

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	95 th 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:
 $CL = CL_0 \cdot (WT/26.8)^{CL_{WT}} \cdot (HOEK/156)^{CL_{HOEK}} \cdot (114/PNGAL)^{CL_{PNGAL}} \cdot (AGE/10)^{CL_{AGE}}$
 $V_c = V_{c0} \cdot (WT/26.8)^{V_{cWT}}$
 $Q = Q_0 \cdot (WT/26.8)^{Q_{WT}}$
 $V_p = V_{p0} \cdot (WT/26.8)^{V_{pWT}}$

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)

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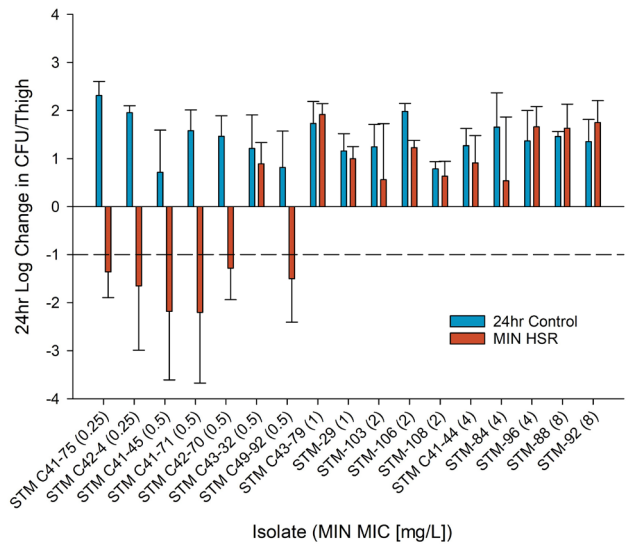
Session: O-14. Have We Peaked? Updates in PK/PD

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. 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 (C_{max}) 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 10⁷ 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 log₁₀ 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 C_{max} and AUC profile. Mean ± standard deviation bacterial burden at 0h across all isolates was 6.03±0.32 log₁₀ CFU/thigh. Bacterial growth was 1.35±0.68 log₁₀ 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 log₁₀ CFU/thigh). All STM with MIC ≥ 1mg/L experienced bacterial growth (1.18±0.79 log₁₀ 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, Tetrphase (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)Contrafact (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*

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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)	
	Ceftazidime	Avibactam
Sample Name		
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 1b. Therapeutic Drug Monitoring of CAZ-AVI concentrations in CSF and Human Plasma (HP) pertaining to patient 2 and 3

Cerebrospinal fluid (CSF)							
Patient ID	Ceftazidime-avibactam (2g/0.5g) dosing time	Sample Collection Time	Time elapsed since last dose (h)	Time relative to 2 nd dosing (h)	Ceftazidime (µg/ml) in CSF	Avibactam sodium (µg/ml) detected in CSF	Avibactam (µg/ml) in CSF
Patient 2	03 Feb 2021 at 23:52	04 Feb 2021, 10:00	10.1	-2.0	26.3	1.72	1.59
		04 Feb 2021, 11:50	12 *	-0.2*	29.1	1.54	1.42
		04 Feb 2021, 14:05	14.2	2.1	21.0	1.62	1.50
		04 Feb 2021, 16:15	16.1	4.3	26.7	2.44	2.25
Patient 3	04 Feb 2021, 1 st dosing at 0:24	04 Feb 2021, 10:10	9.8	0.2	23.0	3.98	3.79
		04 Feb 2021, 12:00	11.4	2.0	35.1	1.90	0.92
		04 Feb 2021, 13:55	13.3	3.9	39.3	1.50	1.48
		04 Feb 2021, 16:10	15.6	6.2	15.0	1.47	1.36
Human plasma (HP)							
Patient ID	Ceftazidime-avibactam (2g/0.5g) dosing time	Collection Time	After 1 st dosing time (h)	Time relative to 2 nd dosing (h)	Ceftazidime (µg/ml) in HP	Avibactam sodium (µg/ml) detected in HP	Avibactam (µg/ml) in HP
Patient 2	03 Feb 2021 at 23:52 (2g/0.5g)	04 Feb 2021, 10:00	10.1	-2.0	112	5.52	5.10
		04 Feb 2021, 11:50	12	-0.2	91.8	4.24	3.91
		04 Feb 2021, 14:05	14.2	2.1	69.8	1.19	1.10
		04 Feb 2021, 16:15	16.1	4.3	202	17.5	16.2
Patient 3	04 Feb 2021, 1 st dosing at 0:24	04 Feb 2021, 10:10	9.8	0.2	56.6	5.14	4.75
		04 Feb 2021, 12:00	11.4	2.0	53.8	3.45	3.19
		04 Feb 2021, 13:55	13.3	3.9	110	14.0	12.9
		04 Feb 2021, 16:10	15.6	6.2	84.8	7.22	6.67

Conclusion. Measuring CZA concentration levels in CSF was achieved in 3 patients with complicated CNS infections. Post-infusion concentrations indicated that adequate CAZ and AVI exposures were attained in the CSF. Notably, avibactam was shown to achieve concentrations ≥ 1 µg/ml in the CSF throughout the dosing interval. For avibactam and ceftazidime, the PK/PD target correlated with bacterial killing is $\sim 50\%$ fT $>$ MIC. In 2 out of 3 patients, concentrations were determined to be above the respective MICs throughout the entire dosing interval in the CSF. All patients attained clinical and microbiological cure. A novel CZA TDM method was successfully employed to establish that CZA maintains therapeutic CSF concentrations that exceed the MIC throughout the dosing interval.

