Conclusion. PK-RNN-V model is a novel approach to predict patient PK and VAN levels. Our results revealed promising performance of this model. Our model can take a wide range of real-world patient data into the model. Further studies are warranted for external validations and model optimizations.

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64. Novel Biomarkers Improve Estimation of Vancomycin Clearance in Critically Ill Children
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Session: O-14. Have We Peaked? Updates in PK/PD

Background. There are a paucity of robust population PK (popPK) models to inform vancomycin (VAN) dosing in critically ill children. The majority of published models incorporate peak/trough data and rely on flawed estimates of renal function. We sought to develop a popPK model for IV VAN in critically ill children utilizing novel plasma and urinary biomarkers.
Methods. We conducted a prospective observational study of critically ill children prescribed VAN for a suspected infection in the CHOP pediatric ICU. Children < 1 year of age and those receiving ECMO or CRRT were excluded. Five VAN samples were collected from a single dosing interval for each subject. Plasma biomarkers (creatinine [Cr], cystatin C [CysC], NGAL) and urinary biomarkers (CysC, NGAL, KIM-1, osteonectin) were collected the morning of PK sampling; urinary biomarkers were corrected for urine creatinine. Nonparametric popPK modeling was performed using Pmetrics. The impact of renal function (GFR) on VAN clearance (CL) was estimated first, comparing model performance with each biomarker (Cr and plasma CysC). The influence of age, sex, additional biomarkers, PIM3 score, and receipt of vasopressors as covariates was then assessed for relevant PK parameters.

Results. 30 subjects completed the study. Median age was 10 years (range 1-17); 76% were male. The majority (90%) of children received VAN for suspected sepsis. PK sampling occurred at a median of 37.7 hours (range 24.6-94.8) into VAN treatment; 136 VAN samples were included. A 2-compartment model with fixed allometric scaling of 0.75 on clearances and 1 on volumes best described the data. CysC-based GFR as a covariate on VAN CL using the HOEK formula (GFR = 43.2 + (80.35/CysC)) resulted in the best model fit. Age and plasma NGAL were also informative on VAN CL in the final model (Figure 1). During model building, urinary NGAL was also associated with VAN CL (comparable to plasma NGAL) and outperformed Cr, although it was not retained in the final model.

Figure 1. Final population PK model and parameter estimates.

| Parameter | Weighted parameter estimate | Shrinkage % |
|-----------|-----------------------------|-------------|
| CL0       | 2.82                        | 2.44-3.51   | 42.3 |
| CL1       | 0.75                        | 0.68-1.00   | |
| CLHLD     | 0.58                        | 0.56-1.50   | 13.4 |
| CLNGAL    | 0.19                        | 0.16-0.33   | 38.0 |
| CLCAGE    | 0.05                        | 0.05-0.21   | 27.8 |
| V0        | 5.15                        | 3.85-6.52   | 41.5 |
| V1/2      | 3.00                        | 4.46-5.98   | 28.2 |
| Q0        | 0.75                        | 0.60-1.26   | 21.8 |
| V0        | 2.62                        | 2.60-7.12   | 23.7 |

Conclusion. Plasma CysC is a better renal function estimate than Cr to inform VAN clearance in critically ill children. Urinary and plasma NGAL also improved estimation of VAN CL during popPK modeling. Novel biomarkers can better describe VAN exposures in critically ill children than reliance on Cr alone.

65. In Vivo Efficacy of Human Simulated Minocycline (MIN) against Stenotrophomonas maltophilia (STM)

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Session: O-14. Have We Peaked? Updates in PK/PD

Background. The current susceptibility breakpoint for MIN against STM is 4mg/L, yielding >99% of isolates susceptible. Unfortunately, there are limited pre-clinical and clinical data to support this breakpoint for STM. The purpose of this study was to evaluate the efficacy of a MIN human simulated regimen (HSR) against STM across a wide range of MICs in the murine neutropenic thigh model.

