Table 1. Baseline Characteristics of Patients Included in This Study*

	N (%)[a] Total, Pt N = 5483 Enc N = 8689
Gender, male	3069 (55)
Age, median yr. (IQR)	61 (48-73)
Ethics/Race	
Hispanic	783 (14.2)
Non-Hispanic	3905 (71.2)
Other	77 (1.4)
Unknown	718 (13.1)
Race	
White	2003 (36.4)
African American	1069 (19.5)
Asian	83 (1.5)
Others	1829 (33.4)
Weight, median kg, (IQR)[b]	82.9 (65.5 - 101.6)
Height, median cm, (IQR)[b]	172 (165.1 - 181.1)
Comorbidities[b]	
Cerebral vascular diseases	293 (5.2)
Coronary artery diseases	570 (5.0)
Chronic pulmonary diseases	911 (8.0)
Heart failure	924 (8.2)
Hypertension	2296 (20.1)
Diabetes	1330 (11.7)
CKD	779 (6.9)
HIV/AIDS	93 (0.8)
Cancer (solid and hematologic)	513 (4.5)
Solid Organ Transplantation	77 (0.7)
Laboratory results, median (IQR)[c]	
Creatinine, mEq/L	0.99 (0.71-1.44)
Blood urea nitrogen, mg/dL	18 (12-29)
Sodium, mEq/L	139 (136-141)
Potassium, mEq/L	4.0 (3.6-4.3)
Bicarbonate, mEq/L	26 (23-28)
Chloride, mEq/L	105 (101-108)
eGFR, mL/min/1.73m2	77.2 (46.9-102.9)
Glucose, mg/dL	132.5 (103-182)
Calcium, mg/dL	8.5 (8.1-8.9)
Phosphorus, mg/dL	3.1 (2.6-3.8)
Magnesium, mg/dL	2.0 (1.8-2.2)
Protein, total, g/dL	6.8 (6.1-7.5)
Albumin, g/dL	2.6 (2.2 - 3.1)
Bilirubin, total, mg/dL	
White blood cells, k/cm^2	9.6 (6.9-13.5)
Hemoglobin, g/dL	10.2 (8.7-11.9)
Hematocrit, %	31.1 (26.6-36.1)
Platelets, k/cm^2	247 (178-335)
Neutrophils, k/cm^2	7.1 (4.6-10.8)
Lymphocytes, k/cm^2	1.3 (0.8-1.8)
Vital signs, median (IQR)[c]	
Temperature, °C	36.8 (36.6 - 37.1)
Systolic blood pressure, mmHg	125 (112-140)
Diastolic blood pressure, mmHg	66 (57 - 75)
Heart rates, /min	84 (74-96)
Respiratory rates, /min	18 (17-20)
SpO2, %	97.4 (96-98)
O2 flow, L/min	3 (2-5)
Vancomycin (VAN) admin[C]	
Total VAN administration, doses	55,336
VAN dose, median (IQR) gm	1.0 (1.0 - 1.5)
VAN level measurement per pt	18,588
VAN levels, median (IQR) mcg/mL	14.7 (10.3-19.6)

Pt N, Patient number, Enc N, Encounter number, IQR, Interquartile range, N, number, Sc, Screening, HIV, Human Immunodeficiency Syndrome, yr, year

a. Otherwise indicated, the numbers in the table shows number and %.
b. Characteristics at the time of first encounter
c. All available data in the study cohort were summarized.

Table 2. Model Performance Comparing Different Types of PK-RNN-V and Bayesian Models

	Training set Pt N = 3821 Enc N = 6063 MRSE	Validation set Pt N = 839 Enc N = 1287 MRSE	Test set Pt N = 823 Enc N = 1339 MRSE
Bayesian Models			
VTDM	9.30	9.70	8.45
VTDM feedback	7.90	7.22	6.57
PK-RNN-V models			
PK-RNN-V	5.25	5.43	5.69
PK-RNN-V feedback	5.16	5.30	5.64
PK-RNN-V full feedback	5.16	5.30	5.62

Pt N, Patient number, Enc N, Encounter number, MRSE,Mean Root Square Error, PK, Pharmacokinetics, RNN, Recurrent Neural Network, V, Vancomycin, VTDM, Vancomycin Therapeutic Drug Monitoring

VTDM: Basic patient demographics, such as age, gender, weight, and height, vancomycin doses, and levels of creatinine are processed.

