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ORIGINAL RESEARCH ARTICLE

Variability in Meropenem Distribution and Clearance in Children with Sepsis: Population-Based Pharmacokinetics with Assessment of Renal Biomarkers

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Abstract

Background and Objective Meropenem dosing to achieve therapeutic exposure in critically ill children with sepsis is challenging due to a spectrum of renal function, from augmented renal clearance (ARC) to acute kidney injury (AKI). The objective of this study was to define meropenem plasma concentrations and pharmacodynamic exposure metrics in children with septic shock during the first 3 days of PICU hospitalization.

Methods We prospectively evaluated meropenem clearance (CL_{MERO}) and volume of distribution ($V_{1\text{-}MERO}$), innovatively assessing renal biomarkers (serum creatinine [SCr], serum cystatin C [SCys], and neutrophil gelatinase-associated lipocalin [SNgal]), in infants aged ≥ 4 weeks and children on intravenous (IV) meropenem 20 mg/kg every 8 h from 2019 to 2023. Cases with sepsis were matched to controls without sepsis.

Results Analysis included 27 participants (19 cases and 8 controls) with 309 meropenem serum concentrations. Median age was 11.8 (range 0.6–19.6) years, weight 36.3 (7.2–98.0) kg, SCr 0.33 (0.09–2.57) mg/dL, SCys 451.1 (178.3–1824.1) ng/mL, and SNgal 180.7 (23.2–1403.0) ng/mL. A 2-compartment, population pharmacokinetic (PK) model via NONMEM best described data, with weight on V_{MERO} and allometric scaling on CL_{MERO}. Using the final model with SCys in $V_{1\text{-}MERO}$ and estimated glomerular filtration rate (eGFR)-MS in CL_{MERO}, the median $V_{1\text{-}MERO}$ was 0.23 (range 0.07–0.57) L/kg and CL_{MERO} 0.15 (0.05–0.49) L/h/kg, with eGFR–MS 139 (23–365) mL/min/1.73 m^2 from AKI to ARC. Meropenem clearance, $V_{1\text{-}MERO}$ and eGFR-MS were significantly decreased in cases versus controls, with higher variability of eGFR-MS in cases.

Conclusion Wide variation in meropenem concentrations in children with sepsis as compared to those without sepsis prompt close monitoring of GFR and drug concentrations in this population.

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Key Points

Adequate meropenem therapeutic exposure in critically ill children with sepsis is challenging due to variability of renal function that may change daily.

Prompt close monitoring of renal function and meropenem concentrations to refine dosing is essential for antibiotic efficacy and safety.

1 Background

Children admitted to the pediatric intensive care unit (PICU) with sepsis and septic shock are at risk for death and complications from the underlying infection and shock. Recently, multiple studies in adults with septic shock reported hyperfiltration of the kidneys at supra-physiologic rates (termed as augmented renal clearance, ARC) which subsequently raised great concerns for the inadequacy of standard drug dosing to treat these patients [1–3]. Limited population-based pharmacokinetic (PK) studies of commonly used antibiotics have demonstrated that the occurance of ARC in critically ill children, ranges from 12% to as high as 67% using estimation of glomerular filtration rate (eGFR) [4–8]. The consequential aftermath of ARC in children suggests undertreatment of many of our sickest patients [6].

In addition to ARC, children in sepsis and septic shock may also experience acute kidney injury (AKI) during their PICU clinical course [9–11]. Both ARC and AKI alter kidney function, in which eGFR, calculated based on serum creatinine (SCr), is inaccurate in critically ill patients due to their fluctuating hemodynamic and renal perfusion status [12, 13]. The estimation of renal function using eGFR is inaccurate in AKI and ARC due to fluctuating SCr values that timely reflect renal function, particularly in those with anuria in AKI or fluid-overloaded in the ARC, which frequently occurs in critically ill children. In this study using a prospective cohort design, we aimed to evaluate the spectrum of renal function, from ARC to AKI, in critically ill infants and children with sepsis using meropenem PK and different eGFR assessments that integrate SCr and serum cystatin C (SCys) [5, 8]. Evaluation of the meropenem PK, specifically clearance (CL_{MERO}) and volume of distribution ($V_{1\text{-}MERO}$), will help inform dosing recommendations to achieve therapeutic and safe drug exposure in this vulnerable population with a spectrum of renal function, from ARC to AKI.

