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 bacterial species. Potent synergy has also been observed between AVI and peptide antibiotics such as polymyxin B. We hypothesized that sub-bacteriostatic concentrations of AVI may bind PBPs to weaken cell wall integrity and enhance lysis by the membrane attack complex of complement and by endogenous cationic antimicrobial peptides (AMPs) such as human cathelicidin LL-37. Sensitization to endogenous AMPs could improve killing by neutrophils and platelets that release these effectors upon degranulation.

Methods. Using NDM *K. pneumoniae* (NDM-KP) 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-KP.

Results. AVI alone lacked *in vitro* activity against NDM-KP. Addition of AVI to a physiological achievable concentration of LL-37 (2 mM) was bactericidal and resulted in an 8-$\log_{10}$ reduction (below detection limit) in recoverable NDM-KP 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-KP to neutrophil and platelet killing ($P < 0.0001$ and $P < 0.01$, respectively). AVI also sensitized NDM-KP to 20% human serum, resulting in 8-$\log_{10}$ reduction in recoverable NDM-KP 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.

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2391. Liposomal Vancomycin and Cefazolin Combinations for *S. aureus* Biofilms

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Background. Biofilms are sophisticated communities of matrix-encased and surface-attached bacteria that exhibit a distinct and specific resistant/tolerant phenotype to almost all antibacterial agents, with activity reduced 10- to 1,000-fold. Interestingly, this augmented resistance rapidly reverts when bacteria detach from the biofilm and return to a planktonic state. However, in this *in vitro* pharmacokinetic and pharmacodynamic (PK/PD) model we are able to expose biofilms to shear rates that are consistent with human interface and mimic antibiotic penetration and diffusion pathways from serum antibiotic concentration in humans.

Methods. Methicillin-susceptible ATCC 29213 and MRSA 494 strains were evaluated. Initial susceptibility tests were performed by broth microdilution method. Time kill studies were performed to identify synergy patterns for liposomal and commercial antibiotics. Biofilm eradication was investigated using antibiotics vancomycin (VAN) (commercial) vs. liposomal VAN (VAN-L) (Patent#17-1460) and also combination of VAN- cefazolin (commercial) vs. liposomal vancomycin and liposomal cefazolin (CFZ-L) (Patent# 17-1460) in biofilms for strain MRSA 494. Biofilms were generated overnight using the BioFlux Microfluidic system (Fluxion BioSciences) at constant and continuous shear rates to optimize biofilm attachment and creation. Perfusion of antibiotic solutions (free peak concentration) was applied over a 24 h time period. Time lapse pictures were recorded to determine antibiotic biofilm eradication rates over 18h of incubation and pictures were analyzed using Bioflux Montage software.

Results. MIC values demonstrated a 2-fold reduction for liposomal vancomycin vs. commercial vancomycin. Also, combination of liposomal VAN MIC in presence of CFZ-L showed a 15.87-fold reduction in comparison to commercial VAN for 494. Overall, our biofilm results demonstrated a 43.6% improved eradication using VAN-L and CFZ-L combination in comparison to commercial VAN-CFZ combination. We also observed 5.7% improved eradication using VAN-L vs. commercial VAN.

Conclusion. Liposomal form of VAN and CFZ combinations are a promising approach to improved efficacy and reduced VAN resistance in *S. aureus* biofilms.

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2392. Fosfomycin Utilization and Outcomes in a Large VA Medical Center Over a Decade

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Background. Urinary tract infection (UTI) is one of the most common infectious diagnoses and in 2007 accounted for 10.5 million primary care visits in the US Advancing age and comorbidities, such as chronic kidney disease (CKD) and diabetes, affect antimicrobial prescribing habits. Sulfamethoxazole/trimethoprim (SMX-TMP), nitrofurantoin, and fosfomycin are first-line recommendations for uncomplicated cystitis. In an aging male population with potential allergies or contraindications to the above, fosfomycin is a potential option for treatment.

Methods. A retrospective chart review of fosfomycin prescribing habits at a large VA academic medical center. Patients were selected based on fosfomycin prescription in both inpatient and outpatient settings from January 1, 2004 to December 5, 2017. Data reviewed included indication, organism(s), susceptibility, duration of treatment, CKD, and clinical success. Treatment success was defined as no representation with UTI symptoms for 30 days.

Results. 117 cases of UTI in which fosfomycin was used were identified with a median patient age of 70 years old and 90% male. Twenty-five were uncomplicated cystitis, 49 complicated cystitis, and 34 catheter associated infections. Treatment success was obtained in 92% of the uncomplicated cystitis cases, 76% in complicated cystitis cases, and 67% in catheter associated UTIs. In half of all the cases an ESBL bacterium was isolated and 79% were successfully treated with fosfomycin. The most common pathogen identified was *E. coli* 58/118 (49%), followed by *Klebsiella* 25/118 (21%).

