspergillus fumigatus* via inhalation. Treatment with placebo (diluent control), APX001 (104 mg/kg, PO, a human equivalent dose), or posaconazole (POSA, 30 mg/kg, BID [equivalent to 6× the humanized dose]) began 16-hour post-infection and continued daily. To extend the half-life of APX001, mice were administered 50 mg/kg of the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) 2 hours prior to APX001 administration. Mice were sacrificed 48-, 72-, or 96-hour post-infection and their lungs, bronchoalveolar lavage (BAL) and sera were collected. Lung fungal burden was determined by conidial equivalent (CE) using qPCR, while GM was determined using the Platelia ELISA.

Results. Compared with placebo, APX001 or POSA treatment resulted in a gradual decrease in tissue fungal burden over time with APX001 or POSA showing significant reduction as early as 96 and 72 hours, respectively (P < 0.005). Although the super-therapeutic dose of POSA resulted in faster reduction in lung fungal burden after 72 hours, both drugs resulted in similar reduction (~6–7 log) in lung CE vs. placebo after 96 hours. Changes in GM levels in BAL or serum samples mirrored reductions in lung CFU with significant decrease seen after 96 hours or 72 hours for APX001 or POSA, respectively, vs. placebo (P < 0.02) (figure).

Conclusion. A human equivalent dose of APX001 and a super humanized dose of POSA resulted in a time-dependent reduction of lung fungal burden and GM levels when compared with placebo. These results show that GM can be used as a biomarker of APX001 efficacy in immunosuppressed mice.



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

679. *In vitro* Activity of Cefiderocol (CFDC), a Novel Siderophore Cephalosporin, Against Difficult-to-Treat-Resistant (DTR) Gram-Negative Bacterial Pathogens From the Multi-National Sentinel Surveillance Study, SIDERO-WT (2014–2017)

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Background. DTR organisms are defined as nonsusceptible to all high-efficacy, low-toxicity antibiotics (penicillins, cephalosporins, carbapenems, and quinolones), leaving physicians with limited first-line treatment options. Analyses of electronic health records have shown that patients with DTR Gram-negative bacterial infections are more likely to receive inappropriate antibiotic therapy, have longer hospital stay and increased risk of mortality. CFDC is a novel parenteral siderophore cephalosporin with potent activity against aerobic Gram-negative pathogens, including carbapenem-resistant strains. We evaluated the *in vitro* activity of CFDC and comparators against DTR pathogens collected by the SIDERO-WT surveillance study.

Methods. A total of 30,459 clinical isolates of Gram-negative bacilli were systematically collected from United States, Canada, and 11 EU countries during 2014–2017. MICs were determined by broth microdilution for a panel of 7 antibiotics, including CFDC, ceftazidime–avibactam (CZA), ceftolozane–tazobactam (C/T), colistin (CST), cefepime (FEP), meropenem (MEM), and ciprofloxacin (CIP) according to CLSI guidelines. All antibiotics were tested in cation-adjusted Mueller–Hinton broth (CAMHB) except CFDC, for which iron-depleted CAMHB was used. Susceptibility was determined according to CLSI interpretive breakpoints except CST, where EUCAST breakpoints were used. DTR pathogens were defined as being nonsusceptible to FEP, MEM, and CIP according to CLSI breakpoints.

Results. Among 30,459 Gram-negative isolates collected between 2014 and 2017, 9.3% were nonsusceptible to FEP, MEM, and CIP and could be defined as DTR. DTR was most frequently observed in *Acinetobacter* spp. (55.5%), followed by *Burkholderia* spp. (19%), *Pseudomonas aeruginosa* (9.5%), and Enterobacterales (2.7%). Of the 1,173 *Stenotrophomonas maltophilia* tested, 97% had MEM MIC of ≥8 mg/L; however, only 2.9% could be defined as DTR. Cefiderocol was the most active antibiotic tested against DTR isolates with 94.5% DTR-*Acinetobacter* spp., 98.3% DTR-*P. aeruginosa*, and 99.8% DTR-Enterobacterales susceptible (Table 1).

Conclusion. CFDC demonstrated potent activity against DTR Gram-negative pathogens with limited first-line treatment options.

Table 1.

