MIC for RP62a was 0.5 mg/L and the rifampin MIC was 0.015 mg/L. We modeled a growth control of the isolate alone, a 12 mg/kg regimen of daptomycin (*f*Cmax: 14.7 mg/L, Ke 0.09), a daptomycin concentration of 1000 mg/L (2000x MIC), and a combination model of daptomycin 1000 mg/L with rifampin 15 mg/L (1000x MIC). Coupons with bacteria embedded in biofilm were sonicated, vortexed, and plated on Tryptic Soy Agar for colony counts read at 24 hrs. Bactericidal activity was defined as ≥ 3-log10 CFU/mL reduction from the initial inoculum.

Results. The simulated humanized dosing regimen of daptomycin 12 mg/kg ($fAUC_{0\text{-}24}$/MIC: 204) was similar to the growth control model. Bactericidal kill was demonstrated at 24hr and 48hr in the daptomycin 1000 mg/L model ($fAUC_{0\text{-}24}$/MIC: 20,248) but did not fall beneath the limit of detection. The daptomycin and rifampin combination model demonstrated bactericidal kill at 24hr and 48hr and went below the limit of detection.

Conclusion. This study demonstrated that significantly higher concentrations of antibiotics are needed at the site of action to eradicate biofilm than what maximum systemic dosing can provide. Identifying these concentrations provides a foundation for localized antibiotic therapy and further studies are needed to elucidate these concentrations for a variety of antibiotics and biofilm-forming organisms.

Disclosures. **Kerry LaPlante, PharmD**, **Merck** (Advisor or Review Panel member, Research Grant or Support)**Ocean Spray Cranberries, Inc.** (Research Grant or Support)**Pfizer Pharmaceuticals** (Research Grant or Support)**Shionogi, Inc.** (Research Grant or Support)

1324. Target Attainment of Exebacase, a First-In-Class Antibacterial Lysin, to Determine Optimal Doses for Adult Patients with Staphylococcus aureus (S. aureus) Bloodstream Infections (Bacteremia) Including Endocarditis

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Session: P-59. PK/PD studies

Background. Exebacase, a novel, antibacterial direct lytic agent for the treatment of *S. aureus* bacterimia and endocarditis, studied in Phase 1 and 2 trials, demonstrated potential to improve clinical outcomes when used in addition to conventional antibiotics. Objectives were to develop population PK (PPK) model and perform target attainment (TA) simulations to determine optimal clinical doses.

Methods. PPK model was developed with data from 72 patients receiving Exebacase, in addition to the standard of care, as single 2-hr infusion of 0.25 mg/kg (0.12 mg/kg for patients with creatinine clearance (CrCL) < 60 mL/min). PPK model was used for TA simulations of various IV regimens.

Results. 3-compartment model best fit the data, parameters were well estimated (CL=4.2 L/hr (RSE=5.5%), Vc=4.5 L (RSE=8.2%)). Total volume of distribution (V_d) was 20.2 L. Values were lower than estimated previously in healthy subjects, CL=7.1 L/hr and V_d=27.7 L. CrCL was the only clinically meaningful covariate. Patients with moderate and severe renal impairment are expected to have 1.3 to 2-fold higher $AUC_{0\text{-}24}$ or C_{max} than patients with normal renal function. Age was statistically significant on peripheral clearance but was not clinically meaningful (≤4% effect on exposure).

TA simulations were stratified by renal function across a range of fixed as well as weight-based doses (all simulated as 2-hr infusion). In patients with normal renal function or mild impairment, 18 mg dose result in C_{max} and $AUC_{0\text{-}24}$ of 1254 ng/mL and 3026 ng*hr/mL, respectively. In patients with moderate or severe renal impairment, 12 mg dose result in C_{max} and $AUC_{0\text{-}24}$ of 1107 ng/mL and 3099 ng*hr/mL, respectively. In ESRD patients including hemodialysis, 8 mg dose result in C_{max} and $AUC_{0\text{-}24}$ of 910 ng/mL and 3109 ng*hr/mL, respectively. These exposures place >99% subjects above efficacious thresholds of AUC/MIC >0.2 established in animals.

Conclusion. PPK model described exebacase PK in patients adequately. CL and V_d were estimated to be 40% and 17% lower, respectively, than healthy subjects. CrCL was the only clinically meaningful covariate requiring dose adjustment. TA assessments identified doses that achieve minimum efficacy target (AUC/MIC≥0.2) in >99% of patients with *S. aureus*. Based on these simulations, fixed dosing schedule was recommended.

