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Use of Simulation Strategies to Predict Subtherapeutic Meropenem Exposure Caused by Augmented Renal Clearance in Critically Ill Pediatric Patients With Sepsis

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OBJECTIVES The objectives of this study were to 1) define extent and potential clinical impact of increased or decreased renal elimination of meropenem in children with sepsis, based on analysis of renal function during the first 2 days of PICU stay; and 2) estimate the risk of subtherapeutic meropenem exposure attributable to increased renal clearance.

METHODS This retrospective study evaluated patients with a diagnosis of sepsis, receiving meropenem from the PICU at Rady Children's Hospital San Diego from 2015–2017. Meropenem exposure was estimated by using FDA-approved doses (20 and 40 mg/kg/dose) on day 1 and day 2 of PICU stay, based on a population pharmacokinetic (PK) model. For this population with sepsis, we assessed time-above-minimum inhibitory concentration (T>MIC) for pathogen MICs.

RESULTS Meropenem treatment was documented in 105 episodes of sepsis with a 48% rate of pathogen detection. By day 2, increased eGFR (>120 mL/min/1.73 m^2) was documented in 49% of patients, with 17% meeting criteria for augmented renal clearance ([ARC] >160 mL/min/1.73 m^2) and 10%, for decreased function. Simulations documented that 80% of PICU patients with ARC did not achieve therapeutic meropenem exposure for *Pseudomonas aeruginosa* with a MIC of 2, using standard doses to achieve a pharmacodynamic goal of 80% T>MIC.

CONCLUSIONS Approximately 3 of every 20 children with sepsis exhibited ARC during the first 48 hours of PICU stay. Simulations documented an increased risk for subtherapeutic meropenem exposure, suggesting that higher meropenem doses may be required to achieve adequate antibiotic exposure early in the PICU course.

ABBREVIATIONS ARC, augmented renal clearance; CNS, central nervous system; CrCL, creatinine clearance; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; ICU, intensive care unit; MIC, minimum inhibitory concentration; PICU, pediatric intensive care unit; PK, pharmacokinetic; pRIFLE, pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (renal injury assessment score); PTA, probability of target attainment; SCr, serum creatinine; SIRS, systemic inflammatory response syndrome; TDM, therapeutic drug monitoring; T>MIC, time-above–minimum inhibitory concentration

KEYWORDS augmented renal clearance; critically ill; meropenem; Monte Carlo simulation; pediatrics; pediatric intensive care unit; pharmacokinetics

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Introduction

Patients admitted to an ICU with infections causing the clinical syndromes of severe sepsis and septic shock are known to be at high risk for complications from both the infection itself as well as a dysregulated host systemic inflammatory response.[1,2] The prevalence of pediatric severe sepsis in the United States, based on a review of the Pediatric Health Information System database, has been documented to represent 7.7% of all pediatric hospitalizations, with a mortality rate of 14.4% in these children; a mean global pediatric case fatality rate of 19.3% was cited from a recent review of the published literature in the developed world.[3–5]

It has been demonstrated for both adults and children with sepsis, that delayed or inappropriate and ineffective empiric antibiotic therapy is linked to increased morbidity and mortality.[6–10] Of children admitted to the hospital with severe sepsis who die, 35% of deaths occur during the first 3 days of hospitalization, and

49% occur within 7 days of admission, suggesting that infection/inflammation may not come under control and be reversed quickly with antibiotic therapy and maximal ICU support, raising the question of adequate early antibiotic exposure.[11]

For adults, the concept of more rapid renal clearance of certain antibiotics through renal elimination in those with sepsis, described as augmented renal clearance (ARC), is now accepted as a poorly understood but reproducible phenomenon.[12–16] Hypermetabolic states that accompany sepsis may be responsible for increased renal blood flow and therefore increased filtration/secretion of beta-lactam antibiotics, but the renal mechanisms of ARC are not well defined. Recently, we demonstrated that a subset of children admitted to 2 PICUs, treated with either vancomycin or an aminoglycoside (gentamicin or tobramycin), were documented to have ARC as assessed by drug clearance, providing additional evidence for the concept that standard dosing of renally eliminated antibiotics in children in the PICU setting may result in inadequate, subtherapeutic blood and tissue site exposure.[17,18] From these analyses, 12% of those who were treated with vancomycin demonstrated ARC, while 19% of those receiving aminoglycosides demonstrated ARC. However, the population of children evaluated for ARC in these PICUs, receiving antibiotic therapy, was not focused on those with sepsis and shock, suggesting that rates of pediatric ARC may actually be substantially higher in the most critically ill. Other pediatric studies of ARC have reported incidences ranging from 16% to 80%.[19–21] For some commonly used renally eliminated antibiotics with significant toxicity, such as by vancomycin and gentamicin, therapeutic drug monitoring (TDM) is routinely performed to allow for dose adjustment. However, for beta-lactam antibiotics (penicillin, cephalosporins, and carbapenems), TDM is not widely available to ensure appropriate antibiotic exposure for children with sepsis and septic shock, potentially exposing children to subtherapeutic concentrations during the most critical 48 to 72 hours of hospitalization. A study by Cies et al[22] has suggested that beta-lactam TDM may increase microbiologic and clinical response in PICU patients compared to those without active TDM.