Methods. Clinical STM with modal MIN MICS of 0.25-8mg/L were included. Conformational pharmacokinetic (PK) studies were performed in infected neutropenic mice to develop a MIN HSR providing an area under the curve (AUC) and maxiumum concentration (Cmax) exposure similar to MIN 100mg intravenous (IV) q12h at steady-state based on PK parameters from critically ill adult patients. The murine neutropenic thigh infection model was utilized to examine the antibacterial effects of the confirmed MIN HSR against STM. Both thighs of neutropenic ICR mice were inoculated with bacterial suspensions of 10^5 CFU/thigh. Bacterial growth (1.18±0.79 log_10 CFU/thigh) was measured at 24h. Control mice received normal saline. Efficacy was measured as the change in log_10 CFU/thigh over 24h. Control mice received normal saline. Efficacy was measured as the change in log_10 CFU/thigh over 24h.

Results. MIN 22, 10, and 14mg/kg dosed SC at 0, 6, 12, and 18h best recapitulated the human Cmax and AUC profile. Mean ± standard deviation bacterial burden at 0h across all isolates was 6.03±0.32 log_10 CFU/thigh. Bacterial growth was -1.35±0.68 log_10 CFU/thigh in 24h controls. Six of 7 isolates (86%) with MIC ≤ 0.5mg/L achieved 1-log kill with MIN HSR (1.44±1.37 log_10 CFU/thigh). All STM with MIC ≥ 1mg/L experienced bacterial growth (1.18±0.79 log_10 CFU/thigh) (Figure). Efficacy of a minocycline human simulated exposure of 100mg IV q12h recapitulated the human Cmax and AUC profile. Mean ± standard deviation bac

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Conclusion. These data describe the in vivo efficacy of a MIN HSR with exposures similar to MIN 100mg IV q12h in critically ill adults. Lack of antibacterial activity against STM with MICs ≥ 1mg/L justifies a reassessment of the current susceptibility breakpoint.

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66. Utilizing ceftazidime/avibactam therapeutic drug monitoring in the treatment of neurosurgical meningitis caused by Difficult-to-treat resistant (DTR)- Pseudomonas aeruginosa and KPC-producing Enterobacteriales

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Session: O-14. Have We Peaked? Updates in PK/PD

Background. Central nervous system (CNS) infections caused by carbapenem-resistant Enterobacteriales (CRE) and difficult-to-treat resistant (DTR)-Pseudomonas aeruginosa (PA) are a therapeutic challenge. Data demonstrating the pharmacokinetic/pharmacodynamic (PK/PD) properties of newer beta-lactamase inhibitors remains scarce. A clinical challenge lies in selecting an antimicrobial regiment that diffuses across the blood brain barrier and maintains concentrations to achieve PD targets associated with bacterial killing. These complexities compelled us to quantify the pharmacological properties of ceftazidime/avibactam (CZA). Utilizing therapeutic drug monitoring (TDM), we evaluated the adequacy of therapy and aimed to guide precise CNS dosing in the treatment of three patients with neurosurgical meningitis.

Methods. Bacterial identification and susceptibility testing were performed using MicroScan. TDM of CZA was implemented using a dose of 2.5 g infused intravenously over 2 hours, every 8 hours. The concentrations of ceftazidime and avibactam were determined by liquid chromatography/mass spectrometry. For patients 2 and 3, four unique CSF and plasma samples spanning the dosing interval were obtained; including trough values. (See table)

Results. Bacterial identification and CZA MICs for patients 1, 2, and 3 revealed blaKPC (0.25μg/mL), DTR PA (4 μg/mL), and blaKPC. E. cloacae (0.25 μg/mL), respectively. Measured plasma and CSF concentrations of avibactam (AVI) and ceftazidime (CZA) are shown in Table 1.

Table 1a. Therapeutic Drug Monitoring of CZA-AVI depicting dosing, time of samples, and measured concentrations in CSF and Human Plasma (HP)

| Patient 1 | Concentration (μg/mL) |
|-----------|-----------------------|
| Sample Name | Cefazidime | Avibactam |
| CSF #1 (130 min. post-infusion) | 19.007 | 4.242 |
| CSF #2 (184 min. post-infusion) | 17.27 | 3.917 |
| CSF #3 (184 min. post-infusion) | 17.244 | 4.099 |
| CSF #4 (184 min. post-infusion) | 19.727 | 4.148 |
| Blood (184 min. post-infusion) | 61.273 | 13.085 |