Background. Avibactam (AVI) is a broad-spectrum intravenous non-native β-lactam/β-lactamase inhibitor with no reported activity against metallic 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 positively charged proteinaceous PBPs. Previous 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 lysis by the membrane attack complex of complement and by endogenous cationic antimicrobials. Our recent work has shown that AVI synergizes with human cathelicidin LL-37. (APSA) as well as LL37 sensitization to 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 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 an 8-log. 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 metallic 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 Speaker’s Bureau, Consulting fee, Research grant and Research support. Merck: Consultant, Speaker’s Bureau, Consulting fee, Research grant and Research support. Achaogen: Consultant, also observed 5.7% improved eradication using VAN-L vs. commercial VAN. Overall, our biofilm results demonstrated a 43.6% improved eradication using VAN-L vs. commercial vancomycin. Also, combination of liposomal VAN MIC in presence of biotic solutions (free peak concentration) was applied over a 24 h time period.

2391. Liposomal Vancomycin and Cefazolin Combinations for Biofilms in vitro and in vivo

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Poster Abstracts • OFID 2018:5 (Suppl 1) • 5713