Background. Mucormycosis is a life-threatening infection that predominantly occurs in immunocompromised hosts. The antifungal APX001A (manogepix) inhibits Gwt1, an enzyme required for the conserved glycosylphosphatidyl inositol (GPI) post-translational modification in eukaryotes. We previously reported the activity of APX001 (fosmanogepix, the prodrug of APX001A) against *Rhizopus delemar* (minimum effective concentration [MEC] = 0.25 μg/mL). Here we assessed the activity against *R. oryzae,* which has an elevated MEC value.

Methods. *R. oryzae* 99–892 MIC and MEC values were 0.125 μg/mL and 4.0 μg/mL for isavuconazole (ISAV) and APX001A, respectively. ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) and cortisone acetate (500 mg/kg) on Days -2, +3, and +8 relative to intratracheal infection with 2.5×10^5 cells of *R. oryzae* 99–892. For survival studies, treatment with 104 mg/kg APX001 was compared with ISAV (110 mg/kg TID). Oral treatment started on Day +1 through Day +7, relative to infection for survival studies, and through Day +4 for tissue fungal burden studies (assessed by conidial equivalent [CE] using qPCR). Placebo mice received vehicle control. To extend the half-life of APX001, mice were administered 50 mg/kg of the cytochrome P450 inhibitor 1-aminobenzotriazole (ABT) 2 h prior to APX001 administration.

Results. APX001 and ISAV equally prolonged median survival time of mice (n = 20) vs. placebo (12 and 14 days for APX001 and ISAV, respectively, vs. 8 days for placebo). Furthermore, APX001 and ISAV treatment both resulted in 30% 21-day survival vs. 0% survival of placebo mice ($P < 0.05$ by log-rank test). Both drug treatments resulted in ~1.5 $\log_{10}$ reduction in lung and brain CE vs. placebo-treated mice (n = 10, $P < 0.005$ by Wilcoxon rank-sum test).

Conclusion. Despite a higher MEC value, APX001 showed significant efficacy against *R. oryzae* that was as protective as ISAV in immunosuppressed mice. Given the previously reported activity of APX001 against a strain of *R. delemar* with a lower MEC value,APX001 has now been shown to be efficacious against both species of *Rhizopus*, which together are responsible for ~60–70% of isolates causing lethal mucormycosis. Thus, continued investigation of APX001 against mucormycosis is warranted.

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

727. Potency of the β-Lactamase Inhibitor QPX7728 Is Minimally Affected by KPC Mutations that Reduce Potency of Ceftazidime–Avibactam

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Background. In the United States, carbapenem-resistant Enterobacteriaceae (CRE) are mainly represented by KPC-producing strains and ceftazidime–avibactam (C/A) is increasingly used to treat infections caused by KPC-producers. C/A resistant (C/A-R) mutants with mutations in bla_{KPC} can be isolated *in vitro* and were reported in patients treated with C/A. QPX7728 (QPX) is a new ultra-broad-spectrum β-lactamase inhibitor based on a cyclic boronic acid pharmacophore with a potent activity against serine and metallo-β-lactamases. QPX in combination with meropenem (MER), M/Q, or cefepime (FEP), F/Q, has potent activity against all types of CRE (KPC, MBLs and OXA-48). The objective of these studies was to evaluate the activity of QPX in combination with various antibiotics against KPC-producing strains with C/A-R due to mutations in bla_{KPC}.

Methods. Ten strains of KPC-producing *Klebsiella pneumoniae* with C/A MIC varied from 0.5 μg/mL to 8 μg/mL were used in resistance studies using C/A at 2x–8x the MIC (with avibactam [AVI] fixed at 4 μg/mL). Mutations in bla_{KPC} were identified by sequence analysis. Ceftazidime (CAZ), MER and FEP MIC alone and with AVI and QPX (both BLIs at 4 μg/mL) were determined using the reference broth microdilution method. Five C/A-R clinical isolates with mutations in bla_{KPC} were also included in the panel.

Results. Mutations in bla_{KPC} that result in C/A resistance were selected in all strains. Mutants had 4- to 64-fold (16-fold average) increase in C/A MIC that varied from 16 to 128 μg/mL. In contrast, there was a 2-fold increase for CAZ-QPX MICs (MICs between ≤0.125 to 2 μg/mL. Similarly, there was no more than 2-fold increase in MER/QPX and FEP/QPX MICs, and the majority of mutants did not have an increase in MER/QPX or FEP/QPX MICs (MICs varied from ≤0.125 to 1 μg/mL). For five clinical C/A-R isolates, C/A, M/Q and F/Q MIC varied from 16 to ≥128 μg/mL, ≤0.125 to 4 μg/mL, and ≤0.125 to 2 μg/mL, respectively.

