1640. Toward New Anti-Biofilm Therapies: High Mobility Group Box 1 (HMGB1) Protein and Its Structural Variants Can Be Used to Disrupt Bacterial Biofilms (BBs)
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Session: 168. Novel Therapies for Superbugs
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Background. BB-related infections are a major public health problem, as they are notoriously refractory to current treatments. One of the defining characteristics of BBs is the extracellular polymeric substance (EPS). Extracellular DNA and the bacterial DNAABII family of proteins are key components of EPS and are crucial for BBs structural integrity. It is known that targeting DNAABII proteins disrupts BBs. We hypothesized that HMGB1, a DNA-binding eukaryotic protein, could affect BBs as it binds to the same DNA structures as the DNAABII proteins. HMGB1 is comprised of 3 domains, A Box, B Box, and C tail, all of which have different functions. We aimed to determine in vitro the effects of HMGB1 and its individual domains against BBs.

Methods. Klebsiella pneumoniae (KP), a common cause of nosocomial infections, was used for all BBs disruption assays. Human recombinant full-length HMGB1 (rHMGB1; 1–215), a C45S mutation variant (mHMGB1) and the HMGB1 domains A Box (1–89), B Box (90–176), AB Boxes (1–176), B-linker Box (80–179), and B-linker Box C1065 were expressed in E. coli and purified to >95%. To evaluate the effect of HMGB1 and the various domains on established BBs, each protein species were added to preformed BBs at 24 hours. At 40 hours the BBs were washed, stained with LIVE/DEAD®, visualized via confocal laser scanning microscopy and images were analyzed by COMSTAT to calculate average thickness and biomass.

Results. Exogenous rHMGB1 and its individual domains, with the exception of A Box caused a significant reduction (P < 0.05) in average thickness (AT) and biomass (BM) of KP biofilms when compared with untreated KP biofilms (% reduction mean ± SE in AT: 44% ± 0.03, 75% ± 0.04, 63% ± 0.1, 77% ± 0.03, 64% ± 0.08, 54% ± 0.15 and in BM: 61% ± 0.01, 80% ± 0.01, 68% ± 0.02, 67% ± 0.01, 73% ± 0.02, 56% ± 0.02 induced by rHMGB1, mHMGB1, B-Box, B-linker Box, AB Boxes, and B-linker Box C1065, respectively).

Conclusion. Full-length recombinant HMGB1 was able to significantly disrupt established KP biofilms as were all truncated HMGB1 forms containing the B Box domain and could potentially be used as a therapeutic treatment for BB-related infections.

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1641. Treatment of Recurrent Clostridium difficile Infection With SER-109 Reduces Gastrointestinal Carriage of Antimicrobial Resistance Genes
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Background. A healthy gut microbiome is associated with colonization resistance against C. difficile and other pathogens, including bacteria carrying antibiotic resistance genes (AbRC). Designed to facilitate microbiome restoration and reduce the risk of recurrent C. difficile infection (rCDI), SER-109, an investigational microbiome therapeutic, is an ecology of bacterial spores purified from stool by healthy screened donors. We evaluated the impact of engraftment of SER-109 dose species on the abundance of AbRC in rCDI subjects.

Methods. We generated whole metagenomic shotgun (WMS) data for a subset of study subjects with available stool samples receiving SER-109 (n = 66) or placebo (n = 25) from 2 clinical trials (a dose-ranging Phase 1b study and a fixed-dose Phase 2 trial). WMS data from stool was analyzed to (1) quantify the abundance of AbRC (Comprehensive Antibiotic Resistance Database CARD v.1.1.8) and (2) define subjects with significant engraftment of SER-109 dose species. For each subject and antibiotic drug class, we calculated the change in abundance of AbRC between samples collected at baseline (after antibiotic therapy for an episode of C. difficile infection) and following treatment with SER-109 or placebo. We evaluated the effect of SER-109 engraftment on AbRC abundance, independent of dose.

Results. In subjects with significant high-confidence engraftment of SER-109 organisms (n = 30) we observed significantly greater reduction in AbRC relative to placebo at week 1 post treatment. These AbRC were associated with multiple classes of antibiotics including, but not limited to, cephalosporins (P = 0.035), and fluoroquinolones (P = 0.035) (Figure 1). Furthermore, the reduction of AbRC was correlated with the increased abundance of SER-109 dose species, and with a reduction in Proteobacteria (e.g., Enterobacteriaceae) (Figure 2).

