Title

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Subtherapeutic Meropenem Antibiotic Exposure in Children With Septic Shock Assessed by Noncompartmental Pharmacokinetic Analysis in a Prospective Dataset

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OBJECTIVES: To define meropenem plasma concentrations and pharmacodynamic exposure metrics in children with septic shock during the first 3 days of PICU hospitalization.

DESIGN: Pharmacokinetic sampling was undertaken in 19 subjects receiving standard meropenem dosing (20 mg/kg/dose, 8 hr) recruited from March 2019 to March 2022. Sampling occurred once each day following meropenem given 24 hours apart, during the first 3 PICU days. Data analysis was completed in 2023 and noncompartmental analysis was performed to assess pharmacodynamic exposure targets for sepsis. Clearance and volume of distribution at 20 mg/kg/dose were used to simulate mean exposures at 40 and 60 mg/kg/dose.

SETTING: PICU in a tertiary care center.

SUBJECTS: Patients 4 weeks old or older with hypotension requiring fluid resuscitation and vasopressor therapy, receiving meropenem as empiric therapy for sepsis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Augmented renal clearance (ARC) was documented in eight of 19 subjects, previously associated with subtherapeutic plasma concentrations, while three of 19 had acute kidney injury and decreased renal clearance. When assessed by pharmacodynamic exposure targets for sepsis (plasma meropenem concentrations above the minimum inhibitory concentration [MIC] of *Pseudomonas aeruginosa* for 70% or 100% of the dosing interval), ten of 19 and nine of 19 children, respectively, had subtherapeutic plasma meropenem exposures during PICU day 1, even for pathogens with an MIC considered "susceptible" by U.S. Food and Drug Administration criteria. Therapeutic meropenem pharmacodynamic exposures were associated with a positive 24-hour fluid balance on PICU day 1 and a negative 24-hour fluid balance by day 3, although profound variability was noted in fluid administered and renal output.

CONCLUSIONS: Given the variability in meropenem systemic exposure in pediatric septic shock, therapeutic drug monitoring, or monitoring for ARC, is suggested during the first days of hospitalization to allow daily assessments of dosing needs to achieve pharmacodynamic exposure targets for sepsis.

KEYWORDS: meropenem; pediatric intensive care unit; pharmacodynamics; pharmacokinetics; septic shock; severe sepsis

Empiric antibiotic therapy for bacterial sepsis in children is provided emergently, with each hour of delay of antibiotic treatment associated with an increased risk of mortality (1–3). Receiving an antibiotic dose that will achieve an effective exposure for sepsis is essential. Historically, it was

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RESEARCH IN CONTEXT

- Children with septic shock require effective empiric antibiotic exposure for presumed pathogens.
- Standard doses of meropenem used for treatment during the first 3 days of hospitalization frequently fail to achieve effective pharmacodynamic exposure targets for sepsis.
- This study, therefore, aimed to examine meropenem antibiotic exposure in pediatric septic shock.

recognized that sepsis was associated with subtherapeutic beta-lactam antibiotic concentrations in both adults and children, and often associated with augmented renal clearance (ARC) potentially related to increased cardiac output and renal blood flow (4–9). Furthermore, therapeutic exposure (TE) of meropenem is based on the concept requiring the presence of plasma drug concentrations above the minimum inhibitory concentration (MIC) of the pathogen over a specified percentage of the dosing interval (%T > MIC) that correlates with microbiologic and clinical outcomes (10–12). While a time-dependent pharmacodynamic exposure of 40% T > MIC is an appropriate target in immune-competent hosts with noncritical illness, greater exposures of 70% and 100% T > MIC are suggested as targets for adults with sepsis (13, 14). Higher targets, including four times (4×) 100% T > MIC (9, 12), were also suggested as important for clinical and microbiologic cure.

Therefore, at the time of planning our study in 2018, we sought to better define the factors associated with subtherapeutic antibiotic exposure in septic shock. Over the period 2019–2022, we prospectively assessed meropenem plasma concentrations following standard dosing of 20 mg/kg/dose every 8 hours, by measuring meropenem concentrations after a dose administered at the same time each day (e.g., serum concentrations measured after a daily 10:00 AM dose) on days 1, 2, and 3 of PICU hospitalization. We aimed to assess the impact of septic shock and fluid resuscitation early in the hospitalization when the most rapid and profound changes in tissue perfusion and organ function are occurring. We also developed simulations using noncompartmental analysis (NCA) modeling to assess attainment of effective pharmacokinetic/pharmacodynamic targets at doses of 40 and 60 mg/kg/dose.

