β-lactam Therapeutic Drug Management in the PICU*

Jeffrey J. Cies, PharmD, MPH, BCPS-AQ ID, BCPPS, FCCP[1–3]; Wayne S. Moore II, PharmD[1]; Adela Enache, MS[4]; Arun Chopra, MD[1,5,6]

Objectives: To determine whether contemporary β-lactam anti-infective dosing recommendations in critically ill children achieve concentrations associated with maximal anti-infective activity. The secondary objective was to describe the microbiological and clinical outcomes associated with β-lactam therapeutic drug management.

Design: Electronic Medical Record Review.

Setting: A 189-bed, freestanding children's tertiary care teaching hospital in Philadelphia, PA.

Patients: Patients admitted to the PICU from September 1, 2014, to May 31, 2017, with sepsis and those receiving extracorporal therapy with either extracorporeal membrane oxygenation or continuous renal replacement therapy that had routine β-lactam therapeutic drug management.

Interventions: None.

Measurements and Main Results: Eighty-two patients were in the total cohort and 23 patients in the infected cohort accounting for 248 samples for therapeutic drug management analysis. The median age was 1 year (range, 4 d to 18 yr) with a mean weight of 19.7 ± 22.3 kg (range, 2.7–116 kg). Twenty-three patients (28%) had growth of an identified pathogen from a normally sterile site. Seventy-eight of 82 patients (95%) had subtherapeutic anti-infective concentrations and did not attain the primary pharmacodynamic endpoint. All patients in the infected cohort achieved a microbiological response, and 22 of 23 (95.7%) had a positive clinical response.

Conclusions: Overall, 95% of patients had subtherapeutic anti-infective concentrations and did not achieve the requisite pharmacodynamic exposure with current pediatric dosing recommendations. All patients achieved a microbiological response, and 95.7% achieved clinical response with active β-lactam therapeutic drug management. These data suggest β-lactam therapeutic drug management is a potentially valuable intervention to optimize anti-infective pharmacokinetics and the pharmacodynamic exposure. Further, these data also suggest the need for additional research in specific pediatric populations and assessing clinical outcomes associated with β-lactam therapeutic drug management in a larger cohort of pediatric patients. (*Crit Care Med* 2018; 46:272–279)

Key Words: antibiotic; neonatal; pediatric; pharmacodynamics; pharmacokinetics

Pediatric sepsis and septic shock affect approximately 30% of children admitted to the PICU. A diagnosis of pediatric sepsis and septic shock has mortality rate of at least 25%, in addition to an increasing prevalence, and a median per patient hospital cost of $65,624 (interquartile range, $27,300–$169,624) (1–3). From birth through childhood, many developmental changes naturally occur which can have a profound impact on drug exposure and the subsequent response (4). Compared with adults, children have a greater number of functioning nephrons and, therefore, have greater clearance via glomerular filtration (5). As a result, children between the ages of 6 months and 6 years usually have a renal elimination of drugs that is greater than or equal to 2 greater than their adult counterparts 18 years old and older (6, 7). Further, pathophysiologic changes commonly occur during critical illness and can dramatically affect a drugs' pharmacokinetics and pharmacodynamics (8–10). Critically ill patients can have increases in their volume of distribution (Vd) due to fluid balance strategies and intravascular perfusion changes; such increases in Vd will reduce the peak concentrations achieved after an infusion and the subsequent trough concentrations. Furthermore, critically ill patients often have sepsis-induced decreases or increases in cardiac output, which

***See also p. 335.**

[1]The Center for Pediatric Pharmacotherapy LLC, Pottstown, PA.

[2]St. Christopher's Hospital for Children, Philadelphia, PA.

[3]Drexel University College of Medicine, Philadelphia, PA.

[4]Atlantic Diagnostic Laboratories, Bensalem, PA.

[5]NYU Langone Medical Center, New York, NY.

[6]NYU School of Medicine, New York, NY.

Presented, in part, as an oral presentation at the 46th Society of Critical Care Medicine Annual Congress, Honolulu, HI, February 2017.

Dr. Cies is a consultant for Atlantic Diagnostic Laboratories and has received funding from Allergan (grant funding), Merck (grant funding), Thermo Fisher Scientific (honorarium and grant funding), and Atlantic Diagnostic Laboratories (consulting). The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: jeffrey.cies@gmail.com

DOI: 10.1097/CCM.0000000000002817

can result in hypo- or hyperperfusion of the kidneys and alterations in drug clearance (10). Although the concept of augmented renal clearance has been rather well described in the adult ICU population, there is minimal documentation of its effect in the PICU (9).

