was used to simulate 1000 PK profiles for various pediatric age groups, ranging from preterm neonates to adolescents. PK/PD target attainment (PTA) was calculated for targets associated with stasis, 1-log kill, and 2-log kill of Staphylococcus aureus in the murine thigh infection model.

**Results.** Dalbavancin PK was well-characterized by a 3-compartment model. SCM did not find any significant covariates besides albumin, weight, and renal function. VPCs demonstrated that the final model has good predictive performance across the full age range. Simulations showed that single-dose regimens of 22.5 mg/kg for patients < 6 years and 18 mg/kg for patients 6 to < 18 years resulted in PTA ≥94% for MICs up to 2 mg/L for the stasis target and up to 0.5 mg/L for the 2-log kill target. PTA for pediatric patients was similar to adults, and exposures (AUCs) were contained within the range for adults administered 1500 mg.

**Conclusion.** Dalbavancin PK in pediatric patients was well-characterized by a 3-compartment model with allometric scaling of clearance and volume with albumin and renal function included as covariates. Simulations with the final model demonstrate adequate PTA across the entire age range for the regimens used in the phase 3 pediatric study.

**Disclosures.** Timothy J. Carrothers, ScD, AbbVie (Employee); Maxime Lagraauw, PhD, qPharmetra (Employee) Lars Lindbom, PhD, qPharmetra (Employee) Todd Riccobene, PhD, AbbVie (Employee)

### 1322. Quantifying the Effects of Frequently Prescribed Antimicrobials with Perceived Potential for QT Interval Prolongation during the COVID-19 Era

**Background.** Countless diseases and medications have been implicated in the past as causing prolongation of the QT interval. Their unique role through the means of quantifying the definite magnitude of relative risk they contribute during hospitalization still requires further investigation. The aim of this study was to describe the impact of commonly used anti-infectives on the QT interval in hospitalized patients during the COVID-19 era.

**Methods.** Demographic information, medical history, laboratory data, medications, and disease effects were used. Fixed and random effects with between occasion variability were estimated for the parameters with a Bayesian approach using the STAN software.

**Results.** Data from 2180 patients were used with baseline characteristics shown in Table 1. Observed vs. predicted plots based on the training (Figure 1A) and validation data set (Figure 1B) showed excellent fit. The parameters for QT interval comprised of: heart rate, circadian rhythm, gender, and the drug (regressed as the cumulative mg dose administered over time) and disease effects was used. Simulations with the final model demonstrated adequate PTA across the entire age range for the regimens used in the phase 3 pediatric study.

| Table 1. |
|----------|
| QT Intervals | Notes | Observations | Predictions |
|----------------|-------|--------------|-------------|
| Age < 12 yrs | 1.4 | 20.0 | 21.4 |
| 12 yrs to 18 yrs | 1.4 | 20.0 | 21.4 |
| > 18 yrs | 1.4 | 20.0 | 21.4 |

**Conclusion:** The model developed accurately identified the impact baseline risk factors and concomitant medications have on the QT interval. When adjusted for these confounding variables, estimates of QT interval prolongation show that treatment with fluconazole and levofloxacin pose a considerable risk; while treatment with azithromycin or hydroxychloroquine is of moderate risk for QT interval prolongation.

**Disclosures.** All authors: No reported disclosures
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 (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). Coughs with bacteria embedded in biofilm were sonicated, vortexed, and plated on Tryptic Soy Agar. Both 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 (AUdmg/MIC: 204) was similar to the growth control model. Bactericidal kill was defined as ≥24 hr and ≥48 hr in the daptomycin 1000 mg/L (MIC: 20.248) but did not fall beneath the limit of detection. The daptomycin and rifampin combination model demonstrated bactericidal kill at 24 hr and 48 hr 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 eradicable biofilm than what maximum systemic SOC 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.

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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, bacterial direct lytic agent for the treatment of S. aureus bacteremia and endocarditis, studied in Phase 1 and 2 trials, demonstrated potential to improve clinical outcomes when used in addition to conventional antibiotic. 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 (Vd) was 20.2 L. Values were lower than estimated previously in healthy subjects, CL=7.1 L/hr and Vc=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, Vd or Vc 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 C0 = 128 mg/L and AUC0-24 = 524 mg/L for low and high inocula at 1.24 and 18.1 mg/L, respectively. Combination of AMI 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 mg/L. Model fitting results showed a statistically significant difference in EC50 to amikacin between low and high inocula at 1.24 and 18.1 mg/L, respectively. Combination of low-potency amikacin dosing (0.125 mg/L) resulted in an increase in the Emax of amikacin to ~5.68.

Conclusion. The use of ATAM/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 ATAM/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

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 number of days patients 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 twelve 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 4.8-8.6] in the first-order 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. Bayesian software was more efficient than first-order PK calculations for future translation to the clinical setting to improve efficacy and optimize treatment.

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