In children admitted to our tertiary care pediatric ICU with sepsis or septic shock requiring fluid resuscitation (with or without vasopressors) and treated with meropenem, we aimed to define the extent of increased or decreased renal drug elimination during the first 2 days of PICU stay, and estimate the risk of subtherapeutic antibiotic exposure by using both a goal for normal hosts (40% time-above-minimum inhibitory concentration [T>MIC]), as well as a higher goal such as 80% T>MIC (or 100% T>MIC as suggested for adults),[23] which may be required for those who are critically ill or immunocompromised.[24,25]

Materials and Methods

Patients. This study protocol was reviewed and approved by the institutional review boards of the University of California at San Diego (UCSD) and Rady's Children Hospital San Diego (RCHSD). Using an Epic Clarity Report, we identified all patients admitted to the PICU at RCHSD between May 1, 2015, and April 30, 2017, with a diagnosis of sepsis that was inclusive of sepsis syndrome, severe sepsis, septic shock, or systemic inflammatory response syndrome (SIRS), identified from ICD-10 diagnostic coding and billing.[25,26] Standard protocols for fluid resuscitation were used for children, based on pediatric considerations provided in the Surviving Sepsis Campaign.[26] Children with chronic renal failure or children previously receiving meropenem for reasons other than sepsis at the time of their admission to the PICU with sepsis were excluded as we aimed to examine meropenem exposure during the first 48 hours of sepsis.

Individual charts for all study participants were reviewed. Data extracted from patient charts included age at admission, primary admission diagnosis, comorbidities, and laboratory evaluations during the first 48 hours of hospitalization, including bacterial cultures, antimicrobial therapy, and mortality. Data were recorded from the first day of PICU admission or the first day of treatment with meropenem for suspected sepsis, if this date differed from PICU admission date. Serum creatinine (SCr) concentrations were recorded on the first and second days of PICU hospitalization and estimated glomerular filtration rate (eGFR) was calculated by using the Bedside Schwartz formula.[27] Serum creatinine concentrations in all patients were quantified at RCHSD with a method that has been previously described.[28] Cystatin C determinations are not routinely performed to assess renal function at RCHSD. For determination of baseline eGFR for the first and second 24-hour period in the PICU, the lowest value of SCr in each period was used. Serum C-reactive protein (CRP) measurements were obtained daily, per standard of care (normal CRP ≤ 1.0 mg/L). Subjects were assigned to the appropriate pRIFLE (pediatric renal injury assessment score) strata (Risk, Injury or, Failure) if they fulfilled SCr (pRIFLE$_{Cr}$) criterion, as defined by Akcan-Arikan et al,[29] comparing day 1 values with day 2 (Table S).

Monte Carlo Simulation/Probability of Target Attainment (PTA). To assess the impact of varying degrees of renal function on meropenem exposure, we performed exploratory simulations by using the Pmetrics package version 1.5.0 (Laboratory of Applied Pharmacokinetics, University of Southern California Keck School of Medicine, Los Angeles, CA) for R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).[30] A previously published covariate-adjusted 2-compartmental pharmacokinetic (PK) model for meropenem in children was used.[31] Monte Carlo

sampling from the mean and variance values from the published PK model generated a novel population of 1000 parameter sets for each simulated regimen at the various clearance values evaluated. Simulations were performed for the standard, non-meningitis dose of meropenem (20 mg/kg/dose every 8 hours) for empiric therapy of pediatric sepsis as well as for the FDA-approved dose for meningitis (40 mg/kg/dose every 8 hours), assuming dose-proportional, linear kinetics and infusion time of 30 minutes. A free, non-protein bound fraction of 100% (fu = 1) was used for calculations given the low serum protein binding of meropenem of approximately 2%, and a total body weight of 40 kg (as a representative patient with ARC from our PICU population) was used for all simulations. Exposure was simulated for pediatric patients with a range of eGFRs to reflect decreased, normal, and increased renal function. Because the model did not explicitly include eGFR as a covariate, we equated meropenem clearance to eGFR in our simulations and assumed total meropenem clearance is reflective of renal function. Decreased renal function/meropenem clearance was defined as an eGFR = 60 mL/min/1.73 m^2 (representative of ≤60 mL/min/1.73 m^2); normal renal function/meropenem clearance as an eGFR = 100 mL/min/1.73 m^2 (representative of 61–120 mL/min/1.73 m^2); increased renal function/meropenem clearance as an eGFR = 140 mL/min/1.73 m^2 (representative of 121–160 mL/min/1.73 m^2); and augmented renal function as an eGFR = 160 mL/min/1.73 m^2 (representative of 161–200 mL/min/1.73 m^2). These ranges for clearance were based on both the distribution for eGFR (via Bedside Schwartz) in our present patient population and defined eGFR values for augmented renal function.[17–21] We also simulated a population with the same approximate eGFR distribution as documented for our overall PICU pediatric patient population on day 2: 10% with eGFR of 60 mL/min/1.73 m^2 (representative of ≤60 mL/min/1.73 m^2); 40% with eGFR of 100 mL/min/1.73 m^2 (representative of 61–120 mL/min/1.73 m^2); 30% with eGFR of 130 mL/min/1.73 m^2 (representative of 121–160 mL/min/1.73 m^2); and 20% with eGFR of 160 mL/min/1.73 m^2 (representative of ≥161 mL/min/1.73 m^2). From all simulated populations, plasma concentrations were generated every half-hour for the first 24 hours of therapy, and the fraction of the dosing interval (from 0–24 hours) in which the plasma concentrations exceeded the minimum inhibitory concentration (T>MIC), was calculated by using doubling-dilution MICs between 0.25 and 32 mg/L.