2 Methods

Using prospective design, we identified and enrolled infants (aged ≥ 4 weeks) and children (aged < 21 years) who were admitted from March 2019 to January 2023 to the PICU for at least 72 h with sepsis and/or septic shock as defined by the admission diagnosis by the attending physician, with the use of vasopressor therapy for shock; and treated with intravenous (IV) meropenem 20 mg/kg/dose every 8 h over 30 minutes as standard-of-care (maximum of 2000 mg/dose). These case participants were matched to controls who were receiving meropenem as standard-of-care for other approved indications such as appendicitis, but did not demonstrate clinical findings of sepsis or hypotension. The protocol was approved by the University of California San Diego Institutional Review Board for Rady Children's Hospital (Project #181319, July 23, 2018).

Clinical and laboratory assessment was conducted daily from Days 1 to 7 of study enrollment; intensive sampling of serum meropenem concentrations and renal biomarkers: serum creatinine (SCr), serum cystatin C (SCys), and serum neutrophil gelatinase-associated lipocalin (SNgal) were assessed over 8 hours following administration of meropenem, on Days 1 to 3 for cases and on Day 1 for controls. Blood (0.25 mL) was collected at: pre-dose, 0.5-, 1-, 2-, 4-, and 8-h from the start of infusion for the first dose studied; and, pre-dose, 1-, 2-, 4-, 8-h with dosing on the 2 subsequent PICU days starting 24-h and 48-h after the initial dose studied. Sampled blood was immediately placed on ice, and centrifuged within 30 minutes, with plasma frozen at minus 70 °C prior to assay. Data extraction from charts included demographics; comorbid conditions (renal, blood infusion, Pediatric Logistic Organ Dysfunction [PELOD] score, diagnosis, pathogen); medications (antibiotics, diurects, vasopressors; laboratory data [serum C-reactive protein, albumin, lactate]); and renal function (biomarkers, fluid balance). Pertinent data were extracted from the EPIC electronic health record software (Verona, WI) via Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN).

Due to the time-varying nature of some laboratory data (including renal biomarkers) that were necessary for population-based pharmacokinetic (pop-PK) analysis, a carry forward or backward method for the value nearest to the time for missing data was applied. For lactic acid and albumin, age-specific mean values were used when not available due to lack of clinical suspicion for abnormality as part of routine care.

2.1 Meropenem and Renal Biomarker Assays

Quantitative determination of meropenem was accomplished by liquid chromatography multiple reaction monitoring mass spectrometry (LC-MRM-MS) on an AB Sciex API 4000 LC-MS System. Multiple reaction monitoring (MRM) transition ion monitoring was performed in positive electrospray ionization mode with meropenem-d6 as an internal standard. Calibration standards were prepared in human plasma and used to generate an external 7-point calibration curve (313–20,000 ng/mL) using linear regression (1/× weighting) to plot the peak area ratio versus concentration. The calibration curves were linear ($R^2 \geq 0.99$) over the analytically measurable range.

Serum and urine creatinine were determined using the validated LC-MS/MS method [14]. In brief, 5–50 µL of sample were deproteinated and diluted with heavy isotope-labeled internal standard (ISTD) in a single step by adding ISTD in 80% acetonitrile. Twenty microliters of diluted sample were subjected to isocratic, HILIC HPLC with 10 mM ammonium acetate in 65% acetonitrile @ 0.15 mL/min. Creatinine and d3-creatinine ISTD were detected by electrospray ionization tandem mass spectrometry MRM transitions 114 > 44 and 117 > 47, respectively. Quantitation is achieved by comparing results to a synthetic standard calibration curve (0, 0.4, 1, 4, 10, 40 mmol/L for urine and 0, 0.2, 1, 5, 100 µg/mL for serum).