VTDM feedback: The first vancomycin level is used to update the model in addition to VTDM model

PK-RNN-V: Variables listed, but vancomycin level, are included in the model.

PK-RNN-V feedback: The first vancomycin level is used in addition to PK-RNN.

PK-RNN-V full feedback: All vancomycin levels are used to update the models.

Figure 1. Example Predicted Vancomycin Concentration of Each Model

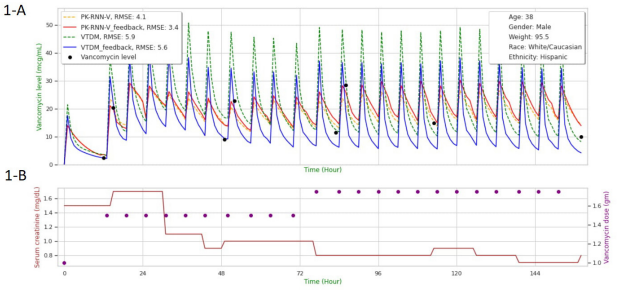


Figure 1-A represents the predicted vancomycin concentrations of each model in an example patient. Each black dot indicates actual vancomycin levels from patients (true levels). The right upper corner legend describes basic patient demographics. Figure 1-B shows the trends of creatinine and vancomycin dose over the encounter. Each purple dot indicates an individual dose of vancomycin.

Description of models: Refer footnote in table 2.

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.

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

64. Novel Biomarkers Improve Estimation of Vancomycin Clearance in Critically Ill Children

Kevin J. Downes, MD[1]; Athena F. Zuppa, MD, MSCE[1]; Anna Sharova, MPH[1]; Lauren Gianchetti, MPH[1]; Emily Duffey, RN[1]; Stuart L. Goldstein, MD[2]; Michael Neely, MD[3]; [1]Children's Hospital of Philadelphia, Philadelphia, PA; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [3]Children Hospital Los Angeles, Los Angeles, California

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, osteopontin) 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 = -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.

Figure 1. Final population PK model and parameter estimates.

Parameter	Weighted parameter estimate		Shrinkage
	Median	95th percentile	%
CL_0	2.82	2.44 - 3.51	42.3
CL_{WT}	0.75		
CL_{HOEK}	0.58	0.56 - 1.50	13.4
CL_{PNGAL}	0.19	0.16 - 0.33	38.0
CL_{AGE}	0.05	0.05 - 0.21	27.8
V_{C0}	5.15	3.86 - 5.82	41.5
V_{C-WT}	1		
Q_0	5.00	4.46 - 5.85	28.2
Q_{WT}	0.75		
V_{P0}	6.28	6.26 - 7.12	23.7
V_{P-WT}	1		
Final model parameterized as: $CL = CL0 \cdot (WT/26.8)^{CLWT} \cdot (HOEK/156)^{CLHOEK} \cdot (114/PNGAL)^{CLPNGAL} \cdot (AGE/10)^{CLAGE}$ $V_C = V_C0 \cdot (WT/26.8)^{VCWT}$ $Q = Q0 \cdot (WT/26.8)^{QWT}$ $V_P = V_P0 \cdot (WT/26.8)^{VPWT}$			

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.