We assessed the percentage who would achieve 40% T>MIC, a target that is considered bactericidal based on animal model data and retrospective review of adult clinical data for most carbapenem/pathogen pairs in non-septic patients.[32] We also assessed a more stringent requirement of 80% T>MIC for patients with sepsis (based on meta-analysis data that suggest decreased mortality for those receiving prolonged or continuous infusions for another beta-lactam antibiotic, piperacillin-tazobactam, to achieve 100% T>MIC).[33] The relatively conservative requirement of 80% T>MIC was chosen to reflect those for whom a greater antibiotic effect is likely to be needed, compared with normal immune hosts. Our goal for target attainment for antibiotic exposure was 90% of all simulated profiles, achieving either 40% T>MIC for normal hosts, or 80% T>MIC for those with immune compromise/critical illness.

Statistical Analysis. Patient demographics were summarized for all patients and stratified by day. For univariate analyses, continuous variables were compared by using the Wilcoxon matched-pairs signed rank test. All statistical analysis was performed with Intercooled Stata, version 14.2 (StataCorp LP, College Station, TX).

Results

Patients. The RCHSD Critical Care service admitted 4305 infants and children between May 1, 2015, and April 30, 2017, an average of 179 admissions per month over 2 years. Two hundred nine episodes of sepsis were identified (5% of PICU admissions), with 105 episodes of sepsis treated with meropenem at the time of PICU admission. The median age of the patients was 10.1 years (IQR, 4.4–15.2 years). When stratified by age group, most of the patients were between 12 and 18 years of age (n = 43). Fifty-four percent (n = 57) of the patients were male. The median weight was 27.2 kg (IQR, 15.4–50.2 kg). Just over half of the patients admitted had negative bacterial cultures (52%), but in 48% (51 episodes of sepsis), a culture was positive from the blood or a tissue site. In evaluating underlying comorbid conditions in sepsis, 80% of children with the diagnosis of sepsis were also documented to have an associated comorbid condition. The most prevalent comorbid condition in 31% was immune compromise (due to chemotherapy and malignancy, stem cell or solid organ transplant, congenital immune deficiency, or other immunocompromising therapies such as anti-inflammatory cytokine/chemokine monoclonal antibodies). Of those with immune compromise for whom data were available (99/105 from total patients, 27/32 from immune compromise) on the absolute neutrophil count at the time of PICU admission, 56% (15/27) had an absolute neutrophil count of ≤1500 cells/μL. Additional patient demographics and comorbid conditions can be found in Table 1A and B, respectively.

Microbiology. Of the 51 episodes of sepsis with positive cultures, 25 (49%) were considered primary bacteremia, with no clinically detectable focus of infection. Of those with positive cultures, 80% were documented to have Gram-negative pathogens, primarily enteric bacilli and *Pseudomonas aeruginosa*, while 20% of those with positive cultures had Gram-positive pathogens, 80% of which were *Staphylococcus aureus* organisms (Table 2). Although primary bacteremia represented the most common documented infection, the next most com-

Table 1A. Patient Characteristics, Demographics (N = 105*)

Variable	Baseline	Day 2	p value
Age, median (IQR), yr	10 (4.4–15.2)	–	–
0 to <2, n (%), yr	17 (16)	–	–
2 to <12, n (%), yr	45 (43)	–	–
12 to 18, n (%), yr	43 (41)	–	–
Weight, median (IQR), kg	27.2 (15.4–50.2)	–	–
Height, median (IQR), cm	127 (98–156.5)		
Male, n (%)	57 (54)	–	–
CRP, median (IQR), mg/L	5.7 (2.4–22.3) n = 103	20.25 (6.175–31.53) n = 90	<0.001
CrCL, median (IQR), mL/min/1.73 m^{2}†,‡	98.54 (52.59–142.3)*	119.9 (79.29–148.3) n = 101	<0.001

CrCL, creatinine clearance; CRP, C-reactive protein
* N = 105 unless otherwise stated given missing variables.
† Data for all patients were unable to be obtained.
‡ Estimated by Bedside Schwartz formula.

