Cefepime Population Pharmacokinetics Using VAMS in Critically Ill Children with MODS

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BACKGROUND

- Multiple Organ Dysfunction Syndrome (MODS), the simultaneous failure or dysfunction of two or more organ systems, affects as many as 57% of critically ill children.
- Sepsis is the leading cause of pediatric MODS and infections (either as an inciting insult or a complication to MODS) can further worsen outcomes of patients with MODS, increasing mortality rates to 50 – 67%. Effective antibiotic dosing is key to improving patient outcomes, but unpredictable changes in organ function make universal dosing strategies difficult.
- Cefepime is a broad-spectrum antibiotic commonly used for empiric treatment of sepsis in children. The pharmacokinetics (PK) of cefepime and many other drugs in critically ill children have been understudied, in part due to challenges of performing PK studies in this population.
- Volumetric absorptive microsampling (VAMS) allows for precisely timed sampling using small blood volumes, but questions arise about generalizability of whole blood sampling (i.e. VAMS) vs plasma.

OBJECTIVES

- To develop a population PK model for cefepime in critically ill children with MODS (using VAMS) accounting for organ function and host inflammation.
- To compare cefepime PK parameter estimates using VAMS to a published population PK model using plasma.

METHODS

- Sample collection and analysis were conducted as part of AMPLE (R01HD103755; MPI: Downes, Scheetz), an ancillary to the PARADIGM study (R01HD095976; PI: Hall), which is a multi-center prospective study of pediatric MODS.
- Eligible patients with MODS receiving cefepime had up to 5 PK samples taken per day over 3 days (up to 15 samples in total). Patients on CRRT were excluded from this analysis.
- VAMS devices were used to collect 20 µL of blood per sample. Total drug concentrations were quantified using LC-MS at the Univ. Michigan.
- Population PK modeling was performed using Monolix version 2023R1. Model compartmentalization and error structure were selected based on data fit. Ultimate covariate inclusion was based on improvements in objective function value ≥ 3.84 and physiological relevance.
- After model development, we re-parameterized our data to be consistent with a published population PK model of cefepime in critically ill children[1] to understand how PK using VAMS (whole blood) compares to a model developed with plasma samples.

RESULTS

- 244 serum cefepime samples from 26 patients (Table 1) were used for model building.
- A two-compartment model with first order elimination, allometric scaling (scaled to weight of 34kg), and proportional residual error was the most appropriate for our data. (Table 2)
- Serum TNF-α and GFR (calculated using the U25 method described by Pierce et.al.)[2] were significant covariates on clearance.

Table 1: Population Characteristics

Categorical	n (%)
No. of male subjects	11 (42.4%)
No. on ECMO	1 (3.8%)
Continuous*	**Median (range)**
Age (years)	9.7 (0.5 - 17.9)
Weight (kg)	34 (5.6 - 213.6)
Height (cm)	131 (64.3 - 198.1)
eGFR (mL/min/1.73m2)**	87 (39 - 227)
TNF-alpha (pg/mL)	145 (21 - 2255)
PELOD Score	5 (0 - 11)
PROULX Score	2 (0 - 5)
MODS Day	1 (0 - 9)

* values at time of first PK sampling
** eGFR calculated with U25 GFR equation

Table 2: Model Parameter Estimates

Parameter	Estimate	RSE %	%CV
CL (L/h)	4.61	6.7	----------
V1 (L)	13.27	13.3	----------
Q (L/h)	3.09	27.9	----------
V2 (L)	9.91	25.9	----------
θ_{GFR}	0.59	0.9	----------
θ_{TNF}	0.60	1.5	----------
ω_CL	0.31	15.8	31.6
ω_V1	0.41	24.9	42.8
ω_Q	0.53	46.9	57.0
ω_V2	0.86	28.7	103.9

Model Equations:

- $CL_i = CL * \left(\frac{WT}{34}\right)^{0.75} * \left(\frac{GFR}{98}\right)^{\theta_{GFR}} * \left(\frac{Ln(TNF)}{5}\right)^{\theta_{TNF}} * e^{\eta_{CL}}$
- $V1_i = V1 * \left(\frac{WT}{34}\right) * e^{\eta_{V1}}$
- $Q_i = Q * \left(\frac{WT}{34}\right)^{0.75} * e^{\eta_Q}$
- $V2_i = V2 * \left(\frac{WT}{34}\right) * e^{\eta_{V2}}$

