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, osteopontin) were collected the morning of PK sampling; urinary biomarkers were corrected for urine creatinine. Nonparametric popPK modeling was performed using Phoenix. 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 = 4.32 + (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.

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.

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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 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 regimen 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 blaCTX-M (0.25μg/mL), DTR PA (4 μg/mL), respect respectively.

| 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 |

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