Disclosures. **Kevin J. Downes, MD**, Merck (Individual(s) Involved: Self): Grant/Research Support **Stuart L. Goldstein, MD**, **Bioporto** (Consultant, Grant/Research Support)

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

Andrew J. Fratoni, PharmD[1]; David P. Nicolau, PharmD[1]; Joseph L. Kuti, PharmD[2]; [1]Hartford Hospital, Hartford, Connecticut; [2]Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, Connecticut

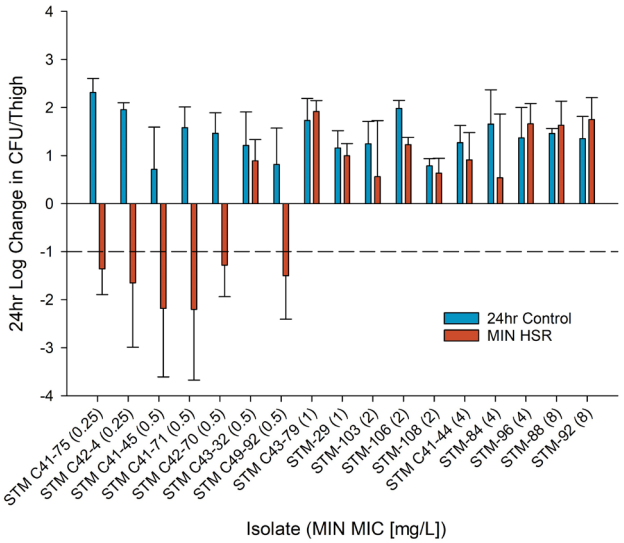
Session: O-14. Have We Peaked? Updates in PK/PD

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. Confirmatory pharmacokinetic (PK) studies were performed in infected neutropenic mice to develop a MIN HSR providing an area under the curve (AUC) and maximum 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 17 STM. Both thighs of neutropenic ICR mice were inoculated with bacterial suspensions of 10^7 colony forming units (CFU)/mL. Two hours after inoculation, the MIN HSR was administered subcutaneously (SC) over 24h. Control mice received normal saline. Efficacy was measured as the change in $\log_{10}$CFU/thigh at 24h compared with 0h controls.

Results. MIN 22, 10, 14, and 10mg/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).

Figure. Efficacy of a minocycline human simulated exposure of 100mg intravenous Q12h in the murine neutropenic thigh model against 17 clinical Stenotrophomonas maltophilia isolates



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.

The study was funded under FDA Contract 75F40120C00171.

Disclosures. **David P. Nicolau, PharmD**, **Abbvie, Cepheid, Merck, Paratek, Pfizer, Wockhardt, Shionogi, Tetraphase** (Other Financial or Material Support, I have been a consultant, speakers bureau member, or have received research funding from the above listed companies.) **Joseph L. Kuti, PharmD**, **Allergan** (Speaker's Bureau)**BioMérieux** (Consultant, Research Grant or Support, Speaker's Bureau)**Contrafect** (Scientific Research Study Investigator)**GSK** (Consultant)**Merck** (Research Grant or Support)**Paratek** (Speaker's Bureau)**Roche Diagnostics** (Research Grant or Support)**Shionogi** (Research Grant or Support)**Summit** (Scientific Research Study Investigator)

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 *Enterobacterales*

Mohamad Yasmin, MD[1]; Amir nutman, MD[2]; Lu Wang, PhD[3]; Steven Marshall, MS[4]; Dafna Yahav[5]; Ke Chen, Lab[3]; Jiping Wang, PhD[3]; Jian Li, PhD[3]; Robert A. Bonomo, MD[6]; [1]Case Western Reserve University, Cleveland, Ohio; [2]Beilinson Hospital, Tel aviv, Tel Aviv, Israel; [3]Monash University, Melbourne, Victoria, Australia; [4]Louis Stokes Cleveland Medical Center, Cleveland, OH; [5]Tel Aviv University, Rabin Medical Center [6]Louis Stokes Cleveland VA Medical Center, Cleveland, OH

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

Background. Central nervous system (CNS) infections caused by carbapenem-resistant Enterobacterales (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 bla_{KPC} *Kp* (0.25μg/mL), DTR PA (4 μg/mL), and bla_{KPC} *E. cloacae* (0.25 μg/mL), respectively. Measured plasma and CSF concentrations of avibactam (AVI) and ceftazidime (CAZ) are shown in Table 1.

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

Patient 1	Concentration (μg/mL)	
Sample Name	Ceftazidime	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