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

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

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.

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2393. Evaluation of Antifungal Treatment in a Neutropenic Mouse Model of Scedosporiosis

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

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