Concentrations of SCys and SNgal were measured using enzyme-linked immunosorbent assay (ELISA) kit (LS Bio, catalog LS-F436 and LS-F10094, respectively) for the quantitative detection of cystatin C and Ngal, respectively, in samples of plasma, serum, and urine. For cystatin C, it is based upon a Sandwich assay principle with a detection range of 312–200,000 pg/mL and sensitivity < 312 pg/mL, with intra-assay CV < 10% and inter-assay CV < 12%. For Ngal, Sandwich assay principle was also applied, which detected levels as low as 3.9 pg/mL with intra-assay CV < 8% and inter-assay CV < 10%.

2.2 Renal Function Assessment

Renal function was assessed using different equations that incorporated SCr and SCys. The SCr values were evaluated by clinical and research assays; and SCys by research assay as described above. For SCr, the modified Schwartz and CKD-EPI formulae were used to calculate eGFR in children aged < 18 and ≥ 18 years, respectively (Online Resource 1) [12, 13]. The age- and sex-dependent Pierce equations were also used to determine eGFR using SCr and SCys [15]. Serum neutrophil gelatinase-associated lipocalin was screened as a covariate in the pop-PK modeling [16]. Based on published literature in pediatrics, the thresholds for ARC and AKI were >160 and ≥ 60 mL/min/1.73 m^2, respectively (Online Resource 2).

2.3 Pharmacokinetic Modeling

We conducted pop-PK modeling of meropenem to characterize the variability in renal function from ARC to AKI. To handle the nonlinearity in the time-varying nature of meropenem's volume of distribution (V_1 and V_2) and clearance (CL_{MERO}), which were expected in our critically ill dynamic patients, pop-PK models were explored by non-linear mixed effects modeling using NONMEM 7.3 (Icon, Dublin, Ireland) with Pirana Workbench (Certara, Princeton, NJ) [17]. One-, two-, and three-compartment models with first-order elimination were tested using ADVAN TRANS functions [18]. The First Order Conditional Estimation method was used with ETA-EPS interaction [19]. Proportional and additive residual error models were explored. To account for the expected variability in size of the participants, both V_{MERO} and CL_{MERO} were normalized to body weight (with allometric scaling of 0.75 for CL_{MERO} and isometric for V_{MERO}) in the base pop-PK model before evaluation of potential covariates [20, 21]. The elimination rate constant (k_e) was calculated by $CL/V_{1\text{-}MERO}$ and half-life by $0.693/k_e$.

The derivation of the final pop-PK was performed in a stepwise fashion with: (1) formulation of base PK model normalized to body weight; (2) Perl-speaks-NONMEM 5.3.0 was used to perform univariable and multivariable analyses. For univariable analysis, covariates that improved the model fit using a likelihood ratio test on the differences in the objective function of 4 ($p \leq 0.05$ for 1 degree of freedom) were selected for multivariate analysis. A forward selection (objective function reduction of 4, p value ≤ 0.05) and backward elimination (objective function reduction of 8, p value ≤ 0.005) were used in the multivariable analysis; (3) inspection of graphical data using goodness-of-fit diagnostic plots to assess the appropriateness of the structure for the base, intermediate and final models; (4) final pop-PK model selection with generation of empirical Bayesian estimates of individual subject PK parameters; and (5) assessment of parameter reliability using the bootstrap technique of 1000 to calculate the 95% confidence intervals (CI) for the population estimates [22]. In Perl-speaks-NONMEM, we employed valid states (or parameter-covariate parameterizations) of none, linear, exponential and power for continuous covariates, and none and linear for categorical covariates. For bootstrap, the model was considered reliable if the parameter estimates were within the 95% CI.

2.4 Statistical Analysis

We conducted statistical analyses using the post hoc dataset from the final pop-PK model that contained Bayesian estimates for both V_{MERO} and CL_{MERO} for each patient's entire duration of therapy. Study participants were divided into two groups (controls and cases), and compared by demographic, laboratory and PK data. For continuous variables, descriptive statistics included number of observations, mean, standard deviation (SD), median, minimum, maximum, and range values. Discrete-variable summaries included counts and proportions. All data and statistical tests were performed using appropriate tests (e.g., t-test for continuous and Chi-square for categorical variables) with two-tailed analyses using R version 4.3.0 (R-project.org, R Foundation for Statistical Computing, Vienna, Austria).