Table 1B. Patient Primary Comorbid Conditions (N = 105)

Category	% of Patients
Malignancy/transplant/immune deficiency	31
Previously normal before ICU admission	20
Primary CNS disorder/dysfunction	20
Gastrointestinal disorders including anatomic anomalies	8
Genetic disorder	8
Hematologic disorder	4
Congenital heart disease	4
Chronic kidney disease	3
Endocrine disorder	1
Pulmonary disease	1

mon source of culture-positive infection was the lower respiratory tract in 20% of children; less common were urinary tract focus (8%) and cellulitis/wound infection (8%) (Table 2).

Vasoactive Agent Therapy. All children received fluid resuscitation, but among the study population, 60% (n = 64) received at least 1 vasopressor agent within the first 24 hours of treatment for sepsis. Of those receiving vasopressors, most received either 1 or 2 drugs (32% and 23% of all children with sepsis, respectively); 5% received 3 or 4 drugs. The most commonly used vasopressors were epinephrine in 52% (n = 33) of all children receiving vasopressors, norepinephrine in 50% (n = 32), and dopamine in 41% (n = 26) (data not shown).

Renal Function. On the first day of PICU hospitalization, 36% had eGFR greater than normal (>120 mL/min/1.73 m^2), increasing to 49% during the second PICU day, and 14% met criteria for ARC (defined as eGFR >160 mL/min/1.73 m^2) on the first PICU day, rising to 17% on the second PICU day (Figure 1A and B). In contrast, 27% of children had eGFR ≤ 60 mL/min/1.73 m^2 during the first hospital day, but this percentage dropped to only 10% by the second PICU day. We assessed renal function with the pRIFLE score for all meropenem-treated children with sepsis in the PICU on day 1 and day 2 of treatment: 10% were documented to be at risk of Acute Kidney Injury (defined as eGFR decreased by 25%) and another 10% had renal failure (defined as eGFR decreased by 75%) noted at 48 hours after admission to the PICU.

Monte Carlo Simulations. The effect of various renal function as defined by decreased, normal, increased, and ARC (as defined in Materials and Methods) was assessed by using the standard meropenem dose of 20 mg/kg for a range of MICs from 0.5 to 32 mg/L (Figure 2A). For those children with ARC, adequate plasma exposure is achieved for 40% T>MIC for pathogens with a MIC up to 2 mg/L (FDA-defined breakpoint for

Table 2. Primary Site of Infection and Predominant Pathogens in Children Diagnosed With Sepsis and Treated With Meropenem as Part of Their Antibiotic Treatment Regimen

Category*	n (%) (N = 105)	Predominant Pathogen†
Culture-negative sepsis	55 (52)	N/A
Bacteremia	26 (24)	*Escherichia coli* (n = 6); *Klebsiella pneumoniae* (n = 4); *Enterobacter cloacae* (n = 2); *Pseudomonas aeruginosa* (n = 2); *Citrobacter freundii* (n = 2); *Staphylococcus aureus* (n = 2)
Respiratory tract infection	10 (9)	*Methicillin-resistant Staphylococcus aureus* (n = 3); *Pseudomonas aeruginosa* (n = 2)
Urosepsis	3 (3)	*Klebsiella pneumoniae* (n = 2)
Cellulitis/wound infection	4 (4)	*Staphylococcus aureus* (n = 3); Group A beta *Streptococcus* (n = 2)

N/A, not applicable

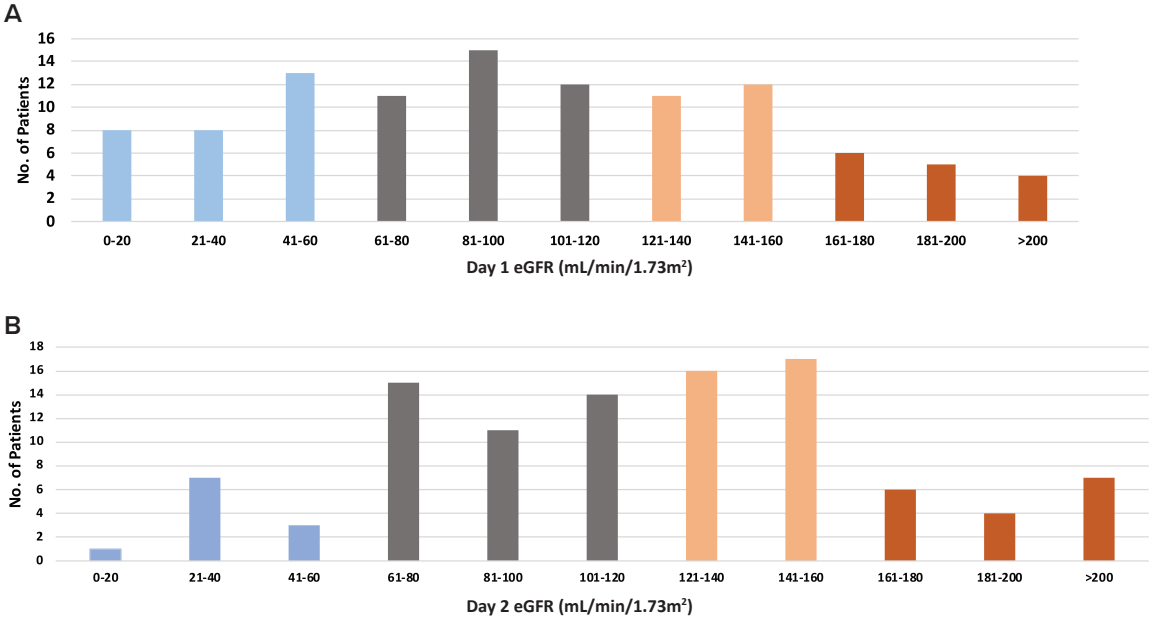
* Two children each with osteoarticular infection, meningitis (n = 4); 1 child with each of the following: necrotizing fasciitis, endocarditis, gastrointestinal infection (n = 3).

