median weight was 112.7 kg (IQR 99.8 - 122.6) and the median BMI was 36.8 kg/m$^2$ (IQR 33.1 - 41). The median total daily vancomycin dose at initiation was 28.7 mg/kg/day (IQR 25.4 - 31.2). Vancomycin accumulation occurred in 99 patients (61.1%) within the first 10 days of therapy and AKI occurred in 21 patients (14.9%). No factors studied, including age, gender, obesity class, initial dose, SCr, or frequency were associated with accumulation.

***Conclusion.*** Most patients with obesity experienced vancomycin accumulation within the first 10 days of therapy. Providers should be cautious when assessing a vancomycin concentration early in the treatment course.

***Disclosures.*** **All Authors**: No reported disclosures

**1103. Minocycline (MIN) Pharmacodynamics (PD) against *Stenotrophomonas maltophilia* (STM) in a Neutropenic Murine Thigh Infection Model**

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**Session:** P-62. PK/PD Studies

***Background.*** Antibiotic treatment options for serious STM infections are limited. MIN displays in vitro activity against STM; however, limited data supports optimal dosing for STM. Herein, we employed the murine neutropenic thigh infection model to assess MIN PD against STM.

***Methods.*** Four clinical STM isolates with MIN MICs 0.25 – 1 mg/L were included. Both thighs of neutropenic ICR mice were inoculated with bacterial suspensions of $10^7$ colony forming units (CFU)/mL. Mice received uranyl nitrate on Day -3 to provide predictable renal impairment. Two hours after inoculation, MIN or control was administered subcutaneously. Pharmacokinetic (PK) studies of 2.5, 25, 50, and 100 mg/kg were conducted. Previously reported protein binding of 78.1% was used to define free exposure. Dose ranging studies were conducted on all STM to assess in vivo activity over a range of MIN exposures. MIN total daily doses (TDD) of 10, 20, and 50 mg/kg were fractionated q24h, q12h, and q6h against a single STM to determine the PD index best correlated with reductions in CFU/mL. Efficacy was measured in $\log_{10}$CFU/thigh at 24h compared with 0h controls. Composite CFU data were fitted to an $E_{max}$ model to determine the *f*AUC/MIC exposure for stasis and 1 $\log_{10}$ reduction.

***Results.*** MIN PK was linear up to 50 mg/kg and well described by a 1 compartment model with first order absorption and elimination. Mean PK parameters across the linear range were: Vd, 2.97 L/kg; K01, 10.62 1/h; and K10, 0.35 1/h. Mean ± SD bacterial burden at 0h across all isolates was 6.17±0.20 $\log_{10}$CFU/thigh. In 24h controls, bacterial growth was 7.90±0.85 $\log_{10}$CFU/thigh. A dose response was observed across all isolates using TDD of 2-300 mg/kg. PD indices correlated with CFU reductions as follows: *f*AUC/MIC ($R^2$=0.613), *f*Cmax/MIC ($R^2$=0.590), and %*f*T >MIC ($R^2$=0.504). The *f*AUC/MIC needed for stasis and 1 $\log_{10}$ reduction at 24h was 9.6 and 23.6, respectively.

***Conclusion.*** These are the first data describing MIN PD against STM. Against these STM, MIN *f*AUC/MIC was the PD index best correlated with CFU reductions. The exposure thresholds defined in this study will be useful in designing optimal MIN dosing regimens for treating STM infections and re-assessment of the current susceptibility breakpoint.

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**1104. Comparison of Antibiotic Sampling Techniques: Predicting Plasma Vancomycin Concentrations Using Volumetric Absorptive Microsampling (VAMS) from Capillary and Venous/Arterial Whole Blood**

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**Session:** P-62. PK/PD Studies

***Background.*** Therapeutic drug monitoring (TDM) is paramount to optimize the safety and efficacy of vancomycin (VAN). In children, TDM is challenged by difficulty in obtaining venous samples, impeding timely sampling. We assessed the ability of volumetric absorptive microsampling (VAMS) as a novel, whole blood sampling technique to predict plasma VAN concentrations in plasma.