3 Results

We recruited and analyzed 27 children (19 cases and 8 controls) with median age of 11.8 (range 0.6–19.6) years and median weight 36.3 (range 7.2–98.0) kg. Of 309 observed meropenem serum concentrations, 271 were from cases (101–120) and the remaining 38 controls (201–212; Online Resource 5). Demographic data and baseline clinical characteristics were not significantly different between cases and controls, except for vasopressor use, fluid balance, PELOD score, c-reactive protein, serum albumin, and appendicitis (Table 1). In fact, most (88%) controls had appendicitis, but they were not in shock and did not have sepsis. In addition, all serum biomarkers, including SCr, SCys, and SNgal, were significantly different between case and control groups (Online Resource 3). The quartile ranges for meropenem PK parameters and renal biomarkers are provided in Online Resource 3 for case and control subjects.

A 2-compartment (2-CMT) model, as compared with 1-CMT, significantly improved the fit of data by −33 change in objective function value (OFV). As anticipated, the inclusion of normalized weight on $V_{1\text{-MERO}}$ and $V_{2\text{-MERO}}$, and normalized allometric weight on CL_{MERO} and Q_{MERO} significantly improved model fit, with change in OFC by − 56.

Table 1 Baseline clinical characteristics[a]

Clinical characteristic	Total $N = 27$	Control $n = 8$	Case $n = 19$	p-value
Age, y	11.8 (0.6–19.6)	10.2 (1.9–14.7)	14.2 (0.6–19.6)	0.9
4 wk to <6, *n* (%)	11 (41)	2 (25)	9 (47)	
6 wk to <12, *n* (%)	3 (11)	3 (38)	0 (0)	
≥ 12 wk, *n* (%)	13 (48)	3 (37)	10 (53)	
Male sex, *n* (%)	18 (67)	5 (63)	13 (68)	0.9
Weight, kg	36.3 (7.2–98.0)	42.4 (10.0–66.1)	36.3 (7.2–98.0)	0.7
Body surface area[b] m^2	1.18 (0.37–2.15)	1.26 (0.50–1.78)	1.18 (0.37–2.15)	0.7
Lean body mass[b] kg/m^2	27.24 (5.72–60.11)	30.23 (8.45–47.07)	27.24 (5.72–60.11)	0.8
Race/ethnicity				0.9
Hispanic	20 (74)	6 (75)	14 (74)	
Caucasian	19 (70)	4 (50)	15 (79)	
African-American	0 (0)	0 (0)	0 (0)	
Asian	0 (0)	0 (0)	0 (0)	
Other/unknown	8 (30)	4 (50)	4 (21)	
Vasopressor use, *n* (%)	11 (41)	0 (0)	11 (58)	0.02
Diuretic use, *n* (%)	1 (4)	0 (0)	1 (5)	0.8
Blood transfusion, *n* (%)	4 (15)	0 (0)	4 (21)	0.3
Appendicitis, *n* (%)	8 (30)	7 (88)	1 (5)	< 0.001
Fluid balance, mL/kg/24 h[b]	0.29 (−12.1 to 17.8)	2.31 (−2.4 to 6.2)	0.28 (−12.1 to 17.8)	0.02
Pediatric logistic organ Dysfunction (PELOD) score	2 (0–11)	0 (0–0)	6 (0–11)	< 0.001
C-Reactive protein, mg/L				
Highest value	7.4 (0.1–35.3)	0.1 (0.1–2.8)	26.1 (1.5–35.3)	< 0.001
Serum albumin, g/dL				
Highest value	2.8 (2.1–4.3)	4.3 (3.8–4.3)	2.8 (2.2–3.5)	< 0.001
Lowest value	2.8 (2.1–4.3)	4.3 (3.8–4.3)	2.6 (2.1–3.5)	< 0.001
Serum bicarbonate, mEq/L				
Highest value	25.0 (18.0–43.0)	24.3 (22.0–26.0)	25.0 (18.0–43.0)	0.3
Lowest value	22.5 (18.0–38.0)	24.3 (22.0–26.0)	22.0 (18.0–38.0)	0.7
Serum lactate, mg/dL				
Highest value	1.4 (1.1–15.5)	1.4 (1.4–1.4)	1.6 (1.1–15.5)	0.07