Conclusion. Restoration of the gut microbiome with SER-109 in subjects with a history of rCDI is associated with a reduction in abundance of antibiotic resistance genes. These observations suggest that microbiome therapeutics could play a role in more rapidly decolonizing drug-resistant bacteria.
1642. Safety and Efficacy of Bacteriophage Therapy: Analysis of Clinical Case Series Data
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Methods. Patients were treated with AB-PA01 (4-phenyl targeting P. aeruginosa) produced in a Good Manufacturing Practice facility and delivered as an aerosol at a mean dose of 10e6 PFU/L. Patients were treated with AB-PA01 in 240 adults who were infected with 137 (57.1%) in 30 days. A majority of patients (62.8%) were immunocompromised. This study was powered to maximize statistical power in determining the efficacy and efficacy against enterococcal BSI.

Results. Compared with our previous observations for DAP monotherapy, adding DAP plus AB-PA01 to bacteriophage therapy showed ongoing susceptibility to the BT products when changes in sensitivity to the individual phage components observed in some patients. Bacteriophage kinetics showed bloodstream clearance within a few hours after IV infusion and an inferred initial bacteria/phage ratio of ~200 for the patients when infected with 137 (57.1%) in 30 days. A majority of patients (62.8%) were immunocompromised. This study was powered to maximize statistical power in determining the efficacy and efficacy against enterococcal BSI.

Conclusion. Compared with our previous observations for DAP monotherapy, adding DAP plus AB-PA01 to bacteriophage therapy showed ongoing susceptibility to the BT products when changes in sensitivity to the individual phage components observed in some patients. Bacteriophage kinetics showed bloodstream clearance within a few hours after IV infusion and an inferred initial bacteria/phage ratio of ~200 for the patients when infected with 137 (57.1%) in 30 days. A majority of patients (62.8%) were immunocompromised. This study was powered to maximize statistical power in determining the efficacy and efficacy against enterococcal BSI.

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1644. A Potent Broadly Neutralizing Antibody Isolated From Human Memory B-cells Binding to Conserved Site IV of the RV1 F Protein
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Background. Respiratory syncytial virus (RSV) infection is a major public health burden for infants and the elderly worldwide. Currently, there are

1663. Pharmacodynamics (PD) of Daptomycin (DAP) in Combination Therapy for Entercoccal Bloodstream Infection (BSI)
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Background. DAP is frequently employed in combination with a second anti-antibiotic for enterococcal BSI. We previously observed that a free drug area under the curve to MIC ratio (AUC/MIC) > 20 was predictive of survival when DAP was administered as the initial drug. For the extent to which combination therapy affects DAP PD remains unexplored.

Methods. This study pooled data from 7 published trials assessing outcomes in DAP treated enterococcal BSI. AUC/MIC was calculated using a published population pharmacokinetic model based on creatinine clearance, 90% protein binding, and baseline DAP MIC for each patient that received ≥72 hours of DAP as part of a combination antibiotic regimen. The AUC/MIC threshold predictive of 30-day survival was determined by classification and regression tree analysis and confirmed by multivariable logistic regression. To control for comorbidities, the threshold was examined in the low-acuity patients only (APACHE II score <21, Charlson co-morbidity index <5, or Pitt bacteremia score <4). Monte Carlo simulation was performed to determine the probability of target attainment (PTA) for a range of MICs.

Results. In total, 240 adults were included and 137 (57.1%) were alive at 30 days. A majority of patients (62.8%) were immunocompromised. Combination therapy with DAP plus AB-PA01 was observed in 157 (65.4%) patients and with a 9-lactic and 1 other active agent in 34 (14.2%) patients. Low-acuity patients (n = 135) were less likely to survive when AUC/MIC >12.3 was achieved (63.2% versus 20.0%, P = 0.015). This difference remained significant when controlling for BSI source and immunosuppression (P = 0.017). The PTA for a 6 mg/kg/day dose was 95.2% at MIC=2 mg/L and 43.0% at MIC=4 mg/L; PTA for a 12 mg/kg/day dose was 95.2% at 4 mg/L.

Conclusion. Compared with our previous observations for DAP monotherapy against enterococcal BSI, a lower DAP PD exposure was required when administered with at least one additional antibiotic. For combination therapy with DAP, a AUC/MIC >12.3 was associated with 30-day survival. As part of an active combination therapy regimen, DAP 6 mg/kg/day was appropriate for treatment of BSI caused by enterococci with MICs ≤2 mg/L, while 12 mg/kg/day was optimal for isolates with MICs >4 mg/L.

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