Acinetobacter spp. (n, 1794)	Breakpoints (S, R)	MIC_{50}	MIC_{90}	% S	% I	% R
Cefiderocol	≤4, ≥16	0.25	2	94.5	2.5	3
Colistin†	≤2, ≥4	1	8	85	–	15
Ceftazidime-avibactam*	N/A	32	>64	–	–	–
Ceftolozane-tazobactam*	N/A	32	>64	–	–	–
P. aeruginosa (n, 470)	Breakpoints (S, R)	MIC_{50}	MIC_{90}	% S	% I	% R
Cefiderocol	≤4, ≥16	0.25	1	99.8	0.2	0
Colistin†	≤2, ≥4	1	2	98.3	–	1.7
Ceftazidime-avibactam	≤8/4, ≥16/4	16	>64	49.5	–	50.5
Ceftolozane-tazobactam	≤4/4, ≥16/4	8	>64	48.8	5.7	45.5
Enterobacterales (n, 573)	Breakpoints (S, R)	MIC_{50}	MIC_{90}	% S	% I	% R
Cefiderocol	≤4, ≥16	1	4	98.3	1.5	0.2
Colistin†	≤2, ≥4	1	>8	68.2	–	31.8
Ceftazidime-avibactam	≤8/4, ≥16/4	1	>64	78.2	–	21.8
Ceftolozane-tazobactam	≤2/4, ≥8/4	>64	>64	2.05	1.65	96.3

*No Breakpoint available; †EUCAST Breakpoint

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

680. *In vitro* Activity of Ceftazidime–Avibactam and Comparator Agents Against *Pseudomonas aeruginosa* from ICU and Non-ICU Wards Collected in Latin America and Globally as Part of the ATLAS Surveillance Program 2016–2017

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Background. Ceftazidime–avibactam (CAZ-AVI) is a β-lactam/non-β-lactam β-lactamase inhibitor combination that can inhibit class A, C and some class D β-lactamases but not class B metallo-β-lactamases (MBLs). Antimicrobial resistance due to these β-lactamases and other mechanisms is increasing and is especially high in ICUs. This study evaluated the *in vitro* activity of CAZ-AVI and comparators against *Pseudomonas aeruginosa* isolates from patients in ICU and non-ICU wards.

Methods. Nonduplicate clinical isolates were collected in 2016–2017 in Asia/Pacific, Europe, Latin America, and Middle East/Africa. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2019 breakpoints. PCR and sequencing were used to determine the β-lactamase genes present in all isolates with meropenem (MEM) MIC >2 µg/mL.

Results. The activity of CAZ-AVI and comparators is shown in the table. Susceptibility rates among global *P. aeruginosa* were generally lower for isolates from patients in ICU than non-ICU wards, but this difference was small for CAZ-AVI (89% and 92% susceptible, respectively) and for amikacin and colistin. Among MEM-nonsusceptible (NS) isolates, CAZ-AVI was active against 72% and 70% of isolates, respectively, of which 18.4% and 18.7% were MBL-positive. CAZ AVI inhibited >83% of MEM-NS MBL-negative isolates globally. In Latin America (LA), CAZ-AVI was active against 87% of isolates from both ward types. Susceptibility rates were generally lower than the global average, especially among MEM-NS isolates and isolates from non-ICU wards. The proportion of MBL-positive isolates in the MEM-NS subset was only slightly higher in LA than globally (19.2% and 19.5% in ICU and non-ICU wards, respectively), suggesting the presence of additional resistance mechanisms. Only colistin exceeded the activity of CAZ-AVI against isolates collected globally and in LA.

Conclusion. CAZ-AVI showed potent antimicrobial activity, second only to that of colistin, against *P. aeruginosa* isolates from both ICU and non-ICU wards, with >88% of isolates collected globally testing as susceptible. Activity was in part compromised by MBLs, although additional resistance mechanisms may also be responsible.

		Drug (% Susceptible)				
Region/phenotype	Ward type (n)	CAZ-AVI	CAZ	MEM	AMK	CST
Global						
All *P. aeruginosa*	ICU (2024)	88.8	69.7	63.8	88.4	99.7
	Non-ICU (4856)	92.3	78.8	76.5	91.3	99.8
MEM-NS	ICU (733)	71.6	39.3	0.0	72.4	99.5
	Non-ICU (1142)	69.5	40.9	0.0	67.4	99.6
MEM-NS MBL-negative	ICU (598)	87.3	47.8	0.0	84.3	99.3
	Non-ICU (929)	83.7	49.8	0.0	79.0	99.5
Latin America						
All *P. aeruginosa*	ICU (434)	86.6	67.5	61.5	80.9	99.5
	Non-ICU (731)	86.9	69.8	66.4	81.8	99.6
MEM-NS	ICU (167)	67.1	35.3	0.0	60.5	100
	Non-ICU (246)	61.0	32.1	0.0	51.6	99.2
MEM-NS MBL-negative	ICU (135)	82.2	43.0	0.0	73.3	100
	Non-ICU (198)	74.2	39.4	0.0	60.6	99.0

[a]Includes isolates from Asia/Pacific, Europe, Latin America, and Middle East/Africa
CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; AMK, amikacin; CST, colistin; NS, nonsusceptible; MBL, metallo-β-lactamase

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

681. *In vitro* Activity of the β-Lactamase Inhibitor QPX7728 in Combination with Several β-Lactams Against *Acinetobacter baumannii* (AB) and *Pseudomonas aeruginosa* (PSA)

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Background. QPX7728 (QPX) is a novel broad-spectrum boron-containing inhibitor of serine- and metallo-β-lactamases (MBLs). We evaluated the *in vitro* activity of QPX combined with several β-lactams against carbapenem-resistant AB (CRAB) and PSA clinical isolates with varying β-lactam resistance mechanisms.