[a]Numbers represent median (range) unless otherwise stated

[b]Equations for body surface area = (height [m] × weight [kg])/3600; lean body mass = 3.5 × (0.0215×W0.6469 ×H0.7236) + 2; weight in kg and height in cm; and fluid balance = input − output (mL/kg/24 h)

Using a 2-CMT model with normalized weight, 42 intermediate models were created to characterize the meropenem PK parameters of $V_{1\text{-MERO}}$ and CL_{MERO} (Online Resource 4). Based on a univariate forward covariate screening, eGFR by the modified Schwartz and Pierce methods, presence of complicated appendicitis, and renal biomarkers were strong covariates for the PK parameters. The SCr measurements evaluated by both clinical and research assays produced comparable results in our pop-PK modeling. In addition, serum albumin (particularly its low value) was a significant covariate for $V_{1\text{-MERO}}$. After stepwise covariate modeling and selecting the model with the lowest OFV, the final PK model incorporated allometric weight and eGFR-MS as covariates for CL_{MERO}, and weight for V_{MERO} and also SCys on $V_{1\text{-MERO}}$ (Table 2). The inter-subject variability for $V_{1\text{-MERO}}$ and $V_{2\text{-MERO}}$ was assumed to be equal to prevent overfitting.

For the final model, scatterplots demonstrated good fit between observed and predicted population and individual concentrations (Fig. 1A). The conditional weighted residuals (CWRES), which were calculated based on the FOCE method, demonstrated that higher observed concentrations were under-predicted by the final model (Fig. 1B). The post hoc Bayesian population estimates for V_{MERO} and CL_{MERO} were similar to the median bootstrap analysis values, and were within the 95% CIs obtained from the bootstrap analysis (Table 2). While V_{MERO} was statistically different, with decreased median V_{MERO} for cases, the range of $V_{1\text{-MERO}}$ for cases was wider demonstrating the significant variability in meropenem distribution in children with sepsis (Online Resource 3). Similarly, CL_{MERO} was significantly lower in cases than in controls.

Table 2 Final population-based pharmacokinetic model with bootstrap results[a]

Parameter	Estimate	SE of estimate	Median bootstrap estimate	95% CI bootstrap
θ_{V1}	9.74	3.90	9.57	5.07–15.22
$\theta_{V1\text{-SCys}}$	0.449	0.428	0.421	0.113–1.63
θ_{V2}	4.53	1.23	4.45	2.78–6.53
θ_{CL}	9.72	2.37	9.78	7.23–13.16
$\theta_{CL\text{-eGFR-MS}}$	0.169	0.0967	0.195	0.105–0.514
θ_{Q}	1.66	0.400	1.61	0.84–3.89
η_{V1}, η_{V2}	0.306	0.0739	0.287	0.153–0.464
η_{CL}	0.487	0.103	0.483	0.286–0.687
ε	0.133	0.0205	0.127	0.093–0.173

CI confidence interval, *CL* clearance in L/h, *SE* standard error, *V* volume of distribution (1 = central compartment; 2 = peripheral compartment) in *L*; $\eta_{X=}$ intersubject random effect associated with *V*1, *V*2 or CL as denoted in subscript; ε _ = residual random effect, Wt weight in kg; eGFR-MS by Modified Schwartz = estimated glomerular filtration rate in mL/min/1.73 m^2; and SCys = serum cystatin in ng/mL

[a]Final pharmacokinetic model was:

$V1\ (L) = \theta_{V1} * (Wt/70) * (1+ \theta_{V1\text{-SCYS}} * SCys/0.45)$

$V2\ (L) = \theta_{V2} * (Wt/70)$

$CL\ (L/h) = \theta_{CL} * (Wt/70)^{0.75} * [eGFR/140]^{\theta CL\text{-eGFR-MS}}$