METHODS

This prospective, noninterventional, observational study was reviewed and approved by the University of California San Diego and Rady Children's Hospital of San Diego (UCSD/RCHSD) Institutional Review Board (IRB) on July 23, 2018 (Project No. 181319 "Longitudinal Assessment of Beta-Lactam Antibiotic Exposure in Critically Ill Children with Sepsis in the PICU to Predict Dosing Requirements"). The study was considered minimal risk, and informed consent was obtained from parents (and assent from participants as appropriate) to review patient medical records and collect blood for plasma meropenem concentration analysis. Throughout this work, all project members followed the ethical practices for human research consistent with the UCSD/RCHSD IRB requirements and the 1975 Helsinki Declaration. A preliminary report of this work has appeared in abstract form in 2023 (15).

Children were identified for enrollment between March 2019 and March 2022 by a diagnosis of sepsis with hypotension requiring fluid resuscitation and vasopressor therapy, receiving meropenem as standard-of-care empiric therapy at 20 mg/kg/dose every 8 hours, and survival likely beyond 24 hours. Exclusions from enrollment included those children who had already received greater than or equal to 3 doses of meropenem, those with chronic renal failure or receiving hemodialysis or peritoneal dialysis, and those less than 4 weeks of age.

Blood Sampling, Handling, and Assays

Blood was collected for plasma meropenem concentration analysis (0.25 mL) at the following times: predose, 0.5, 1, 2, 4, and 8 hours from the start of infusion (SOI) for the first dose studied and pre-dose, 1, 2, 4, and 8 hours with dosing on the 2 subsequent PICU days starting 24 and 48 hours after the initial dose studied. The sampled blood was immediately placed on ice and centrifuged within 30 minutes, with the plasma frozen at –70°C before the assay.

Meropenem plasma concentrations were analyzed by liquid chromatography-tandem mass spectrometry. The analytically measurable range for this assay was 313–20,000 ng/mL.

Patient Data

We reviewed and collected fluid balance data for both 8 hours (FB8) and 24 hours (FB24) following the start of meropenem infusion, on each day during the 3 days of study. These data were held within the electronic medical record and included: IV fluids, blood products administered, and fluid output, primarily urine. Daily weights were not routinely collected on critically ill infants and children.

Noncompartmental Analysis

NCA was performed using Phoenix WinNonlin, Version 8.4 (Certara, Princeton, NJ) from pharmacokinetic data collected at the standard treatment dose of 20 mg/kg/dose, with simulation at higher doses of 40 and 60 mg/kg/dose. Initial parameter estimates for volume of distribution (Vd) and clearance were determined from our overall study population, as well as from those determined to have ARC, defined as those having an estimated glomerular filtration rate (eGFR) of greater than or equal to 160 mL/mL/1.73 m^2 (8, 16). Post hoc, for more clarity, we have defined sepsis-related acute kidney injury (AKI) using a 2020 definition of eGFR of less than 60 mL/min/1.73 m^2 (17). Renal function by eGFR was determined at the time of meropenem concentration assessment, using the modified "Bedside Schwartz" assessment (18) and Cockcroft and Gault (19) formulas for children 1–17 years old and 18 years old or older, respectively.

The estimates from children with ARC provided the basis for simulation of exposure at higher doses of 40 and 60 mg/kg/dose. Plasma protein binding of meropenem of 2% was considered negligible.

Analysis of Risk Factors for Subtherapeutic Meropenem Exposure

We assessed %T > MIC for an 8-hour dosing interval at 40%, 70%, and 100% T > MIC for each MIC (1, 2, 4, and 8 μg/mL) following 20, 40, and 60 mg/kg doses for the initial 3 days of PICU hospitalization to define those with TE vs. subtherapeutic exposure (SE). Risk factors assessed for SE included eGFR, FB8, and FB24.

The U.S. Food and Drug Administration breakpoints for meropenem activity against *Pseudomonas aeruginosa* are: susceptible (S) at less than or equal to 2 μg/mL, intermediate (I) at 4 μg/mL, and resistant (R) at greater than or equal to 8 μg/mL. Susceptibility data from pediatric clinical isolates in 2018 are provided in **Figure S1** (http://links.lww.com/PCC/C595; see SENTRY-mvp.jmilabs.com).