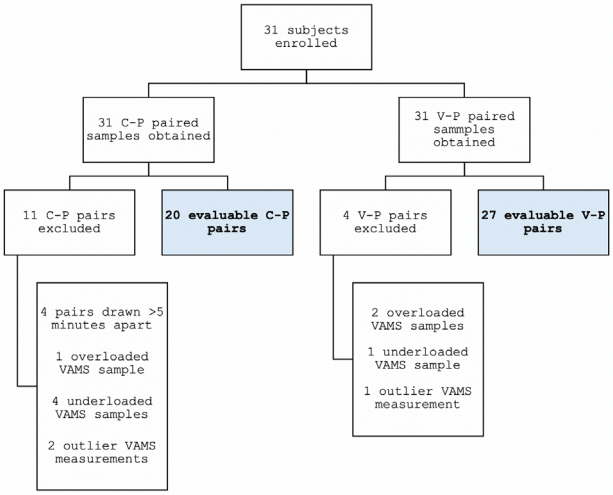
***Methods.*** We conducted a prospective pilot study among critically ill children prescribed VAN for clinical care. Coincident with VAN TDM in plasma (P), we collected 20 µL of capillary whole blood (C) and venous/arterial whole blood (V) using VAMS. Paired VAMS-P samples drawn >5 mins apart and VAMS samples with over- or under-loaded filter tip on visual inspection were excluded. Plasma concentrations were measured via chemiluminescent immunoassay in the Chemistry Laboratory. VAMS C and V concentrations were measured using LC/MS in the Bioanalytic Core Laboratory. Plasma concentrations were predicted from whole blood VAMS with Passing-Bablok regression using 3 methods: 1) uncorrected VAMS measures, 2) hematocrit-corrected VAMS, and 3) lab-corrected VAMS (Figure 1). We then assessed bias, imprecision, and accuracy of plasma predictions from VAMS (C and V) as compared to coincident P concentrations for each technique (Figure 1).

Figure 1. Methods for relating whole blood vancomycin concentrations collected via VAMS to plasma concentrations and measure to evaluate predictive performance.

| Method | Technique for predicting plasma from VAMS |
|---|---|
| Uncorrected VAMS | 1. Predicted plasma calculated from Passing-Bablok regression of measured plasma on uncorrected VAMS |
| Hematocrit-corrected VAMS | 1. Hct-corrected VAMS = VAMS / 1-(Hct / 100)<br>2. Predicted plasma calculated from Passing-Bablok regression of measured plasma on HCT-corrected VAMS |
| Lab-corrected VAMS | 1. Lab-corrected VAMS = VAMS / 0.718[a]<br>2. Predicted plasma calculated from Passing-Bablok regression of measured plasma on lab-corrected VAMS |
| **Predictive performance measure** | **Equation** |
| Bias, calculated as median percentage predictive error (MPPE) | Median of ([VAMS] – [plasma] / [plasma]) x 100% |
| Imprecision, calculated as median absolute percentage predictive error (MAPE) | Median of (\|[VAMS] – [plasma] / [plasma]\|) x 100% |
| Accuracy, calculated as proportion of samples with MAPE within 20% | Number of pairs with MAPE <20% / evaluable pairs |
| [a] Correction factor derived from lab validation study in CHOP Bioanalytic Core. | |

***Results.*** Paired samples were collected from 31 enrolled subjects (Figure 2), with a median age of 3.3 years (range 0.1-17.9). Measured P concentrations ranged from 4.6 - 54.9 mg/L. 11 C samples (29%) and 3 V samples (10%) were excluded due to collection issues. Prediction results are shown in Figure 3. The 3 prediction techniques had similar performance characteristics, with each method displaying minimal bias (-0.4-2.0%) and reasonable imprecision (13.7-20.2%). The accuracy of prediction of P concentrations using VAMS was better for V than C samples.

Figure 2. Flow diagram from sample collection to evaluation.




Abbreviations: C-P, capillary VAMS-plasma; V-P, venous/arterial VAMS-plasma; VAMS, volumetric absorptive microsampling.

Figure 3. Performance of 3 techniques to predict plasma vancomycin concentrations using whole blood collected via VAMS.

| Capillary VAMS-plasma (n = 20 paired samples) | | | |
|---|---|---|---|
| | **Method 1 Uncorrected VAMS** | **Method 2 Hematocrit-corrected VAMS** | **Method 3 Lab-corrected VAMS** |
| Regression equation[a] | P = 1.32 * C – 1.37 | P = 0.90 * C – 0.34 | P = 0.95*C – 1.38 |
| Pearson correlation | .939 | .926 | .938 |
| Bias[b] | 0.3% | -0.4% | 1.7% |
| Imprecision[c] | 14.7% | 20.2% | 19.1% |
| Accuracy[d] | 60% | 50% | 55% |
| **Venous/Arterial VAMS-plasma (n = 27 paired samples)** | | | |
| | **Method 1 Uncorrected VAMS** | **Method 2 Hematocrit-corrected VAMS** | **Method 3 Lab-corrected VAMS** |
| Regression equation[a] | P = 1.17 * V + 1.05 | P = 0.79 * V + 1.36 | P = 0.82 * V + 1.28 |
| Pearson correlation | .941 | .941 | .941 |
| Bias[b] | 0.0% | 0.0% | 2.0% |
| Imprecision[c] | 15.9% | 13.7% | 16.0% |
| Accuracy[d] | 67% | 70% | 70% |

