Background. Avibactam (AVI) is a broad-spectrum intravenous non-β-lactam/β-lactamase inhibitor with no reported activity against metallo-β-lactamases such as New Delhi metallo-β-lactamases (NDM). Structural similarities between β-lactamases and bacterial penicillin-binding proteins (PBPs) have led investigators to explore and confirm the hypothesis that AVI may interact with PBPs of several Gram-negative and positive bacteria, leading to synergy. Potential synergy has also been observed between AVI and peptide antibiotics such as polymyxin B. We hypothesized that sub-bactericidal concentrations of AVI may bind PBPs to weaken cell wall integrity and enhance lyse by the membrane attack complex of complement and by endogenous cationic antimicrobial peptides (AMPs) such as human cathelicidin LL-37. (誉B) due to sensitization of AMPs could improve killing by neutrophils and platelets that release these effectors upon degranulation.

Methods. Using NDM K. pneumoniae (NDM-K) as a model, we performed LL-37 kill curves and killing assays with human serum, neutrophils and platelets in the presence or absence of AVI 4 μg/mL against NDM-K.

Results. AVI alone lacked in vitro activity against NDM-K. Addition of AVI to a physiological achievable concentration of LL-37 (2 mM) was bactericidal and resulted in an 8-log. reduction (below detection limit) in recoverable NDM-K CFU at 6 and 24 h; no bactericidal activity was seen in bacteria treated with LL-37 or AVI alone (P = 0.0001). AVI pretreatment dramatically sensitized NDM-K to neutrophil and platelet killing (P < 0.0001 and P < 0.01, respectively). AVI also sensitized NDM-K to 20% human serum, resulting in 8-log. reduction in recoverable NDM-K CFU within 6 h (P < 0.0001), an effect abrogated by heat treatment to inactivate complement.

Conclusion. AVI demonstrates potent synergy with peptide antibiotics and the innate immune system in vitro. Since AVI alone has scant direct antimicrobial activity and no direct inhibitory effect on metallo-β-lactamases, it is less likely to increase selective pressures toward antibiotic resistance. The use of AVI in combination with other antibiotics against drug-resistant bacterial pathogens warrants further study.

Disclosures. G. Sakoulas, Allergan: Consultant and Speaker, Consulting fee and Speakers’ Bureau honorarium. Sunovion: Speaker, Speaker honorarium. The Medicines Company: Speaker, Consulting fee. Paratek Pharmaceuticals: Consultant, Consulting fee. Cidara Therapeutics: Scientific Advisor, None. Arsanis Pharmaceuticals: Scientific Advisor, None.

2391. Liposomal Vancomycin and Cefazolin Combinations for S. aureus Biofilms Razeh Kebriaei, PhD1; Ketki Bhise, PhD candidate2; Samaresh Sau, PhD3; Seth Rice, PPCF, FACP1; Amy Riemenschneider1; Vin Sun Iyer, PhD4,5; and Michael J. Rybak, PharmD, MPH6, PhD7,8; Pharmacy Practice, Wayne State University, Detroit, Michigan, *Pharmacy, Wayne State University, Detroit, Michigan, ‡Wayne State University, Detroit, Michigan, ¶Pharmacy Practice, Wayne State University, Detroit, Michigan, †Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, Michigan, ‡Anti-Infective Research Laboratory, College of Pharmacy, School of Medicine, Division of Infectious Diseases, Wayne State University, Detroit, Michigan

Session: 250. Treatment of AMR Infections Saturday, October 6, 2018: 12:30 PM

Background. Biofilms are sophisticated communities of matrix-encased and surface-attached bacteria that exhibit a distinct and specific tolerant phenotype to almost all antibacterial agents, with activity reduced 10- to 1,000-fold. Interestingly, face-attached bacteria that exhibit a distinct and specific resistant/tolerant phenotype that ESBL producing bacteria can be treated successfully with fosfomycin in a male population as well as uncomplicated cystitis. However, caution should be used with cathereted patients as treatment was less effective regardless of isolated bacteria.

Disclosures. All authors: No reported disclosures.

2393. Evaluation of Antifungal Treatment in a Neutropenic Mouse Model of Scedosporiosis Sondus Alkhazraji, PhD1; Tseglegiorgis Gebremariam, MS2; Abdullah Algarhi, MS3; Clara Baldwin, PhD2; Nathan P. Wiederhold, PharmD2; Therese Kitt, MD2 and Ashraf S. Jaffer, PharmD1; Department of Pharmacology and Toxicology, Beth Israel Medical Center, Torrance, California, *UT Health San Antonio, San Antonio, Texas, †Astellas Pharma Global Development, Inc., Northbrook, Illinois

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Background. Scedosporiosis is a rare fungal infection with high mortality rates. Because clinical trials are hard to conduct, we developed a murine model for evaluating the efficacy of currently used antifungals in treating scedosporiosis.

Methods. MIC of isavuconazole (ISAV), posaconazole (Posa), voriconazole (Vori), and micafungin (MICA) were determined against 9 clinical isolates of Scedosporium apiospermum, S. boydii and Lomentospora prolificans using the CLSI M38 method. ICR mice were immunosuppressed with cyclophosphamide (200 mg/kg) on day −7 and cortisone acetate (500 mg/kg) on days −2, +3, and +8 relative to intratracheal infection with 3.0 × 106 cells of S. apiospermum. For fungal burden studies, mice were dosed 8 h post infection and continued for 3 days. Mice were sacrificed on day +4. Survival and tissue fungal burden (by qPCR) served as efficacy endpoints.

Results. S. apiospermum was the most susceptible to all antifungals with MICs of 0.25 μg/mL and azole MICs of 1 μg/mL. S. boydii was also susceptible to MICA (0.125–0.5 μg/mL) but with variable susceptibility to azoles (1–16 μg/mL). In vivo, S. boydii was the most susceptible to all 4 antifungals with MIC of 0.25 μg/mL and azole MICs of 1 μg/mL. In contrast, L. prolificans strains were resistant (MIC MIC of 0.25 μg/mL and azole MIC of 1 μg/mL). S. apiospermum was used to treat fungal burden studies. mice were dosed 8 h post infection and continued for 7 days. For fungal burden studies, mice were dosed 8 h post infection and continued for 3 days. Mice were sacrificed on day +4. Survival and tissue fungal burden (by qPCR) served as efficacy endpoints.

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