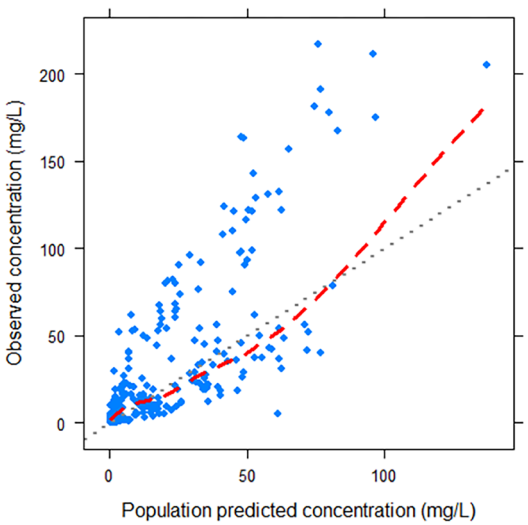
$Q\ (L/h) = \theta_{Q} * (Wt/70)^{0.75}$

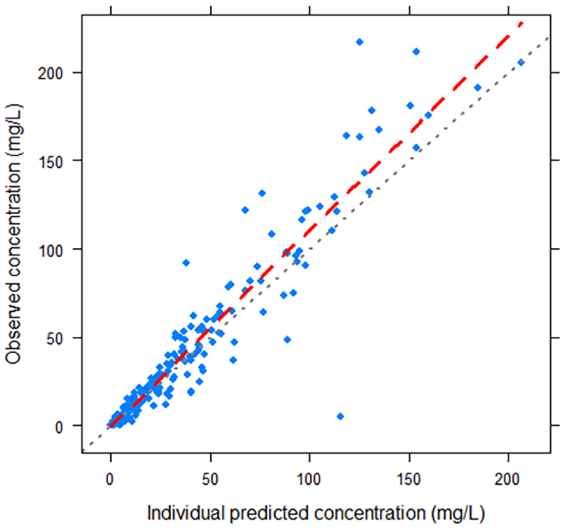
4 Discussion

Meropenem's PK profile was best described by a 2-compartment model with first-order elimination, similar to previously published studies in both pediatrics and adults [23–28]. To our knowledge, this is the first study to assess renal biomarkers, specifically SCys and SNgal, in a popPK model of meropenem in children. Serum cystatin C is an extracellular biomarker that is not secreted nor reabsorbed by the kidney, making it an ideal biomarker for eGFR. Serum cystatin C, when adjusted for BSA, may be a more accurate way to determine eGFR compared to SCr in pediatric patients [29]. Serum cystatin C has also be used to predict AKI in pediatric patients with decompensated cirrhosis [30]. While SCys was an important covariate for CL_{MERO} in univariable analysis, it unexpectedly became a significant covariate for $V_{1\text{-MERO}}$ (central compartment) in our final PK model. As SCys is an extracellular biomarker, this may reflect fluid varability in our cohort to thereby impact $V_{1\text{-MERO}}$. The impact of SCys on meropenem's Vd should be further explored.

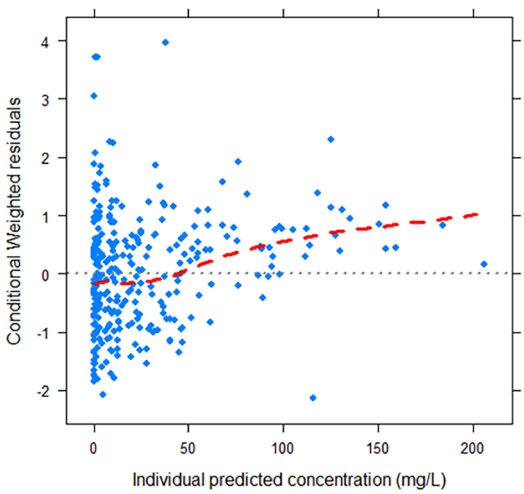
In hospitalized infants and children, the $V_{1\text{-MERO}}$ and CL_{MERO} were previously reported to range from 0.235 to 0.57 L/kg and 0.33 to 0.55 L/h/kg, respectively [23, 28, 31]. Previously published $V_{1\text{-MERO}}$ and CL_{MERO} were similar to our control non-septic participants (i.e., 0.29 L/kg and 0.29 L/h/kg, respectively). However, our compartmental popPK analysis showed decreased $V_{1\text{-MERO}}$ and CL_{MERO} for septic children (i.e., cases, 0.19 L/kg and 0.14 L/h/kg, respectively). The difference between the CL_{MERO} in our study and previous studies is likely due to the extreme variability of kidney function in our cohort, evident by a wide range of 0.05 to 0.39 L/kg/h (up to 8 times difference). Furthermore, the population evaluated in other studies was non-septic, clinically stable, received continuous renal replacement therapy or extracorporeal membrane oxygenation, or small sample size with limited age range; unlike our critically ill children with sepsis with elevated PELOD, CRP and vasopressor use [23, 27, 31]. Physiological changes in septic patients can cause profound changes in their hemodynamic status and renal function. In particular, sepsis can lead to changes in renal perfusion and has been associated with decreased (AKI) or increased (ARC) clearance for renally eliminated drugs, like meropenem.