Summary statistical data are presented as counts and proportions. Population data are summarized using means and SDs, and for data not normally distributed, by medians and interquartile ranges (IQRs).

RESULTS

We recruited 19 children with sepsis who met study inclusion criteria and had blood collected on sequential days for meropenem analysis. Demographic and physical data in the participants were: male (13/19), Hispanic (14/19), median age (IQR) 8.610 years (13.19 yr) (**Fig. S2**, http://links.lww.com/PCC/C595, for bimodal distribution), median weight (IQR) 31.4 kg (40.5 kg), and median body mass index (IQR) 18.20 kg/m^2 (5.15 kg/m^2). **Table 1** summarizes the primary diagnosis and pathogen. Subjects with rapid resolution of symptoms over 24–48 hours and discharged from the PICU were not further studied. Of the 19 children enrolled on PICU day 1, 18 of 19 were still in the PICU on day 2, and 14 of 19 on day 3.

Longitudinal Assessment of ARC and AKI

Of the 19 participants, eight had ARC at the time of enrollment (day 1); ARC persisted in seven of these eight during day 2 and five of eight on day 3. One subject with ARC on day 1 had an apparent resolution on day 2 but had ARC again on day 3. In the three of 19 participants with eGFR within the normal range on day 1, one of three developed ARC on day 2 (still present on day 3), and two of three developed ARC on day 3.

Regarding AKI, three of 19 met criteria on day 1, with two of three children resolving AKI by day 3. Overall, one of 19 children enrolled in the study required hemodialysis on day 2 and was only included in the day 1 data analysis.

TABLE 1.
Primary Diagnosis and Pathogen

Subject	Primary Diagnosis	Primary Pathogen	Positive Test Methodology
Subject 1	Hemophagocytic lymphohistiocytosis	None detected	
Subject 2	Febrile neutropenia	*Escherichia coli* (confirmed extended-spectrum beta-lactamase)	Culture (blood)
Subject 3	Status epilepticus	*Enterococcus faecalis*	Culture (urine)
Subject 4	Ventilator-associated pneumonia	*Pseudomonas aeruginosa*	NGS[a] (blood)
Subject 5	Toxic shock syndrome	*Staphylococcus aureus*	Culture (vaginal)
Subject 6	Poland syndrome (with multiple organ system failure)	No primary pathogen identified	Culture
Subject 7	Necrotizing enterocolitis	*Klebsiella pneumoniae*	Culture (peritoneal)
Subject 8	Kidney transplant	*E. coli*	NGS (blood)
Subject 9	Intussusception	No primary pathogen identified	
Subject 10	Ventilator-associated pneumonia	*Fusobacterium nucleatum*	NGS (blood)
Subject 11	Complicated appendicitis	*Streptococcus anginosus* group	Culture (peritoneal)
Subject 12	Cellulitis of lymphatic malformation	*E. coli*	Culture (blood)
Subject 13	Febrile neutropenia	*Streptococcus pyogenes*	NGS (blood)
Subject 14	Pyelonephritis	No primary pathogen identified	
Subject 15	B-cell leukemia with central line-associated bloodstream infection	*K. pneumoniae*	Culture (blood)
Subject 16	Toxic shock syndrome	*Staphylococcus aureus*	Culture (vaginal)
Subject 18	Schizencephaly and aspiration pneumonia	*E. coli*	NGS (blood)
Subject 19	Autism spectrum disorder and aspiration pneumonia	*Prevotella nigrescens*	NGS (blood)
Subject 20	Splenorenal shunt	*Phocaeicola vulgatus*	NGS (blood)

NGS = next-generation sequencing.
[a]NGS (by Karius test).

Plasma Meropenem Concentration

Plasma meropenem concentrations for each participant, in relation to drug dosing, is shown in **Figure 1** for each of the 3 days of study. Reference lines highlight clinically relevant MICs for *P. aeruginosa* and provide the pharmacodynamic antibiotic exposure targets of 40% T > MIC (3.2 hr after administration) for noncritical infections, and 70% and 100% T > MIC (5.6 and 8 hr after administration) for sepsis. The percentage of participants who achieve these targets, by day of study, is shown in **Table 2**. For an MIC of less than or equal to 2 µg/mL (S), 19 of 19 children achieved the required exposure for cure of noncritical infections (40% T > MIC), but for those requiring higher exposures for sepsis (70% or 100% T > MIC), only ten of 19 (53%) and nine of 19 (47%) children, respectively, achieved adequate exposure on the day of admission. For an MIC of 4 µg/mL (I), nine of 19 (47%) achieved adequate exposure at 70% T > MIC, and seven of 19 (37%) at 100% T > MIC on day 1. During day 2 and day 3 of the study, overall mean exposures appeared similar. **Figure S3** (http://links.lww.com/PCC/C595) is an exploratory plot of the diminishing proportion of patients achieving treatment success on day 1 in relation to the increasing MICs of pathogens, in the context of the higher %T > MIC requirement for sepsis.