Conclusion. These data indicate that KPC mutations that affect the potency of C/A have minimal effect on the potency of QPX7728 combinations with either CAZ, MER or FEP indicating the potential differences in binding sites for these inhibitors in KPC. Further studies of QPX combinations are in progress.

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728. Activity of Eravacycline Against Contemporary Gram-Negative Clinical Isolates From New York City Hospitals

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Background. Antibiotic-resistant Gram-negative bacteria, including KPC-producing *Enterobacteriaceae* and carbapenem-resistant *A. baumannii*, have been problematic hospital pathogens in NYC and other areas. Eravacycline (ERV), a fluorocycline antibiotic released in the USA in 2018, has demonstrated *in vitro* activity against many of these strains. We tested the activity of ERV against a recent collection of clinical isolates from NYC hospitals.

Methods. For a 3-month period in 2017, all unique patient isolates of *E. coli*, *K. pneumoniae*, *Enterobacter* spp., and *A. baumannii* were collected from 7 hospitals in Brooklyn, NY. MICs were performed by broth microdilution for ERV and Tigecycline (TGC) and agar dilution for other antibiotics according to CLSI methodology. Cephalosporin-resistant isolates were screened by PCR for common carbapenemases.

Results. The susceptibility results for tetracycline and ERV are listed in the Table. Overall, 95% of the *Enterobacteriaceae* were inhibited by ≤ 0.5 μg/mL of ERV, the FDA-suggested breakpoint. Of 1,876 isolates of *E. coli*, 4 possessed KPC. ERV MICs for these 4 isolates were 0.125–0.25 μg/mL. Of 518 isolates of *K. pneumoniae*, 20 possessed KPC. The ERV MIC_{50} and MIC_{90} for these isolates were 1 and 1 μg/mL, respectively. Of 172 isolates of *Enterobacter* spp., 3 possessed KPC. ERV MICs for these 3 isolates were 0.5–1 μg/mL. Of 45 isolates of *A. baumannii*, 11 isolates possessed a carbapenemase (OXA23 in 8, OXA24 in 2, and KPC in 1). The ERV MIC_{50} and MIC_{90} for these isolates were 1 and 2 μg/mL, respectively. Overall, ERV MICs were two-fold lower than TGC MICs for *A. baumannii*.

Conclusion. ERV possesses significant *in vitro* activity against contemporary clinical isolates of *Enterobacteriaceae* and *A. baumannii* from NYC, including many carbapenemase producing strains.

	MIC_{50}	MIC_{90}	Range	Percent susceptible
	μg/ml			
E. coli (n=1876)				
Tetracycline	2	>8	≤0.25 - >8	60%
Eravacycline	0.25	0.5	≤0.015 - 2	
K. pneumoniae (n=518)				
Tetracycline	2	>8	≤0.25 - >8	73%
Eravacycline	0.5	1	0.06 - 4	
Enterobacter spp. (n=172)				
Tetracycline	4	>8	1 - >8	67%
Eravacycline	0.5	1	0.125 - 4	
A. baumannii (n=45)				
Tetracycline	>8	>8	2 - >8	29%
Tigecycline	0.5	4	0.125 - 8	
Eravacycline	0.25	2	0.03 - 4	

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729. Comparing Length of Stay and Clinical Outcomes for Hospitalized Patients at Bridgeport Hospital who Received Baloxavir Marboxil (BM) or Oseltamivir Phosphate (OP) During the 2018–2019 Influenza Season

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Background. BM has been approved for the management of acute uncomplicated influenza in otherwise healthy individuals between age 12 and 64, and found to have a greater reduction in viremia. The original trial excluded hospitalized patients and those with co-morbidities.

Methods. This is a single-center, retrospective analysis of hospitalized patients diagnosed with influenza between October 1, 2018 and March 31, 2019. This study excluded those diagnosed before the addition of BM to the hospital formulary; those who were not treated with antivirals, treated before admission, or treated with both antivirals; those younger than 12 years old; and those who remain hospitalized. The relationship between length of stay and antiviral used was ascertained using t-test and multivariate linear regression. Due to heterogeneity in reasons for hospitalization, analysis was stratified by the main reasons for hospitalization. T-test and Wilcoxon's rank-sum test were used for continuous variables, and Pearson's chi-squared test was used for categorical variables. The significance level was 0.05.