[a] Equations derived from Passing-Bablok regression of plasma concentrations on predicted plasma concentrations from VAMS.
[b] Bias calculated as median percentage predictive error (MPPE).
[c] Imprecision calculated as median absolute percentage predictive error (MAPE).
[d] Accuracy defined as proportion of samples with MAPE <20%.
Abbreviations: C, capillary whole blood concentration via VAMS; P, plasma concentration; V, venous/arterial whole blood concentration via VAMS.

***Conclusion.*** Our pilot highlights the challenges of using VAMS for TDM. Sample collection issues were common. When VAMS is used, education on collection techniques is imperative. The predictive performance of VAMS was modest and V sampling had higher accuracy than C, although our sample size was small. Larger studies will be needed to further evaluate the predictive performance of the regression equations derived by our study.

***Disclosures.*** **Kevin J. Downes, MD**, **Merck, Inc.** (Grant/Research Support)

### 1105. Population Pharmacokinetic Analyses for Tebipenem After the Administration of Tebipenem Pivoxil Hydrobromide

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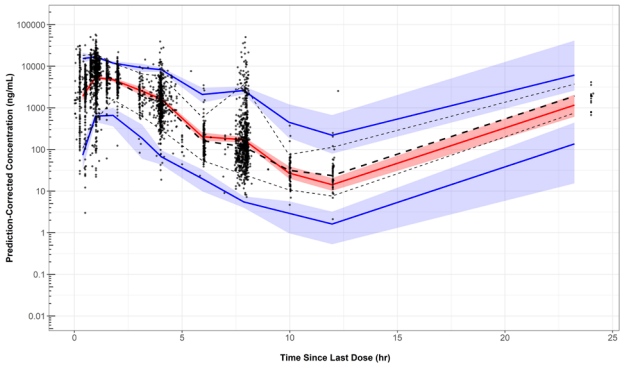
**Session:** P-62. PK/PD Studies

***Background.*** Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral prodrug that is converted to tebipenem (TBP), the active moiety. TBP is a carbapenem with activity against multidrug-resistant Gram-negative pathogens, including extended-spectrum-β-lactamase-producing Enterobacterales and is being developed for treating complicated urinary tract infections (cUTI) and acute pyelonephritis (AP). Data from three Phase 1 studies and one Phase 3 study in patients with cUTI/AP were used to develop a population pharmacokinetic (PPK) model for TBP and identify covariates that described the variability in TBP pharmacokinetics (PK).

***Methods.*** The PPK model was developed using TBP plasma and urine concentration-time data from the above-described Phase 1 and 3 studies. TBPPI-HBr doses, which ranged from 100 to 900 mg, were administered as single or multiple doses every 8 hours. After development of the structural model, stepwise forward and backward selection procedures were used to identify significant covariate relationships. The robustness of the final PPK model was assessed using a prediction-corrected visual predictive check (PC-VPC).

***Results.*** The final dataset included 3448 plasma concentrations from 99 Phase 1 subjects and 647 Phase 3 patients and urine concentrations from 128 Phase 1 subjects. A two-compartment model with linear, first-order elimination and transit compartments to describe the rate of drug absorption after oral administration of TBP-PI-HBr best described TBP PK. The most clinically significant covariate effect, which would warrant dose adjustment, was the relationship between apparent oral clearance and creatinine clearance. In contrast, age, body size, sex, and fed status each had a minimal impact on TBP exposure. The PC-VPC showed good agreement between median simulated plasma concentrations based on the final PPK model and the median observed plasma concentrations for the pooled dataset (Figure 1).

Figure 1. Prediction-corrected visual predictive check plot for the final population PK model using the pooled analysis dataset




Circles represent prediction-corrected observed plasma concentrations while the black lines represent the median and 5th and 95th percentiles of the observed data. The solid red line represents the median model predicted concentration values.The solid blue lines represent the 5th and 95th model predicted concentration values. Shaded areas represent the 95% model predicted confidence interval around the 5th, median, and 95th model predictions.

***Conclusion.*** A robust description of TBP plasma PK in subjects and patients with cUTI/AP was achieved, such that derived measures of TBP plasma exposure are expected to be both accurate and precise. The population PK model was considered appropriate for model-based simulations and the assessment of PK-PD relationships for TBP.

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