Methods. A total of 503 CRAB (meropenem [MEM] MIC ≥8 µg/mL) and 762 PSA clinical isolates were tested by the reference broth microdilution method against β-lactams alone and combined with QPX (4 µg/mL and 8 µg/mL). PSA isolates were selected to represent the normal distribution of MEM, ceftazidime–avibactam (CAZ-AVI), and ceftolozane-tazobactam (TOL-TAZ) resistance according to 2017 surveillance data (representative panel). Additionally, 262 PSA isolates that were either nonsusceptible (NS) to MEM (MIC, ≥4 µg/mL) or to TOL-TAZ (MIC, ≥8 µg/mL), or resistant (R) to CAZ-AVI (MIC, ≥16 µg/mL) (challenge panel) were also tested. Within this 262 strain challenge set, 56 strains carried MBLs and the majority also had nonfunctional OprD.

Results. Against CRAB, QPX at 4 and 8 µg/mL increased the potency of all β-lactams tested. MEM-QPX was the most potent combination (table) displaying MIC_{50}/MIC_{90} at 1/8 and 0.5/4 µg/mL with QPX at fixed 4 and 8 µg/mL, respectively. Susceptibility (S) to MEM was restored in >95% of strains. Against the 500 PSA from the representative panel, S for all QPX combinations was >90%. For the challenge panel, TOL-QPX and piperacillin (PIP)-QPX were the most potent combinations, restoring S in 76–77% of strains. TOL-QPX and MEM-QPX or cefepime (FEP)-QPX restored the MIC values to S rates when applying the CLSI breakpoint for the compound alone (comparison purposes only) in ~90% and ~75% of non-MBL-producing strains, respectively, vs. 60–70% for TOL-TAZ and CAZ-AVI. PIP-QPX reduce the MIC values to S values for PIP-TAZ in ~60% of MBL-producing strains vs. 20–30% and 3–7% for other QPX combinations and non-QPX tested combinations, respectively.

Conclusion. Combinations of QPX with various β-lactam antibiotics displayed potent activity against CRAB and resistant PSA isolates and warrant further investigation.

	MIC_{50}/MIC_{90} (µg/ml) (% inhibited at the β-lactam alone breakpoint for CLSI [for comparison only])								
	MEM	MEM-QPX	TOL-TAZ	TOL-QPX	FEP	FEP-QPX	PIP-TAZ	PIP-QPX	CAZ-AVI
CRAB (503)	>32/>32 (1.0)	0.5/4 (99.8)	32/>32 (2.0)	8/32 (40.2)	>32/>32 (0.6)	16/32 (41.2)	ND	ND	ND
PSA (500), representative panel	0.5/16 (84.8)	0.25/8 (91.6)	0.5/4 (91.8)	0.5/1 (97.6)	4/32 (74.4)	2/8 (90.2)	8/128 (71.6)	ND	2/8 (92.2)
PSA (262), challenge panel	16/>64 (41.6)	4/>64 (66.0)	8/>64 (48.9)	1/>64 (77.1)	32/>64 (19.8)	8/>64 (64.9)	128/>256 (16.8)	16/32 (76.0)	16/>64 (48.0)
PA (no MBL) (206)	8/64 (51.0)	4/16 (75.7)	4/>64 (60.7)	1/4 (91.7)	32/>64 (24.3)	8/16 (76.2)	128/>256 (19.4)	8/32 (80.1)	8/64 (61.2)
PA (MBL) (56)	>64/>64 (7.1)	64/>64 (30.4)	>64/>64 (5.4)	>64/>64 (23.2)	>64/>64 (3.6)	64/>64 (23.2)	128/>256 (7.1)	16/64 (60.7)	>64/>64 (3.6)

QPX at fixed 8 µg/ml. AVI and TAZ at fixed 4 µg/ml. Breakpoints: MEM ≤ 8 µg/ml; TOL ≤ 4 µg/ml; FEP ≤ 8 µg/ml; CAZ ≤ 8 µg/ml, PIP ≤ 16 µg/ml.
ND, not done.

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