Figure 1: Individual and Population Predictions vs Observations

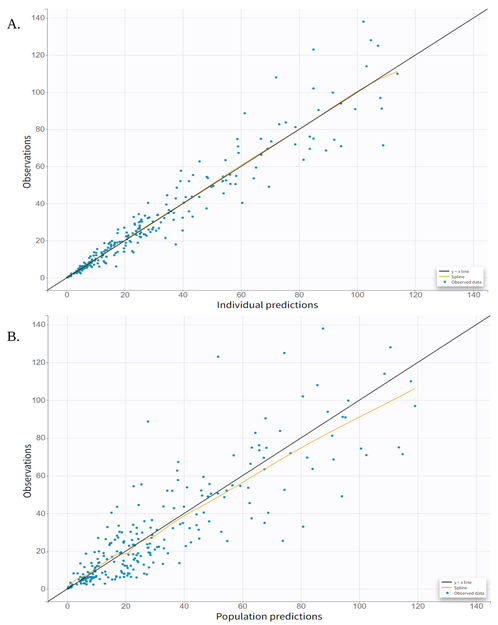


Figure 2: Population Predictions vs Population Weighted Residuals

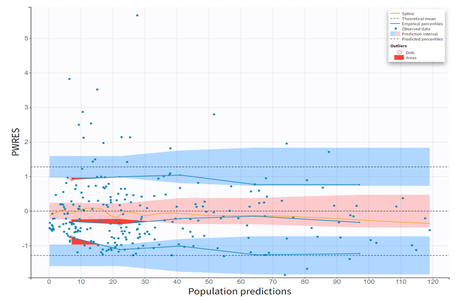
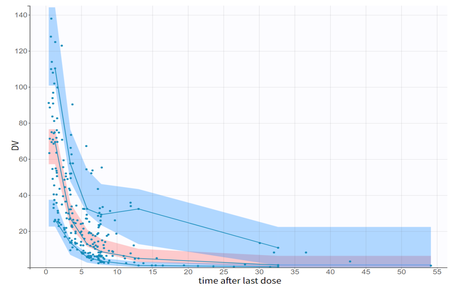


Figure 3: Visual Predictive Check (time after last dose)



RESULTS

Table 3: Our Data Parameterized as Previously Published Model

	De Cacqueray et al model		AMPLE Study	
Parameter	Estimate (%RSE)	95% CI	Estimate (%RSE)	95% CI
CL (L/h)	1.21 (7)	1.04 – 138	2.24 (10)	1.79 – 2.69
V1 (L)	4.80 (13)	3.57 – 6.02	5.92 (9)	4.82 – 7.02
θ_{GFR}	0.37 (35)	0.12 – 0.62	0.47 (36)	0.14 – 0.80
ω_CL	0.39 (14)	0.28 – 0.50	0.36 (16)	0.25 – 0.47
ω_V1	0.35 (27)	0.16 – 0.54	0.39 (18)	0.25 – 0.53
σ	0.39 (9)	0.32 – 0.46	0.28 (5)	0.25 – 0.31

Model Equations:

- $CL_i = CL * \left(\frac{WT}{9}\right)^{0.75} * \left(\frac{GFR}{153}\right)^{\theta_{GFR}} * e^{\eta_{CL}}$
- $V_i = V * \left(\frac{WT}{9}\right) * e^{\eta_{V1}}$

CONCLUSION

- A two-compartment model best described cefepime PK; GFR and TNF-α were found to impact cefepime CL in our model, reducing objective function value by 32.27 and 4.54 points, respectively.
- The PK of cefepime in our population using VAMS was largely comparable to that published in other critically ill children using plasma, although our study population was older and exclusively had MODS.
- Use of VAMS in our study facilitated population PK model creation using very small volumes with richer sampling. Future studies evaluating VAMS in TDM are warranted.

REFERENCES

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2. Pierce, Christopher B., Alvaro Muñoz, Derek K. Ng, Bradley A. Warady, Susan L. Furth, and George J. Schwartz. "Age- and Sex-Dependent Clinical Equations to Estimate Glomerular Filtration Rates in Children and Young Adults with Chronic Kidney Disease." Kidney International 99, no. 4 (April 2021): 948–56.

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