NCA Modeling

Table S1 (http://links.lww.com/PCC/C595) shows individual structural parameters following a 20 mg/kg/

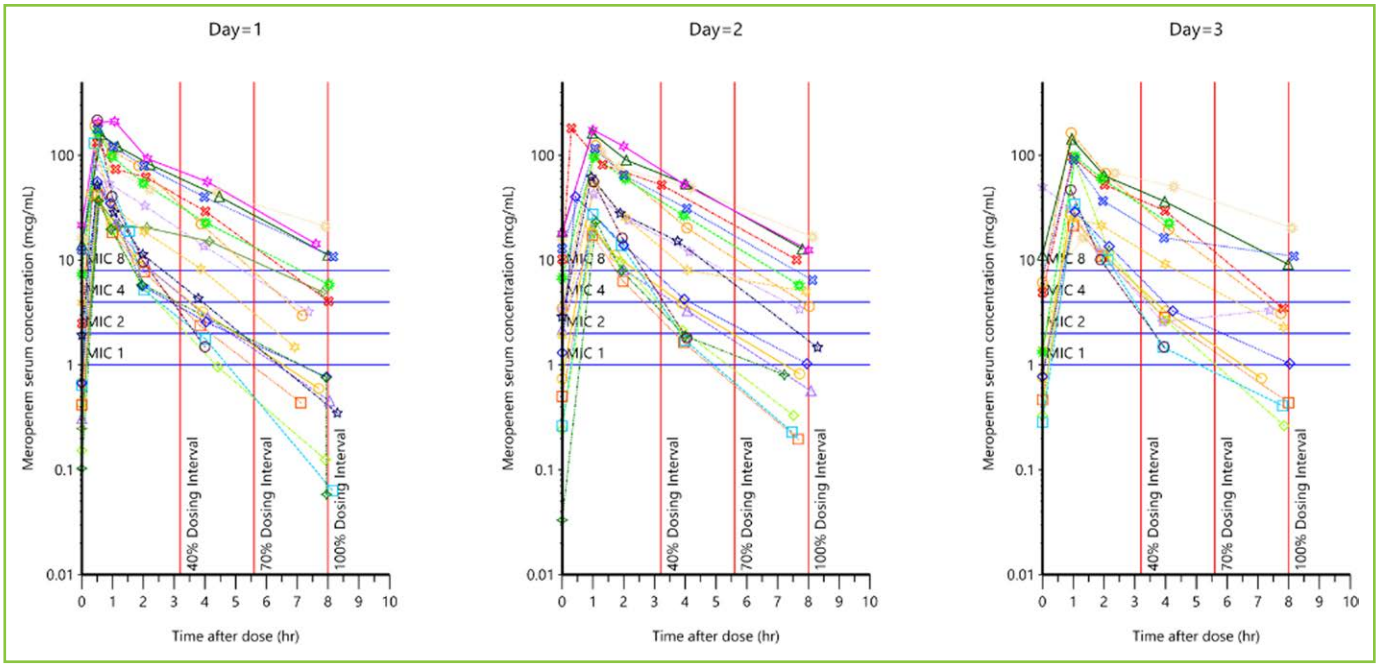

Figure 1. *Individual pharmacokinetic plots* following a 20 mg/kg dose of meropenem during the first 3 d of PICU hospitalization, indexed to minimum inhibitory concentrations (MICs) (μg/mL). The pharmacodynamic targets are shown by *lines* perpendicular to the *x*-axis for 40% (nonserious infection goal), 70% and 100% (sepsis goals) for time > MIC during the 8-hr dosing interval. As the MIC of the pathogen increases from 1 to 8 μg/mL, the percentage of children who achieve the target decreases (data also provided in Table 2). The attainment of the target is modestly improved by day 2 and day 3 of hospitalization.

TABLE 2.