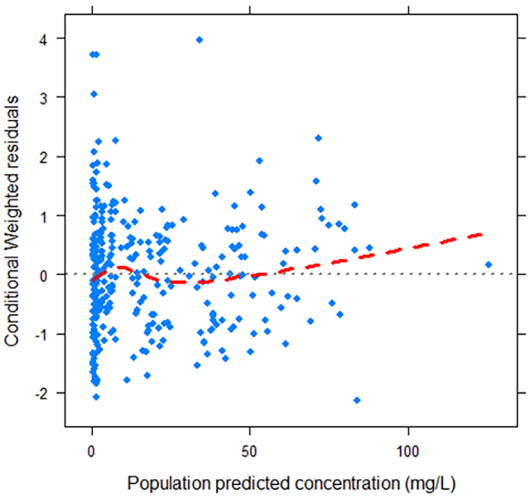
a) Observed versus Predicted Concentrations

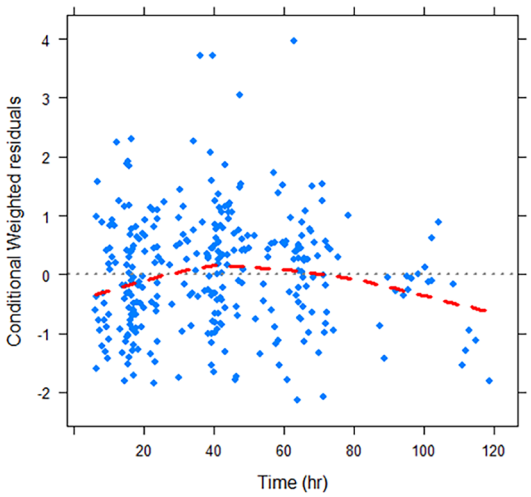




b) Conditional Weighted Residuals







◂**Fig. 1** Goodness-of-fit plots for the final meropenem population-based pharmacokinetic model, showing: observed concentrations versus population and individual predicted concentrations (**a**); and conditional weighted residuals versus individual predicted concentration, population predicted concentration, and time, respectively; (**b**) with the dashed line representing the line of identity or unity and the solid line representing the local regression smooth line (loess curve) Time refers to time after dose

Similarly, we observed decreased $V_{1\text{-MERO}}$ in our cohort of septic children as compared to other studies, with minimal effect on the half-life due to consistent magnitude of change in both $V_{1\text{-MERO}}$ and CL_{MERO} [23, 27, 31]. This difference in $V_{1\text{-MERO}}$ is likely contributed by age, with older children in our cohort compared to those studied by Blumer (i.e., aged < 1 to 19 years vs 2 months to 12 years, respectively) and younger age in the studies by Cies et al (mean age, 3.1 ± 2.9 years) and Saito (median 1.4 [range 0.03–14.6] years) [23, 31]. Drug distribution alters with age, resulting from changes in body composition [32]. Furthermore, as a hydrophilic antibiotic, the V_{MERO} is affected by total body water content and the flow of extracellular fluids [33].