Disclosures. Parviz Ghahramani, PhD, PharmD, MSc, MBA, Consultant to ConatFect (Consultant) Tatiana Khariton, PhD, Consultant to ConatFect (Consultant) Joannellyn Chiu, PhD, Consultant to ConatFect (Consultant) Cara Cassino, MD, ContraFect Corporation (Employee)ContraFect Corporation (Employee)

1325. Things that go Bump in the Night: Combating Klebsiella pneumoniae co-producing New Delhi metallo-beta-lactamase (NDM) and Mobile Colistin Resistance (MCR)

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Session: P-59. PK/PD studies

Background. The scourge of MBLs among Gram negatives, such New Delhi Metallo-beta-lactamase-producing *Klebsiella pneumoniae,* has resulted in an overwhelming need for new treatmens. Worryingly, additional acquisition of plasmid-mediated polymyxin resistance through the *mcr* gene can produce strains resistant to all last line agents. The novel combination of aztreonam (ATM, which is not an MBL substrate) with avibactam (AVI, to inhibit extended spectrum beta-lactamases that inactivate ATM) has been proposed to restore ATM activity.

Methods. *K. pneumoniae* SZ04 harboring $bla_{NDM\text{-}5}$, $bla_{CTX\text{-}M\text{-}55}$, and *mcr-1* ($MIC_{ATM}$ = 128 mg/L, $MIC_{Polymyxin\ B}$ = 4 mg/L, $MIC_{Amikacin}$ = 1 mg/L, $MIC_{ceftazidime/avibactam}$ > 16/4 mg/L) was studied at two initial inoculum (10^6 and 10^8 cfu/mL) over 24h in static time kills (SCTK). Concentration arrays of 2-, 3-, and 4-drug combinations of low- and package insert-dose polymyxin B (PMB) ± low- and package insert-dose amikacin (AMI) ± package insert dosing of ATM/AVI were simulated in > 200 individual arms of SCTK. Data were summarized using the Log Ratio Area (LRA) which is calculated by integrating the area under the bacterial killing curve, normalizing to the growth control, then log-transforming. A Hill-type function was fit to the data in order to determine the maximum effect (E_{max}) and drug concentration for 50% effect (EC_{50}).

Results. When simulating the maximum free concentration of amikacin 15 mg/kg (52 mg/L) in combination with package insert concentrations of ATM/AVI, there was a marked reduction of 3.22 in the LRA compared to the growth control for the 10^8 cfu/mL starting inocula. Combining ATM with low amikacin (0.813 mg/L) and polymyxin B (0.125 mg/L) resulted in a reduction in LRA of 4.32 at 10^6 cfu/mL. Model fitting results showed a statistically significant difference in EC_{50} to amikacin between low and high inocula at 1.24 and 18.1 mg/L, respectively. Combination of AMI with low-concentration PMB (0.125 mg/L) resulted in an increase in the E_{max} of amikacin to -5.68.

Conclusion. The use of ATM/AVI combinations is a promising option against MBL and MCR co-producing *K. pneumoniae*. Low-dose strategies of polymyxin or amikacin dosing in combination with ATM/AVI is merits further testing for future translation to the clinical setting to improve efficacy and optimize treatment.

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1326. Vancomycin Area Under the Concentration-Time Curve (AUC) Estimation Using a Bayesian Approach Versus First-Order Pharmacokinetic Equations: A Pilot Study

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Session: P-59. PK/PD studies

Background. Current guidelines endorse area under the concentration-time curve (AUC)-based monitoring over trough-only monitoring for systemic vancomycin. Vancomycin AUC can be estimated using either Bayesian modeling software or first-order pharmacokinetic (PK) calculations. The objective of this pilot study was to evaluate and compare the efficiency and feasibility of these two approaches for calculating the estimated vancomycin AUC.

Methods. A single-center crossover study was conducted in four medical/surgical units at Brigham and Women's Hospital over a 3-month time period. All adult patients who received vancomycin were included. Patients were excluded if they were receiving vancomycin for surgical prophylaxis, were on hemodialysis, if vancomycin was being dosed by level, or if vancomycin levels were never drawn. The primary endpoint was the amount of time study team members spent calculating the estimated AUC and determining regimen adjustments with Bayesian modeling compared to first-order PK calculations. Secondary endpoints included the number of vancomycin levels drawn and the percent of those drawn that were usable for AUC calculations.

Results. One hundred twenty-four patients received vancomycin during the study, of whom 47 met inclusion criteria. The most likely reasons for exclusion were receiving vancomycin for surgical prophylaxis (n=40) or never having vancomycin levels drawn (n=32). The median time taken to assess levels in the Bayesian arm was 9.3 minutes [interquartile range (IQR) 7.8-12.4] versus 6.8 minutes (IQR 4.8-8.0) in the 2-level PK arm (p=0.004). However, if Bayesian software is integrated into the electronic health record (EHR), the median time to assess levels was 3.8 minutes (IQR 2.3-6.8, p=0.019). In the Bayesian arm, 30 of 34 vancomycin levels (88.2%) were usable for AUC calculations, compared to 28 of 58 (48.3%) in the 2-level PK arm.

Conclusion. With EHR integration, the use of Bayesian software to calculate the AUC was more efficient than first-order PK calculations. Additionally, vancomycin levels were more likely to be usable in the Bayesian arm, thereby avoiding delays in estimating the vancomycin AUC.

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1327. Vancomycin Dosing by AUC_{24}/MIC in Comparison to Traditional Trough Dosing in Office Infusion Centers (OICs)

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