Conclusion. Fosfomycin is an antibiotic recommended for simple cystitis due to its safety profile, less collateral damage (gut flora disturbance), and low resistance as currently known. This review displays the largest ESBL cohort identified in the literature and uniquely used in a predominant male population. These findings suggest 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 catheterized 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

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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) and cortisone acetate (500 mg/kg) on days −2, +3, and +8 relative to intratracheal infection with 3.0×10^7 cells of *S. apiospermum*. For survival studies, treatment with placebo (vehicle control), ISAV (110 mg/kg, tid, po), POSA (30 mg/kg, tid, po), VORI (40 mg/kg, qd, po), MICA (3 or 10 mg/kg, qd, ip) or a combination of MICA (10 mg/kg) + ISAV (110 mg/kg) began 16 h post infection and continued for 7 days. For fungal burden studies, dosing began 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 4 antifungals with MICA MIC 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 contrast, *L. prolificans* strains were resistant (MICA MIC 2–4 μg/mL and azole MIC >16 μg/mL). *S. apiospermum* DI16-478 was used to test *in vivo* efficacy. Only MICA (10 mg/kg) treatment prolonged survival of mice ($n = 10$) vs. placebo (median survival time = 8 days for MICA vs. 5 for placebo, $P < 0.03$ by log rank) and reduced fungal burden in lungs (primary target organ), brains and kidneys ($P \leq 0.02$, by Wilcoxon

rank sum). None of the azoles prolonged survival despite the significant reduction in the lung fungal burden ($P < 0.002$), possibly due to lack of reduction of fungal burden in kidneys and brains. MICA+ISAV did not enhance survival nor reduce tissue fungal burden vs. placebo.

Conclusion. Despite the *in vitro* activity of tested antifungals, only MICA demonstrated modest efficacy in mice infected with *S. apiospermum*. A combination of MICA+ISAV was ineffective in this model. Continued investigations of other drug combinations to treat scedosporiosis are needed.

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2394. Different *Clostridioides difficile* Ribotypes Among Patients With Colonization, Initial Clinical Disease, and Recurrent Clinical Disease

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Background. *C. difficile* is the most common cause of hospital infections with a spectrum of presentation from asymptomatic carriage to severe recurrent diarrhea. Certain *C. difficile* ribotypes are associated with severe disease, but there are little data on ribotypes in asymptomatic carriers or severe recurrent disease. The aim of this study was to compare virulence potential of C.diff ribotypes with clinical disease severity.

Methods. This retrospective study included patients aged ≥18 years at NorthShore University HealthSystem (NUHS) from February 1, 2015 to May 30, 2017. Three groups of patients with positive PCR test for C. diff toxin gene were selected: (1) Asymptomatic patients positive for rectal carriage; (2) symptomatic outpatients with a single positive test (CDI); and (3) patients with recurrent CDI who underwent FMT. Clinical data were extracted from the Enterprise Database Warehouse. Isolates underwent fluorescent PCR ribotyping and were assigned to clades. Ribotypes with "high" (e.g., 027 and 078) and "low" (e.g., 106) virulence potential were defined as such. Virulence potential of cryptic ribotypes were considered "unknown." We used X^2 and independent samples median tests to compare categorical and continuous variables, respectively.

Results. 129 C. diff isolates (asymptomatic, $N = 66$; CDI, $N = 33$; FMT, $N = 30$) were ribotyped with 60 types identified. Median age was higher in asymptomatic patients [80.5 (IQR 70.8–90) years] compared with both CDI and FMT [69 (58–81) and 69 (51–83.5) years, respectively, $P = 0.004$] Low virulence ribotypes were identified more frequently in asymptomatic carriers than those with CDI or FMT (22/66 vs. 8/33 vs. 1/30, respectively, P = 0.006). High virulence ribotypes were found in all groups, with highest frequency in the FMT group (23/30) vs. asymptomatic (25/67) or CDI (13/33), $P = 0.001$).

Conclusion. Patients with severe or recurrent CDI had ribotypes associated with high virulence potential. In addition, asymptomatic carriers were more likely to have ribotypes of C.diff historically associated with a low virulence potential. Molecular C.diff typing may have a role in evaluating asymptomatic C.diff colonization vs. clinical disease.