Results. The study population (n = 145) has a mean age of 66.5 years; of whom, 43% are male. In terms of patient characteristics, those treated with BM (n = 105) vs. OP (n = 40) were older, less frequently admitted to ICU and of differing ethnic composition. The length of stay was similar in those treated with BM vs. OP in both univariate and multivariate linear regression (5.5 (5.3) vs. 8.2 (11.4) days, $P = 0.33$). In addition, the length of stay was similar in those treated with BM vs. OP when stratified by reasons for hospitalization: pneumonia/bronchitis (6.6 (7.1) vs. 8.2 (9.2) days, P = 0.43), obstructive airway disease exacerbation (5.5 (4.8) vs. 4.8 (8.0) days, $P = 0.56$), elderly with multiple co-morbidities (5.0 (4.0) vs. 3.4 (6.8) days, $P = 0.63$), reactive airway disease (4.1 (4.8) vs. 7.4 (1.5) days, $P = 0.27$) or congestive heart failure exacerbation (9.8 (9.0) vs. 5.6 (5.0) days, $P = 0.43$).

Conclusion. In hospitalized patients with co-morbidities diagnosed with influenza, there was no difference in length of stay in those who received BM vs. OP. This highlights the need to clarify the role of BM in this population, particularly given its comparable symptom reduction, greater cost, and the emergence of PA138T viral mutant.

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730. Cefiderocol for the Treatment of *Achromobacter xylosoxidans* Infections in Two Lung Transplant Patients with Cystic Fibrosis

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Background. *Achromobacter xylosoxidans*is a highly resistant Gram-negative bacterium that causes chronic infections in patients with cystic fibrosis (CF). Treatment options for *A. xylosoxidans* are limited. In the peri-lung transplant setting, the treatment of *A. xylosoxidans* infections is especially challenging. Cefiderocol is a novel siderophore cephalosporin antibiotic with broad anti-Gram-negative activity, including against *A. xylosoxidans*. We report here two cases of compassionate use of cefiderocol in CF lung transplant recipients with *A. xylosoxidans* infection.

Methods. Cefiderocol was obtained through compassionate use from its manufacturer, with approval from the local Institutional Review Board. In the first case, it was used as salvage treatment, and in the second case as a planned part of the peri-transplant regimen.

Results. A male in his 20s with CF and a trimethoprim-sulfamethoxazole (TMP-SMX) allergy was chronically colonized by *A. xylosoxidans*, which was sensitive only to piperacillin–tazobactam (PIP-TAZ), and TMP-SMX. After lung transplant, he developed *A. xylosoxidans*bacteremia, and extended-infusion PIP-TAZ was started. Repeat bronchoscopy grew *A. xylosoxidans*. Due to lack of improvement, cefiderocol was added to PIP-TAZ with rapid clinical improvement. However, after completing his course, he was readmitted with *A. xylosoxidans* pneumonia. He was treated with 6 weeks of cefiderocol and imipenem and has been well since with an 8-month follow-up. In the second case, cefiderocol was used as part of the planned peri-transplant regimen for a female with CF in her late teens, with chronic *A. xylosoxidans* colonization, which was intermediate to PIP-TAZ, and resistant to all other drugs tested. Her native lungs grew 4+ *A. xylosoxidans* at the time of explant. Post-transplant, she was treated with 5 weeks of meropenem and 6 weeks of cefiderocol. At four-month follow-up, she is doing well. However, she is asymptomatically colonized with *A. xylosoxidans*post-transplant. Isolates from both cases were susceptible to cefiderocol (case #1 MIC = 0.12; case #2 pretreatment MIC = 1, post-treatment MIC.

Conclusion. Cefiderocol may be a useful option for lung transplant recipients with *A. xylosoxidans* infections.