† Only pathogens isolated in ≥2 patients are reported.

"susceptible" for *P aeruginosa*). For those with critical illness or immune compromise, the proportion of children who achieved the required antibiotic exposure ("target attainment") of 80% T>MIC, by degree of renal function as assessed by eGFR category and by pathogen MIC (MIC ranges, 0.25–32 mg/L), is shown in Figure 2B. For these children, receiving standard meropenem dosing (20 mg/kg), it is not possible to achieve adequate plasma exposure for those with ARC or increased renal function (eGFR, 120–160 mL/min/1.73 m^2) even for a pathogen with a MIC of 0.5 mg/L. For those with normal renal function, adequate plasma exposure is achieved for pathogens with a MIC of 1 mg/L but not for those with MICs of ≥2 mg/L.

When the dose of meropenem is increased 2-fold to 40 mg/kg/dose every 8 hours (the approved dose for meningitis), the likelihood of achieving an effective concentration in plasma is improved (Figure 3A and B). For immune-competent children, even in the presence of ARC, children should still be able to achieve an adequate 40% T>MIC exposure for pathogens with a MIC of 4 mg/L, but not at MICs ≥8 mg/L (Figure 3A). For those with critical illness or immune compromise, considering a target of 80% T>MIC shown in Figure 3B, adequate plasma exposure can be expected with ARC only when MICs are 0.25 mg/L or less. For those with

Figure 1. Estimated glomerular filtration rate: (A) day 1 and (B) day 2*.

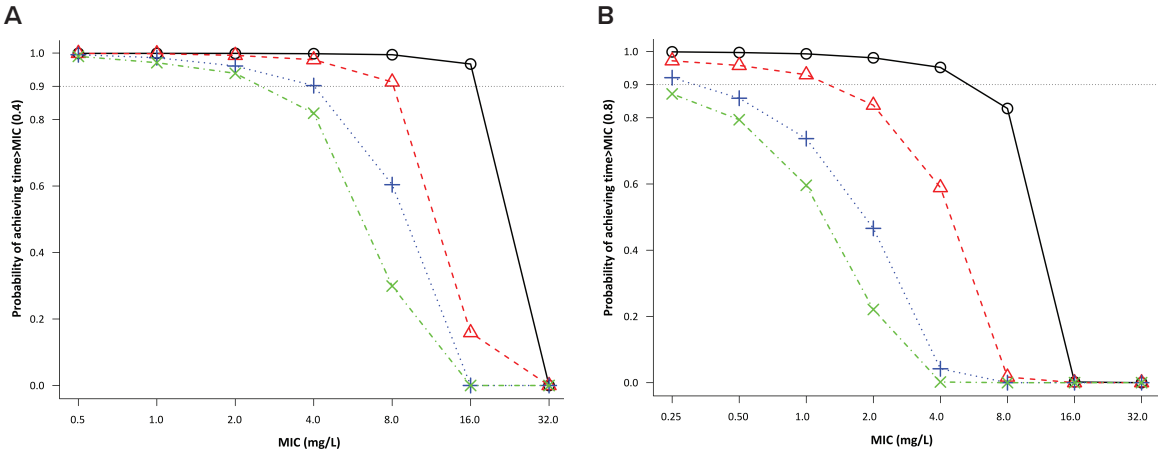


eGFR, estimated glomerular filtration rate

* Calculated by using the Bedside Schwartz Equation[27]

Decreased (≤60); Normal (>60 to 120); Increased (>120 to 160); ARC (>160)

Figure 2. Probability of target attainment in plasma defined by 40% T>MIC (A) and 80% T>MIC (B), by clearance* and by pathogen MIC, using the FDA-approved non-meningitis dosing of meropenem at 20 mg/kg/dose†.



ARC, augmented renal clearance; CL, clearance; eGFR, estimated glomerular filtration rate; MIC, minimum inhibitory concentration; PTA, probability of target attainment;T>MIC, time-above-minimum inhibitory concentration

* Decreased renal function/meropenem clearance: eGFR = 60 mL/min/1.73 m², normal renal function/meropenem clearance: eGFR = 100 mL/min/1.73 m², increased renal function/meropenem clearance: eGFR = 140 mL/min/1.73 m², ARC: eGFR = 160 mL/min/1.73 m².