Percentage of Participants Likely to Achieve an Appropriate Pharmacodynamic Exposure for Noncritical infections (40% Time Above the Minimum Inhibitory Concentration) Versus Sepsis (70% and 100% Time Above the Minimum Inhibitory Concentration), for Pathogens With Minimum Inhibitory Concentrations of 1, 2, 4, and 8 μg/mL, Following 20 mg/kg of Meropenem, by Day of PICU Hospitalization

Percent of Time Above the Minimum Inhibitory Concentration (Day of Hospitalization)	Minimum Inhibitory Concentration			
	1 (Susceptible)	2 (Susceptible)	4 (Intermediate)	8 (Resistant)
Day 1				
40%	100	100	68	53
70%	79	53	47	37
100%	53	47	37	21
Day 2				
40%	100	100	78	56
70%	83	61	56	39
100%	61	50	39	22
Day 3				
40%	100	100	86	50
70%	84	62	46	38
100%	62	54	23	23

dose, by day of study, for each participant. The median (IQR) values for observed Vd in the terminal elimination phase (Vz_obs, L/kg) on days 1, 2, and 3 were: 0.269 (0.487), 0.376 (0.626), and 0.473 (0.527), respectively. The median (IQR) values of meropenem clearance (Cl_obs, L/kg/hr) were 1.46 (0.205), 0.142 (0.628), and 0.225 (0.223), respectively. Means (SD) are also provided on Table S1 (http://links.lww.com/PCC/C595). Substantial variability was documented between subjects.

Augmented Renal Clearance

Using WinNonlin NCA, we also calculated structural parameters for the eight of 19 participants with ARC (eGFR > 160 mL/min/1.73 m^2; **Table S2**, http://links.lww.com/PCC/C595). On day 1, Vd and Vz_obs (L/kg) was 0.48 ± 0.29 L/kg, and observed clearance and Cl_obs was 0.27 ± 0.16 L/hr/kg. On comparing participants with ARC on day 1 with the overall population on day 1 (Tables S1 and S2, http://links.lww.com/PCC/C595), the data showed a higher mean Vz_obs, 0.48 ± 0.29 vs. 0.37 ± 0.29 L/kg ($p = 0.012$). The data for clearance showed 0.27 ± 0.14 vs. 0.18 ± 0.14 L/kg/hr ($p = 0.032$). Over the 3 days of the study, Vz_obs was 0.48 ± 0.29 L/kg on day 1 ($n = 8$), 0.81 ± 0.46 L/kg on day 2 ($n = 7$), and 0.44 ± 0.35 L/kg on day 3 ($n = 5$) ($p = 0.012$). The clearance data were 0.27 ± 0.16 L/hr/kg on day 1, 0.40 ± 0.24 L/hr/kg on day 2, and 0.24 ± 0.18 L/hr/kg on day 3 ($p = 0.032$).

Acute Kidney Injury

For the three participants with AKI, we did not observe a change in clearance in two of the three between day 1 and day 2. The other participant had a further deterioration in renal function after day 1 and required dialysis.

Simulation

Assuming linear pharmacokinetic, meropenem exposures were simulated based on mean structural parameter values from children with ARC on the first day of study of Vz_obs (0.46 L/kg) and Cl_obs (0.26 L/hr/kg). For doses of 20 mg/kg, 40 mg/kg, and 60 mg/kg, we assessed 70% and 100% T > MIC exposure for pathogens with MICs of 1, 2, 4, and 8 μg/mL. The mean plasma pharmacokinetic concentration documented to fall below 2.0 μg/mL (S) following 20, 40, and 60 mg/kg doses, occurred at 5.7, 6.9, and 7.6 hours after the SOI, respectively, which represented 71%, 86%, and 95% T > MIC over an 8 hours dosing interval (**Table S3**, http://links.lww.com/PCC/C595). Similarly, simulated plasma exposure dropped below 4 μg/mL (I) at 4.45, 5.7, and 6.4 hours following 20, 40, and 60 mg/kg doses, respectively, representing 56%, 71%, and 80% T > MIC for an 8-hour dosing interval.