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731. Pharmacokinetics of Gepotidacin (GSK2140944) in Subjects with Hepatic Impairment

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Background. Gepotidacin (GEP), a first in class novel triazaacenaphthylene bacterial topoisomerase inhibitor, inhibits bacterial replication and has *in vitro* and *in vivo* efficacy activity against key pathogens, including drug-resistant strains, associated with a range of infections. In a previous absorption, distribution, metabolism, and excretion study for GEP, the mean recovery of radioactivity in urine and feces accounted for approximately 31.2% and 52.5%, respectively, of [^{14}C]-GEP administered as a single oral dose. GEP was eliminated mainly as parent in urine, accounting for approximately 20% of the administered dose. Elimination via metabolism accounted for a total of 13% to 19% of the dose. Average total intravenous clearance of approximately 43 L/hour and renal clearance (CLr) of approximately 16 L/hour provides a hepatic clearance of 27 L/hour, suggesting that hepatic clearance is a major route of elimination of GEP.

Methods. Participants with normal and varying degrees of hepatic impairment (HI) received a single oral dose of GEP 1,500 mg. PK collections of blood, urine and saliva were performed.

Results. Relative to normal hepatic function, GEP Cmax and AUC(0-∞) in plasma were increased by 1.2-fold in subjects with moderate, and between 1.7-fold to 1.9-fold in severe HI. The fraction of dose excreted in urine increased with an increase in hepatic impairment. GEP urine concentrations remained high over a 12-hour period. Saliva concentrations displayed a linear relationship with plasma (both total and unbound) concentrations (R^2 = 0.76). The geometric mean ratio of saliva AUC to unbound plasma AUC values ranged from 0.746 to 0.839 across all groups. Administration of 1,500 mg oral GEP was generally tolerated.

Conclusion. An increase in the dosing interval or dose reduction may be required in patients with severe hepatic impairment.

Geometric mean (%CVb) estimates for key GEP plasma PK parameters:

Parameter (unit)	Normal Hepatic Function (N=9)	Moderate Hepatic Impairment (N=8)	Severe Hepatic Impairment (N=8)
AUC(0-∞) (µg•hr/mL)	15.9 (44.1)	19.5 (42.6)	25.4 (30.1)
Cmax (µg/mL)	3.20 (85.0)	3.91 (64.1)	5.54 (42.7)
t1/2 (hr)	9.07 (14.9)	8.52 (12.3)	8.21 (15.2)
CL/F (L/hr)	94.4 (44.1)	76.9 (42.6)	59.0 (30.1)
Vz/F (L)	1235 (57.5)	945 (50.3)	699 (41.7)

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732. Posaconazole Serum Drug Levels Associated with Pseudohyperaldosteronism

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Background. Posaconazole is an extended-spectrum triazole used in the treatment and prophylaxis of many fungal diseases. There have been case reports of posaconazole-induced pseudohyperaldosteronism; however, its occurrence and association with serum posaconazole drug levels need further investigation.

Methods. In this single-center retrospective observational study, we examined the occurrence of posaconazole-induced pseudohyperaldosteronism (PIPH), diagnosed either clinically or via laboratory abnormalities, and evaluated differences in serum posaconazole concentration and clinical characteristics between those with and without this syndrome.

Results. Sixty-nine patients receiving posaconazole were included; of whom, 16 (23.2%) met the definition of PIPH. Patients with PIPH were significantly older (61.1 vs. 44.7 years, P = 0.007), more frequently had hypertension prior to starting posaconazole (68.8% vs. 32.1%, P = 0.009), and were more frequently prescribed posaconazole for active treatment instead of prophylaxis compared with patients without PIPH (62.5% vs. 24.5%, P = 0.005). Patients with PIPH had a significantly higher median serum posaconazole level than those without PIPH (3.0 vs. 1.2 µg/mL, P = 0.0001). There was a positive correlation between serum posaconazole level and change in systolic blood pressure (r = 0.37, P = 0.01), a negative correlation between serum posaconazole level and change in serum potassium (r = −0.39, P = 0.006), and a positive correlation between serum posaconazole level and serum 11-deoxycortisol (r = 0.69, P < 0.0001).

Conclusion. Posaconazole is associated with secondary hypertension and hypokalemia, consistent with pseudohyperaldosteronism, and development is associated with higher serum posaconazole concentrations, older age, and baseline hypertension. Management may include dose reduction, the addition of an aldosterone antagonist, or an alternative triazole agent.

FIGURE 1. Correlation of posaconazole with clinical and laboratory variables.

(A) Correlation between serum posaconazole concentration and change in systolic blood pressure (n=69); **(B)** between serum posaconazole concentration and change in serum potassium (n=68); and **(C)** between serum posaconazole concentration and serum 11-deoxycortisol (n=35).