† Meropenem is FDA approved in children ≥3 months of age for treatment of complicated skin and skin structure infections and complicated intra-abdominal infections at 20 mg/kg/dose every 8 hours.

–○– Decreased; –△– Normal; –+– Increased; –×– ARC

increased clearance, but not ARC, adequate exposure is achieved for pathogens with a MIC of 0.5 mg/L. Those with normal renal function should receive an appropriate exposure for pathogens with MICs of ≤2 mg/L. Patients with decreased renal function will have adequate exposure up to a MIC of 8 mg/L.

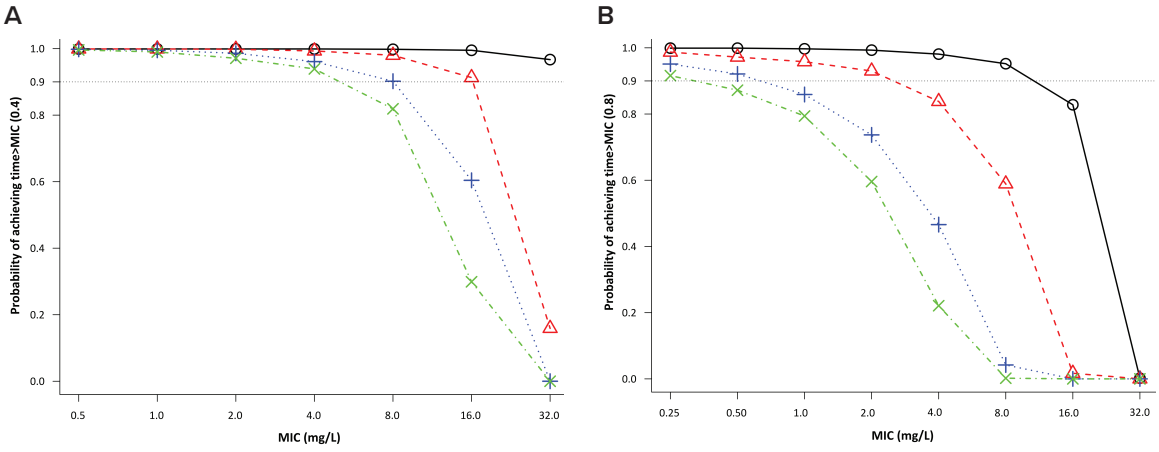
Using the weighted creatinine clearance (CrCL) distribution (estimated by eGFR) from the entire RCHSD PICU patient population (Figure 1), 20 mg/kg/dose and 40 mg/kg/dose every 8 hours achieved the target of 40% T>MIC (for otherwise healthy patients) for pathogens with MICs of ≤4 mg/L and MICs of 8 mg/L, respectively, in 90% of children (Figure 4A). When the target was increased to 80% T>MIC for those with critical illness or immune compromise, the probability of target attainment goal was only achieved for relatively low MICs of ≤0.5 mg/L, and ≤1 mg/L, respectively, in 90% of our population (Figure 4B).

Discussion

Sepsis (including SIRS, sepsis, severe sepsis, and septic shock) requiring fluid resuscitation represented 5% of all PICU admissions in our institution, similar to other reports (Global Epidemiology of Pediatric Severe Sepsis: The Sepsis Prevalence, Outcomes, and Therapies Study[34] (Weiss et al. 2017, SPROUT study), with approximately half of these diagnoses associated with documented positive cultures of blood or a tissue site. While 40% of our evaluated population responded to initial fluid challenges, 60% required 1 or more vasopressors to stabilize blood pressure, providing a marker of the severity of illness in our population. CRP concentrations also reflected the severity of illness in our PICU population, with both elevated concentrations at the time of diagnosis and significant increases on day 2. In evaluating the presence of underlying comorbid conditions that we documented in our population with sepsis, only 20% of children were documented to be previously healthy, recognizing that those with associated comorbidities may require a greater antibiotic exposure to contain and eradicate infection.

Substantial numbers of children admitted to the PICU had increased renal function and ARC (defined as eGFR of 120–160 and >160 mL/min/1.73 m³, respectively) during the first 2 days of hospitalization, highlighting the potential of subtherapeutic dosing of antibiotics eliminated by renal mechanisms. As the exact renal mechanisms of ARC are still unknown, the most common hypothesis is that patients with ARC develop glomerular hyperfiltration due to increased cardiac output parallell to increaed renal blood flow (i.e., clearance).[14,35] This hyperfiltration can be caused by the manifestations of SIRS occuring during sepsis, which causes decreased systemic vascular resistance and increased cardiac output. Animal models have already shown that both renal blood flow and cardiac output increase in early sepsis.[34] If hyperfiltration is the cause of ARC in critically ill children, there is potential for ineffetive antmicrobial therapy at a crucial time in treatment. As others have also noted the occurrence of ARC in criti-

Figure 3. Probability of target attainment in plasma defined by 40% T>MIC (A) and 80% T>MIC (B), by clearance* and by pathogen minimum inhibitory concentration, using the FDA-approved meningitis dosing of meropenem at 40 mg/kg/dose†.