Analysis of Risk Factors for Subtherapeutic Exposure

Following a 20 mg/kg dose for the entire study population, those children with a SE defined as below 40%, 70%, or 100% T > MIC of the dosing interval (for MICs of 1, 2, and 4 μg/mL), were compared with those with TE with respect to clinical and laboratory parameters for the 3 study days. Assessed by an exposure threshold of 40% T > MIC, all children achieved TE for pathogens with an MIC of 1 and 2. For a MIC of 4 on day 3 of study, those with a TE had a median difference in fluid balance of –4 mL/kg at 0–24 hours after start of meropenem infusion (FB24), compared with those with SE (**Table S4**, http://links.lww.com/PCC/C595). Assessed by 70% T > MIC (**Table S5**, http://links.lww.com/PCC/C595) for an MIC of 1, on day 1, those with a TE had a positive FB8 and FB24 (FB24 of over 4 mL/kg compared with those with a SE). There was extensive variability in the eGFRs, and we failed to identify differences between TE and SE groups (106 ± 127 vs. 190 ± 90 mL/min/1.73 m^2). By day 3, those with TE had a statistically significant, negative FB24 of 4 mL/kg, relative to those with SE (similar to the day 3 assessment with an exposure of 40% T > MIC), but the eGFR in the TE and the SE groups were no different (170 ± 113 vs. 297 ± 96 mL/min/1.73 m^2).

Assessed by 100% T > MIC (**Table S6**, http://links.lww.com/PCC/C595), SE on day 3 was associated with a two-fold higher eGFR for an MIC of 4: 218 ± 112 vs. 112 ± 61 mL/min/1.73 m^2. Most children with subtherapeutic concentrations met eGFR criteria for ARC. **Figures S4** and **S5** (http://links.lww.com/PCC/C595) provide graphs, by day of study, of therapeutic vs. subtherapeutic populations for eGFR, FB8, and FB24, for MICs of 1, 2, and 4 μg/mL, for 70% T > MIC and 100% T > MIC, from data presented in Tables S5 and S6 (http://links.lww.com/PCC/C595).

AT THE BEDSIDE

- In this prospective study of the pharmacokinetics of meropenem in pediatric septic shock during the first 3 days of hospitalization, we have observed great between-subject exposure resulting in substantial variability, with pharmacodynamic exposure targets for sepsis not achieved in approximately half of the subjects studied.
- This analysis adds to our understanding of how often exposure targets are achieved during initial periods of fluid resuscitation and pressor therapy in septic shock
- Therapeutic monitoring of beta-lactam antibiotic plasma concentrations would allow individualized dosing to better achieve sepsis exposure targets for each patient.

Data on impact of concurrent medications on meropenem concentrations were reviewed by nonlinear mixed effects modeling and were not found to be statistically significant (data not shown).

DISCUSSION

In this 2019–2022 study of 19 children with septic shock, almost half had subtherapeutic plasma meropenem exposures for sepsis when assessed for pathogens with MICs interpreted as "susceptible" by the FDA, which placed these children at potential risk of microbiologic and clinical treatment failure. Therapeutic meropenem antibiotic exposures were defined by a pharmacodynamic, time-dependent metric (%T > MIC) that identifies a microbiologic endpoint of one-log decrease in pathogen load 24 hours into beta-lactam antibiotic therapy based on animal models and validated in retrospective human studies (11, 20). While 30–40% T > MIC is often accepted as the desired goal for infections in noncritically ill, immune-competent hosts, retrospective data suggest that for sepsis in adults, a higher T > MIC is required, with suggestions varying from 60–80% to 100% T > MIC, or 100% T > 4 × MIC (12–14, 21, 22). Additional complexity is inherent in defining a beta-lactam antibiotic exposure target for sepsis outcomes based on the extensive inter-patient variability in antibiotic plasma and tissue concentrations considering differences in fluid resuscitation and organ dysfunction following PICU hospitalization. Little prospective published data are available for targets for children with septic shock.

In this prospectively assessed population with septic shock requiring vasopressors, eight of 19 children (42% [95% CI, 20–64%]) demonstrated ARC defined by eGFR greater than 160 mL/min/1.73 m^2. Our study showed a high proportion of children with ARC relative to recent reviews (23), although no universally accepted definition of ARC has been accepted for pediatrics (8, 24). While we confirmed that ARC can be associated with subtherapeutic antibiotic concentrations for beta-lactam antibiotics (24–28), SE was not uniformly associated with a higher eGFR, requiring the use of therapeutic monitoring to achieve TE, rather than extrapolating from eGFR.

