Background. Mucormycosis is a life-threatening infection that predominantly occurs in immunocompromised hosts. The antifungal APX001A (manopexa) inhibits its Gwl1, an enzyme required for the conserved glycosylphosphatidyl inositol (GPI) post-translational modification in eukaryotes. We previously reported the activity 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 µg/mL for salvaconazole (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 × 10⁷ 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-amino-benzoiazoflato (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 for placebo mice (n = 10, P < 0.05 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) is primarily 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 blaKPC 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, and cephalosporin (FEP) and QPX (both BLIs at 4 µg/mL) were determined using the reference broth microdilution method. The study population was 105 K. pneumoniae, 20 A. baumannii, and 5 A. baumannii-clade isolates which were collected from 7 hospitals in Greater New York City.

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 MIC and QPX/QMX MICs, and the majority of mutants did not have an increase in MICs between ≤0.125 to 2 µg/mL. Similarly, there was no more than 2-fold increase in MER/QPX MICs, and the majority of mutants did not have an increase in MICs between ≤0.125 to 2 µg/mL. A 2-fold increase for CAZ-QPX MICs was observed for QPX (both BLIs at 4 µg/mL) were determined using the reference broth microdilution method.

Results. Mutations in blaKPC 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 or FEP/QPX MICs. 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 MICs for these isolates were ≤0.125–0.25 µg/mL. Of 518 isolates of K. pneumoniae, 20 possessed KPC. The ERV MICₕ₅₀ and MICₚ₂₀ for these isolates were 1 and 1 µg/mL, respectively. Of 172 isolates of Enterobacter spp., 3 possessed KPC. ERV MICs for these isolates were 0.5–4 µg/mL. Of 45 isolates of A. baumannii, 11 isolates possessed a carbapenemase (OXA23 in 8, OXA23 in 4, and KPC in 1). The ERV MICₕ₅₀ and MICₚ₂₀ for these isolates were 1 and 2 µg/mL, respectively. Overall, ERV MICs were twofold 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.