ARC, augmented renal clearance; CL, clearance; eGFR, estimated glomerular filtration rate; MIC, minimum inhibitory concentration; PTA, probability of target attainment;T>MIC, time-above-minimum inhibitory concentration

* Decreased renal function/meropenem clearance: eGFR = 60 mL/min/1.73 m^2, normal renal function/meropenem clearance: eGFR = 100 mL/min/1.73 m^2, increased renal function/meropenem clearance: eGFR = 140 mL/min/1.73 m^2, ARC: eGFR = 160 mL/min/1.73 m^2.

† Meropenem is FDA approved in children ≥3 months of age for treatment of complicated skin and skin structure infections and complicated intra-abdominal infections at4 mg/kg/dose every 8 hours.

–O– Decreased; –△– Normal; –+– Increased; –×– ARC

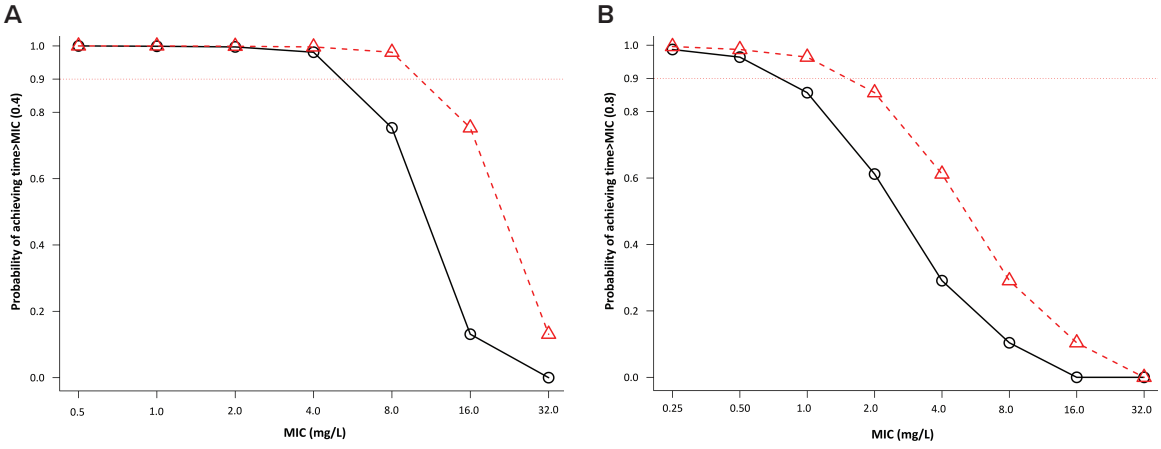
cally ill children,[20,36,37] standard FDA-approved pediatric doses of antibiotics that were determined to be safe and effective in children who were not critically ill, and have been routinely used to treat children with sepsis, may no longer be appropriate.[38]

For children with ARC requiring only 40% T>MIC for meropenem to optimize clinical and microbiologic outcomes, antibiotic exposure may only be adequate for infections caused by Gram-negative pathogens with a MIC of ≤8 mg/L, even at the "meningitis" dose of 40 mg/kg/dose every 8 hours. Although most non-carbapenemase Enterobactericeae are susceptible to meropenem at a MIC of <8 mg/L, many clinical isolates of *P aeruginosa*, particularly nosocomial isolates, express resistance at this level.[32] Our model calculations used traditional assumptions that achieving an exposure in 90% of children was adequate, although for this PICU population there is justification to increase the proportion of critically ill children who should attain the desired antibiotic exposure to 95% or 98%. Our model calculations assumed that 80% T>MIC would be appropriate for those with sepsis and those not capable of a normal immune response; others believe that even greater exposure at 100% T>MIC is required.[7,27]

To provide adequate antibiotic exposure for 90% of immunocompromised patients (potentially including all critically ill children) admitted to our PICU with ARC, requiring 80% T>MIC, only pathogens with a MIC of 0.25 mg/L or less would be adequately covered when using standard-dose therapy. Of great concern, even if the meningitis dose of 40 mg/kg were used, just over 10% of children with ARC would still not receive an adequate exposure for pathogens with a MIC as low as 0.5 mg/L, suggesting that a dose higher than 40 mg/kg would be needed early in the PICU course to create the same exposure for these children as that demonstrated originally to be safe and effective in children with non-sepsis infections in 1996.