WinNonlin NCA simulation was used to document mean meropenem exposures that would occur at 40 and 60 mg/kg/dose. At 40 mg/kg/dose, TE of 86 %T > MIC was achieved for pathogens with an MIC of two or less, currently considered susceptible for *P. aeruginosa* by the FDA. For more resistant pathogens with MICs of four or eight, %T > MIC exposures of 71% and 56%, respectively, were achieved. Using 100%T > MIC as the desired target, a simulated subject at 40 or 60 mg/kg/dose only achieved adequate exposure for an MIC of 1 μg/mL, emphasizing the potential need for higher meropenem doses, more frequent dosing, prolonged/continuous infusion, or the use of alternative antibiotic therapy; better outcomes using prolonged infusions were recently published in adults (29) and under study in some clinical trials in children (ClinicalTrials.gov registration number NCT02687906).

We found TEs were also associated with a positive fluid balance on day 1 and a negative fluid balance noted on day 3. The mechanism for greater meropenem exposure associated with positive fluid balance on day 1 is not straightforward. Higher meropenem concentrations were noted in septic adults with fluid retention (defined as > 10% increase in body weight compared with admission weight), associated with decreased renal clearance of meropenem (30). TE associated with a negative fluid balance at day 3 suggests that renal elimination of initial fluid used in resuscitation may be occurring, resulting in higher meropenem plasma concentrations.

TE to antibiotics during the first 3 days of PICU hospitalization is likely to result in better outcomes. A 2017–2019 retrospective cohort of critically ill children suggested an associated lower mortality of 2.1% for those with extended infusion and increased antibiotic exposure compared with 19.6% for those with standard intermittent infusion (31).

Sources of bias exist in our prospective study. Our definitions of ARC and AKI were both based on eGFR using the Bedside Schwartz equation (18) incorporating a single value of serum creatinine (SCr), rather than more complex estimating equations using changes in SCr and urinary output. As reviewed in 2022 by Dhont et al (32), SCr is a relatively poor indicator of rapid changes in renal function over minutes to hours. Better, practical assessments of renal function are needed. Larger, prospective studies are needed to better capture variability in renal function and meropenem clearance following PICU admission, both within and between patients. That said, based on these considerations, we believe that therapeutic drug monitoring is the preferred method to ensure adequate beta-lactam antibiotic exposure in pediatric septic shock during the first days of PICU hospitalization and stabilization (21). Daily assessment for ARC should also identify those at highest risk of subtherapeutic antibiotic exposure.

Future prospective collaborative studies should investigate and validate doses required to achieve the high target attainment required for sepsis (> 90%), including evaluation of higher doses (40 and 60 mg/kg/dose) and evaluation of prolonged or continuous infusion of meropenem.

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REFERENCES

1. Kollef MH, Sherman G, Ward S, et al: Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115:462–474
2. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinantof survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
3. Ferrer R, Martin-Loeches I, Phillips G, et al: Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit Care Med* 2014; 42:1749–1755
4. Bilbao-Meseguer I, Rodriguez-Gascon A, Barrasa H, et al: Augmented renal clearance in critically ill patients: A systematic review. *Clin Pharmacokinet* 2018; 57:1107–1121
5. Troger U, Drust A, Martens-Lobenhoffer J, et al: Decreased meropenem levels in intensive care unit patients with augmented renal clearance: Benefit of therapeutic drug monitoring. *Int J Antimicrob Agents* 2012; 40:370–372
6. Huttner A, Von Dach E, Renzoni A, et al: Augmented renal clearance, low beta-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study. *Int J Antimicrob Agents* 2015; 45:385–392
7. De Cock PA, Standing JF, Barker CI, et al: Augmented renal clearance implies a need for increased amoxicillin-clavulanic

acid dosing in critically ill children. *Antimicrob Agents Chemother* 2015; 59:7027–7035