Disclosures. Robert A. Bonomo, MD, entasis (Research Grant or Support) Merck (Grant/Research Support) NIH (Grant/Research Support) VA Merit Award (Grant/Research Support) VenatoRx (Grant/Research Support)

67. Agreement Among Bayesian Dosing Software for Calculating Vancomycin Area Under the Curve

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

This abstract has been withdrawn.

68. Comparison of Cardiovascular Risk Assessment Calculators in the US Military HIV Natural History Study

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Session: O-15. HIV Co-infections and Co-morbidities

Background. People living with HIV (PLHIV) have increased risk of cardiovascular disease (CVD), however CVD risk assessment can be challenging as HIV-related factors are not included in most calculators. We compared CVD risk calculators in US Military HIV Natural History Study (NHS) participants.

Methods. The NHS database was screened for participants enrolled between 2009-2019 who were ≥ 40 years of age with no previous history of CVD or statin use. Of the 399 participants meeting criteria, 385 (96.5%) had available data to assess 3 CVD risk calculators: Atherosclerotic CVD risk calculator (ASCVD), Framingham Risk Calculator (FRC), and the Data Collection on Adverse Effects of Anti-HIV Drugs Study (DAD) risk calculator. Risk calculators were applied cross-sectionally at the first available time point at or after age 40 years and calculators were compared using a Wilcoxon signed rank test. Demographic and HIV-related characteristics were analyzed as independent variables.

Results. Participants were predominantly male (91.1%), mostly White (49.6%) or Black/African American (44.7%), and commonly had a history of tobacco use (38.9%).

The mean age at HIV diagnosis and at CVD risk calculation was 33 and 41.8 years, respectively (Table 1). Overall, there was significant variability between calculators with mean scores of 3.66%, 2.50% and 1.38% for ASCVD, FRC, and DAD, respectively for all pairwise comparisons ($p < 0.001$; Table 2). When assessing those with CVD risk $\geq 7.5\%$, a clinically relevant threshold, the proportion of individuals with risk $\geq 7.5\%$ varied for the ASCVD (10.4%), FRC (7.5%), and DAD ($< 0.8\%$) calculators. Associations or trends toward higher CVD risk was observed among the various calculators for race/ethnicity and both age < 30 years and CD4 ≤ 350 cells/uL at HIV diagnosis (Table 2).

Characteristic	N (%) or Mean (±SD)
Mean age at HIV diagnosis	33 (±7.97)
<30 years	238 (61.8)
≥ 30 years	147 (38.2)
Race/ethnicity	
White	191 (49.6)
Black/African American	172 (44.7)
Other	22 (5.7)
Mean CD4 count at HIV diagnosis (cells/uL)	494 (±261)
≤ 350 cells/uL	102 (25.9)
> 350 cells/uL	237 (61.6)
Missing	46 (11.9)
Mean CD4 count at nadir (cells/uL)	301 (±170)
≤ 350 cells/uL	260 (67.5)
> 350 cells/uL	125 (32.5)
Mean time from HIV diagnosis to first HAART	3.1 (±4.23)
<3.1 years	247 (65.9)
≥ 3.1 years	128 (34.1)
Age at calculator application	42 (±4.18)
Ever Smoker	150 (38.9)
Current smoker	65 (16.8)
HAART, highly active antiretroviral therapy	

Characteristics	ASCVD	FRC	DAD	P-values		
				ASCVD vs. FRC	ASCVD vs. DAD	FRC vs. DAD
All participants	3.66%	2.50%	1.38%	<0.001	<0.001	<0.001
Age at HIV diagnosis						
<30 years	3.90%	2.94%	1.47%	<0.001	<0.001	<0.001
≥ 30 years	3.29%	1.80%	1.23%	<0.001	<0.001	0.001
P-value	0.079	<0.001	0.078			
Race/ethnicity						
White	2.74%	2.81%	1.50%	0.170	<0.001	<0.001
Black/African American	4.73%	2.03%	1.18%	<0.001	<0.001	<0.001
Other	3.31%	3.55%	1.92%	0.667	<0.001	0.001
P-value	<0.001	0.010	0.029			
CD4 count at HIV diagnosis						
≤ 350 cells/uL	3.95%	2.62%	1.42%	<0.001	<0.001	<0.001
> 350 cells/uL	3.37%	2.28%	1.18%	<0.001	<0.001	<0.001
Missing	4.53%	3.41%	2.28%	0.032	<0.001	0.003
P-value	0.072	0.057	<0.001			
CD4 count at nadir						
≤ 350 cells/uL	3.69%	2.53%	1.41%	<0.001	<0.001	<0.001
> 350 cells/uL	3.60%	2.45%	1.32%	<0.001	<0.001	<0.001
P-value	0.818	0.795	0.584			
Time from HIV diagnosis to first HAART						
<3.1 years	3.47%	2.47%	1.34%	<0.001	<0.001	<0.001
≥ 3.1 years	4.11%	2.57%	1.48%	<0.001	<0.001	<0.001
P-value	0.093	0.756	0.438			

Conclusion. Since significant variability among CVD risk calculators was observed in the NHS cohort, it may be challenging to apply overall CVD risk calculators in a clinically relevant manner. HIV-related factors, such as duration of HIV infection and CD4 nadir, are not accounted for in CVD calculators and may be indicators of increased CVD risk. Future studies are warranted in order to determine the optimal clinical use of CVD risk calculators for PLHIV.

Disclosures. All Authors: No reported disclosures