For children with sepsis admitted to our PICU and assessed as a single population "weighted" by renal function (i.e., using the weighted CrCL distibtuion from the patient population), immunocompetent children (requiring 40% T>MIC) received adequate therapy at standard dosages for pathogens with MICs up to 4 mg/L. For those with immune compromise, only 30% of those receiving standard dosage and 60% of those receiving high dosage would have an adequate exposure for pathogens having a MIC of 4 mg/L. Given the critical nature of the antibiotic exposure defined by PK/PD as related to the MIC of the pathogen, susceptibilities of meropenem against Gram-negative pathogens in each PICU should be assessed in order to predict the adequacy of antibiotic exposure for each unit. Other dosing strategies that include prolonged or continuous infusion may also achieve the increase in exposure that provides the required increase in the T>MIC needed to improve outcomes.[33,39] Further studies comparing these dosing strategies in pediatric patients are warranted.

Figure 4. Probability of target attainment in plasma defined by 20 and 40 mg/kg/dose for 40% T>MIC (A), 20 and 40 mg/kg/dose for 80% T>MIC (B) by creatinine clearance distribution* from patient population†.



CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; MIC, minimum inhibitory concentration; PTA, probability of target attainment; T>MIC, time-above-minimum inhibitory concentration

* Estimated GFR distribution from current pediatric patient population: 10% with eGFR = 60 mL/min/1.73 m^2; 40% with eGFR = 100 mL/min/1.73 m^2; 30% with eGFR = 130 mL/min/1.73 m^2; and 20% with eGFR = 160 mL/min/1.73 m^2.

–O– 20 mg/kg/dose; –△– 40 mg/kg/dose

Although our data demonstrate that approximately 27% of patients admitted to the PICU with sepsis have evidence of poor renal function on day 1 (Figure 2A), likely to be caused by the significantly decreased renal perfusion that often accompanies septic shock (prerenal azotemia), almost 2/3 of those children resolved their poor renal function as assessed by eGFR (as defined by SCr) by day 2. Comorbid, preexisting renal dysfunction in these children may be partly responsible for decreased function. Those with decreased renal function will have meropenem plasma concentrations that are elevated, as compared with those with normal renal function. In general, beta-lactam antibiotics are well tolerated, even with plasma concentrations that are greater than those documented in the original registration trials.[38]

Our analyses modeled plasma concentrations as based on meropenem population PK and renal function. It is difficult to extrapolate effectiveness of these plasma concentrations to various other sites of infection, as the concentration of meropenem at the actual site of infection would be the most appropriate to assess antibiotic exposure and subsequent microbiologic/clinical outcome for pathogens with a specific meropenem MIC. Tissue site-specific meropenem exposure can vary considerably for each potential infection site, as documented for the concentrations in urine, which are much higher than plasma, and concentrations in cerebrospinal fluid, which are much lower. We did not assess the target attainment at each tissue site in our PK model.

Limitations to our study exist. First, this was a retrospective study subject to biases, incomplete data collection, and risks of misclassification. Second, only patients with sepsis (ages 0–18 years) who received meropenem were evaluated, not all children with sepsis. Further, as our patient population data were collected from children in the PICU, not the neonatal intensive care unit, and our youngest patient was 3 months of age, we wish to limit our suggestions to infants and children, not neonates. Although the population PK model we used was derived from all ages, including neonates, caution is advised on extrapolating our suggestions to neonates, given the potential for developmental immature renal function.

We chose this subset of patients for analysis because meropenem is one of the many renally eliminated empiric antibiotics used in the PICU that are likely to result in subtherapeutic plasma concentrations when used in standard doses in children with ARC. In contrast to the ready access to assessment of plasma concentrations of gentamicin and vancomycin, most pediatric tertiary care centers do not have access to timely plasma meropenem concentration assays. Third, SCr, our marker for renal function (eGFR), may not be accurate in children with unstable renal function.[27] Fluid overload is a common complication in children with sepsis. Under such circumstances, a dilutional factor should be considered in the calculation of SCr to avoid overestimation of eGFR, but this requires an instantaneous estimation of fluid overload from accurate weight records, which were not available for our study population.[40] More accurate assessments of renal function in children with sepsis that reflect rapid changes in renal function dur-

ing the first days of PICU hospitalization are needed to better determine drug exposure for all classes of drugs that are primarily eliminated by renal mechanisms; studies to assess these daily changes are ongoing. Fourth, the simulations performed were based on a previously published meropenem population PK model that may not be representative pharmacokinetically (i.e., exposure/predicted concentrations) of the PICU population in this study. Last, as stated in Materials and Methods, we assumed the total meropenem drug clearance is reflective of renal clearance when the unchanged drug is shown to be anywhere from 70% to 80% excreted renally. As such, meropenem drug clearance also involves some degree of hydrolysis and this should be taken into account when interpreting our simulations. However, since ARC is defined solely as increased renal clearance, we wanted to show the effects of ARC on the pharmacodynamic outcomes for meropenem.

Conclusion

Our data suggest that work is urgently needed to optimize dosing strategies for children with sepsis and septic shock, receiving renally eliminated antibiotics in the PICU, as a large proportion of these children exhibit increased and augmented renal function during the first 48 hours of treatment, placing them at risk for subtherapeutic antibiotic exposure during a critical period of uncontrolled infection.

ARTICLE INFORMATION

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