8. Avedissian SN, Bradley E, Zhang D, et al: Augmented renal clearance using population-based pharmacokinetic modeling in critically ill pediatric patients. *Pediatr Crit Care Med* 2017; 18:e388–e394
9. Roberts JA, Abdul-Aziz MH, Lipman J, et al; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases: Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *Lancet Infect Dis* 2014; 14:498–509
10. Drusano GL: Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug.' *Nat Rev Microbiol* 2004; 2:289–300
11. Rizk ML, Bhavnani SM, Drusano G, et al: Considerations for dose selection and clinical pharmacokinetics/pharmacodynamics for the development of antibacterial agents. *Antimicrob Agents Chemother* 2019; 63:e02309–e02318
12. Tam VH, McKinnon PS, Akins RL, et al: Pharmacodynamics of cefepime in patients with Gram-negative infections. *J Antimicrob Chemother* 2002; 50:425–428
13. McKinnon PS, Paladino JA, Schentag JJ: Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents* 2008; 31:345–351
14. Roberts JA, Paul SK, Akova M, et al; DALI Study: DALI: Defining antibiotic levels in intensive care unit patients: Are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; 58:1072–1083
15. Le J, Huynh J, Bradley JS, et al: 2551. Assessing meropenem concentrations in children with septic shock: Population-based pharmacokinetic (PK) modeling of meropenem demonstrates variability from acute kidney (AKI) to augmented renal clearance (ARC). *Open Forum Infectious Dis* 2023; 10:ofad500.2168
16. Hirai K, Ihara S, Kinae A, et al: Augmented renal clearance in pediatric patients with febrile neutropenia associated with vancomycin clearance. *Ther Drug Monit* 2016; 38:393–397
17. Avedissian SN, Skochko SM, Le J, et al: Use of simulation strategies to predict subtherapeutic meropenem exposure caused by augmented renal clearance in critically ill pediatric patients with sepsis. *J Pediatr Pharmacol Ther* 2020; 25:413–422
18. Schwartz GJ, Work DF: Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol* 2009; 4:1832–1843
19. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41
20. Craig WA: Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; 26:1–10; quiz 11–12
21. Abdul-Aziz MH, Alffenaar JC, Bassetti M, et al; Infection Section of European Society of Intensive Care Medicine (ESICM): Antimicrobial therapeutic drug monitoring in critically ill adult patients: A position paper. *Intensive Care Med* 2020; 46:1127–1153
22. Hong LT, Downes KJ, FakhriRavari A, et al: International consensus recommendations for the use of prolonged-infusion beta-lactam antibiotics: Endorsed by the American College of Clinical Pharmacy, British Society for Antimicrobial Chemotherapy, Cystic Fibrosis Foundation, European Society of Clinical Microbiology and Infectious Diseases, Infectious Diseases Society of America, Society of Critical Care Medicine, and Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2023; 43:740–777
23. Schlapbach LJ, Watson RS, Sorce LR, et al; Society of Critical Care Medicine Pediatric Sepsis Definition Task Force: International consensus criteria for pediatric sepsis and septic shock. *JAMA* 2024; 331:665–674
24. Xu WX, Qu Q, Teng XQ, et al: Personalized application of antimicrobial drugs in pediatric patients with augmented renal clearance: A review of literature. *Eur J Pediatr* 2024; 183:51–60
25. Fratoni AJ, Mah JW, Nicolau DP, et al: Imipenem/cilastatin/relebactam pharmacokinetics in critically ill patients with augmented renal clearance. *J Antimicrob Chemother* 2022; 77:2992–2999
26. Andre P, Diezi L, Dao K, et al: Ensuring sufficient trough plasma concentrations for broad-spectrum beta-lactam antibiotics in children with malignancies: Beware of augmented renal clearance! *Front Pediatr* 2021; 9:768438
27. Van Der Heggen T, Dhont E, Willems J, et al: Suboptimal beta-lactam therapy in critically ill children: Risk factors and outcome. *Pediatr Crit Care Med* 2022; 23:e309–e318
28. Avedissian SN, Rohani R, Bradley J, et al: Optimizing aminoglycoside dosing regimens for critically ill pediatric patients with augmented renal clearance: Convergence of parametric and nonparametric population approaches. *Antimicrob Agents Chemother* 2021; 65:e02629-20
29. Abdul-Aziz MH, Hammond NE, Brett SJ, et al: Prolonged vs intermittent infusions of β-lactam antibiotics in adults with sepsis or septic shock: A systematic review and meta-analysis. *JAMA* 2024; 332:638–648
30. Parizkova RC, Martinkova J, Havel E, et al: Impact of cumulative fluid balance on the pharmacokinetics of extended infusion meropenem in critically ill patients with sepsis. *Crit Care* 2021; 25:251
31. Zembles TN, Schortemeyer R, Kuhn EM, et al: Extended infusion of beta-lactams is associated with improved outcomes in pediatric patients. *J Pediatr Pharmacol Ther* 2021; 26:187–193
32. Dhont E, Windels C, Snauwaert E, et al: Reliability of glomerular filtration rate estimating formulas compared to iohexol plasma clearance in critically ill children. *Eur J Pediatr* 2022; 181:3851–3866