As meropenem is a renally eliminated drug, AKI has been associated with lower CL_{MERO} and ARC, to increased CL_{MERO} [34, 35]. In our study, CL_{MERO} was correlated with renal function using eGFR-MS that served as a covariate in our final PK model. In fact, there was a wide range of eGFR-MS in our study population. Patients with ARC were classified as those with eGFR-MS values exceeding 160 mL/min/1.73 m^2 [7, 36, 37]. Our cohort demonstrated a wide range of eGFR values, from 22.9 to 364.8 mL/min/1.73 m^2, with almost half with ARC by our definition. Limitations exist in the accuracy of calculation of eGFR with values above 200 mL/min/1.73 m^2, which are physiologically improbable. Acute decreases in SCr from fluid status may explain the exagerrated eGFR values in some cases.

While we attempted to identify ARC in children with sepsis, we did not collect urine to compare to our eGFR estimations. However, our research group has previously published studies on pediatric ARC and identified thresholds of 130 mL/min/1.73 m^2 using vancomycin and aminoglycoside clearance, and 160 mL/min/1.73 using eGFR by modified Schwartz [5, 7, 38].

With the significant PK variation in both V_{MERO} and CL_{MERO} in septic children, the daily dose of meropenem is expected to change accordingly. Augmented renal clearance can lead to subtherapeutic antimicrobial exposure as meropenem is cleared rapidly, which has been documented for meropenem in critically ill children [27]. This leads to poor target attainment when targeting time above minimum inhibitory concentration ($T >$ MIC), particularly for therapeutic goals of 70% and 100% $T >$ MIC for patients with sepsis. In our cohort, the variability in V_{MERO} was also notable and should not be ignored for evaluation in septic children since V_{MERO} also impacts dose, especially important early in the therapeutic course to optimize drug exposure for the initial effective management of sepsis. Future studies with large sample size should investigate the impact of the PK variability of both V_{MERO} and CL_{MERO} on meropenem dosing in critically ill children using Monte Carlo simulation since higher doses, even incorporating prolonged or continuous infusion, may be needed as reported in children and adults with severe sepsis and septic shock, which is particularly prudent when treating pathogens with high MIC > 4 µg/mL [27, 39–41]. Future studies should also include children with diverse comorbidities and polypharmacy inclusive of those with synergistic risks for renal impairment.

There were several limitations in our study. First, we designed a prospective study to enhance our understanding of PK alterations in septic children, compared to those without sepsis to determine the spectrum of renal function. To maximize sample collection as part of routine care, blood collection of children without sepsis (i.e., controls) was confined to limited PK sampling and first day of study enrollment. In contrast, we measured concentrations more intensively in septic children and up to Day 3 of meropenem therapy. Therefore, our final PK model more reflects children with sepsis. However, even with the limited sampling strategy, coupled to the limited sample size of children without sepsis, differences in PK parameters were already observed.

5 Conclusion

Notable changes and wide variability in meropenem PK, including both V_{MERO} and CL_{MERO}, contribute to different drug exposure in critically ill children. Meropenem exposure may even change daily, necessitating the need to closely monitor renal function in critically ill children with anticipated hemodynamic changes. Due to these dynamic changes, future studies are crucial to evaluate, from a learning health system approach, the feasibility and outcomes in optimal meropenem monitoring inclusive of machine learning paired with current methods that are standard of care.

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Declarations

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Conflict of interest The authors have no competing interests relevant to this article to disclose.

Data availability The data that support the findings of this study are not openly available for reasons of sensitivity and risk of reidentification due to its clinical nature. Data, however, are available from the authors upon reasonable request.

Ethics approval The protocol for this study was approved by the University of California San Diego Institutional Review Board for Rady Children's Hospital (Project #181319, July 23, 2018).

Consent to participate Informed consent to participate in the study was obtained from all participants or their legal guardians.

Consent for publication All participants provided informed consent for the publication of their data.

Code availability Not applicable.

Authors' contribution John Bradley and Jennifer Le contributed to designing and performing the study. Data collection and analysis was performed by John Bradley, Jennifer Le, Julie Huynh, Brandon Vo, Annie Mai, Robert Mak, Jeremiah Momper, Edmund Caparelli, Helen Harvey, and Sean Avedissian. The draft of the manuscript was written by John Bradley, Jennifer Le, Julie Huynh, Brandon Vo, Annie Mai, Erin Bradley, Amy Sitapati, and Karandeep Singh and all authors reviewed and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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