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2395. Mechanism-Based-Susceptibility Testing (MBST) Using Disc Diffusion Assays (DDA) to Guide Treatment of Multidrug- and Extensively Drug-Resistant *Pseudomonas aeruginosa* (MDR-XDR-*Pa*) in a Cystic Fibrosis (CF) Lung Transplant Recipient; Are We Ready for Combination Therapy vs. MDR-XDR-*Pa*?

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Background. Lung infections with MDR-XDR-Pa in patients with CF are challenging due to the emergence of antibiotic resistance. We applied MBST with DDA to guide combination antibiotic therapy in an 18-year-old woman with CF. We investigated if this approach can assist in choosing effective regimens.

Methods. Consecutive *Pa* respiratory isolates were collected between 12/16 and 3/18 and typed with MLST. After automated antibiotic susceptibility (AST) and Kirby-Bauer testing, we performed double or triple DDAs. Combinations were based on mechanisms (MBST) of anti-pseudomonal antibiotics (e.g., targeting of penicillin-binding proteins, β-lactamase inhibition, and cell membrane disruption).

Results. During therapy, 1859 antibiotic-days were administered. Fifteen *Pa* isolates, (9 sequence type (ST) 2100 and 1 ST463) with varying AST patterns were found (figure). MBST with DDA revealed active combinations for isolates resistant to individual antibiotics (table). These combinations led to a microbiological response permitting lung transplantation. Antibiotic regimens were also informed by allergies, clinical and radiologic findings.

Conclusion. Strains with evolving resistance profiles recapitulate the dynamic nature of respiratory infections in CF. Double or triple DDAs identified potential treatment options, e.g., vs. MDR-XDR *Pa*. MBST can support the management of challenging infections.

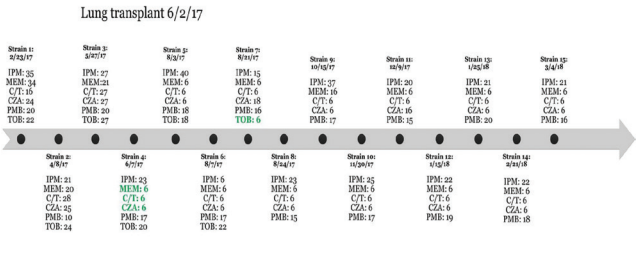
Table: Antimicrobial combinations reflecting zones of inhibition by strain and date.

CZA: ceftazidime–avibactam; C/T: ceftolozane-tazobactam; TOB: tobramycin; PMB: polymyxin B; FOF: fosfomycin; TZP: piperacillin–tazobactam; CIP: ciprofloxacin; IPM: imipenem; MEM: meropenem.

Bold: largest zone

		Combinations + inhibition zones (mm)		
Strain	Date	Combo 1	Combo 2	Combo 3
1	February 23, 2017	CZA + TOB 35	PMB + IPM 38	FOF 40+
2	April 8, 2017	CZA + TOB 31	FOF + CZA 35	PMB + C/T + MEM 39
3	May 27, 2017	FOF + TZP 40	C/T + TOB 37	PMB + CZA 33
4	June 7, 2017	FOF + TZP 15	PMB + CZA + IPM 22	C/T + IPM 24
5	August 3, 2017	FOF + TZP 18	PMB + CZA + IPM 38	C/T + IPM 42
6	August 7, 2017	FOF + TZP 19	PMB + IPM 21	
7	August 21, 2017	FOF + TZP 32	FOF + CZA 26	CZA + TOB 22
8	August 24, 2017	FOF + TZP 28	PMB +I PM 35	C/T + IPM 39
9	October 15, 2017	FOF + IPM 30	PMB + IPM 30	C/T + IPM 30
10	November 30, 2017	PMB+CIP 19	PMB + CZA + IPM 25	PMB + FOF + IPM 25
11	December 9, 2017	FOF + TZP 30	PMB + IPM 25	
12	January 15, 2018	PMB + IPM 23		
13	January 25, 2018	PMB + IPM 26		
14	February 21, 2018	FOF + TZP 20	PMB + CIP 21	
15	March 4, 2018	C/T + IPM 21	CZA + IPM 23	

Timeline of *pseudomonas aeruginosa* isolates depicting gradual emergence of antimicrobial resistance and results of single antibiotic disc diffusion



Bold green items illustrate first instance of resistance to a given antibiotic class
disk diffusion zones are in millimeters
Antibiotic abbreviations are as follows: IPM for imipenem; MEM for Meropenem; C/T for ceftolozane-tazobactam; CZA for ceftazidime-avibactam; PMB for polymyxin; TOB for tobramycin

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2396. Fosfomycin Resistance Among Carbapenem-Resistant Enterobacteriaceae Clinical Isolates in Connecticut, 2017

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