In the setting of sepsis and septic shock, early and appropriate anti-infective therapy has been documented to reduce morbidity and mortality in adults and children (11, 12). It has also been suggested that outcomes related to infection could be improved in critically ill patients by optimizing the pharmacokinetics and pharmacodynamic target attainment of anti-infectives (13, 14). The concept of therapeutic drug management (TDM) for anti-infectives such as vancomycin and aminoglycosides is reasonably well described (15, 16), and there is mounting evidence for this practice to include β-lactam anti-infectives in critically ill adult patients (10, 11, 13, 14, 17) considering β-lactams are the most commonly prescribed class of anti-infectives. From a pharmacokinetic and pharmacodynamic perspective, β-lactams display time dependent anti-infective activity; therefore, the time that the free (unbound) drug concentration is maintained above the minimum inhibitory concentration (MIC) is associated with bacterial killing ($fT > MIC$) (18). In vivo animal investigations have delineated a $fT > MIC$ between 40% and 70% of the dosing interval is required for optimal efficacy (19) and retrospective clinical evaluations have suggested larger drug exposures are required, with β-lactam concentrations up to 4–6 times the MIC for the entire dosing interval (20, 21). However, the practice of β-lactam TDM has not been described in pediatrics, even though the concern of not achieving therapeutic concentrations and exposures is more paramount.

The primary objective of this study was to determine whether contemporary β-lactam anti-infective dosing recommendations in critically ill children achieve concentrations associated with maximal anti-infective activity. The secondary objective was to describe the microbiological and clinical outcomes associated with β-lactam TDM.

MATERIALS AND METHODS

Patient Population and Study Design

Patients with sepsis and those receiving extracorporal therapy with either extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT) that are prescribed β-lactams routinely undergo active TDM, meaning serum concentrations are obtained and dosing regimens adjusted in an attempt to meet certain pharmacokinetic/pharmacodynamic targets. Therefore, data were prospectively collected in consecutive patients requiring β-lactams in our 33-bed PICU and pediatric cardiac ICU from a single freestanding children's hospital (St. Christopher's Hospital for Children, Philadelphia, PA). From September 1, 2014, until June 5, 2017, data from all patients that had β-lactam TDM were eligible for inclusion. Patients were evaluated regardless of anti-infective indication but were expected to remain on their β-lactam for at least 48 hours. β-lactams reviewed for TDM were ampicillin, cefazolin, cefepime, cefotaxime, ceftaroline, doripenem, meropenem, and piperacillin/tazobactam. Patients admitted to the PICU who received a β-lactam for empiric or definitive therapy with an expected duration of greater than or equal to 48 hours and meeting pediatric sepsis criteria (22) or receiving extracorporeal therapy were also eligible for inclusion. Patients who had cystic fibrosis, acute, or chronic renal failure with an estimated creatinine clearance less than 60 mL/min/1.73 m^2 based on the modified Schwartz (23) equation and not receiving CRRT were excluded from this analysis. This study protocol was approved by the Drexel University College of Medicine Institutional Review Board, and the need for informed consent was waived in view of the retrospective nature of the data analysis of the prospectively compiled database.

Blood Sampling and Pharmacodynamic Analysis

A minimum of two blood samples per child were collected and the samples were obtained, when possible, after a dose that permitted collection of each sample in succession as dictated by clinical care by clinical care staff. For standard 30–60-minute infusion regimens, the first blood sample was typically obtained within 20 minutes from the end of the infusion but could be obtained up to 2 hours from the end of the infusion, and the subsequent blood sample(s) were obtained a minimum of 1 hour after the first sample collection. For prolonged (i.e., 3–4 hr infusions) infusion regimens, blood samples were obtained at the end of an infusion and again 1 hour post infusion. For 24-hour continuous infusion regimens, blood samples were obtained a minimum of 8 hours from the start of the infusion. Typically, after a patient is started on therapy, two to three samples are obtained after a given dose (i.e., during the same dosing interval between doses), and patient-specific pharmacokinetic variables are calculated. Doses are then adjusted and often levels are rechecked in order to determine/ensure the target levels were achieved after the respective dosing adjustment. While the minimum volume of blood required for concentration determination is 0.5 mL, most commonly 1–2 mLs per sample was obtained. Depending on the age and size of the patient, 0.5 mL per sample was collected in certain instances. Blood samples for the determination of β-lactam drug concentrations were subsequently sent to the laboratory for immediate processing and concentration determination. Samples were collected in regular red top tubes. Upon receipt in the laboratory, samples were centrifuged within 30 minutes of collection at 3,000 rpm for at least 15 minutes to separate the plasma. Separated plasma was then transferred to a cryo vial and stored at –80°C. Couriers then transported the specimens on dry ice from the hospital laboratory to the reference laboratory. Upon receipt at the reference laboratory, samples were thawed and analyzed. Once the concentration analysis was completed, results were reported to the hospital laboratory and hospital personnel via phone and fax. Samples were analyzed within 24 hours of being collected with the majority of results reported within 8–12 hours of collection allowing for most dosing regimens to be adjusted within 18–24 hours of

initiating therapy. During the study period, β-lactam concentrations were determined by validated liquid chromatography tandem mass spectrometry (U.S. Food and Drug Administration guidelines: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic Laboratories (Bensalem, PA).

The pharmacodynamic target for β-lactams is an unbound concentration above the MIC of the infecting organism for 40–70% of the dosing interval (ƒT > MIC) (19–21). For convenience, a ƒT > 4–6 × MIC for 40% of the dosing interval was chosen as the primary pharmacodynamic target for analysis based on previous work (13). Additionally, a ƒT > 4–6 × MIC for at least 40% of the dosing interval is the target most commonly used internally at our institution in this patient population when designing and adjusting dosing regimens. An upper limit of ƒT = 6 × MIC was chosen to allow for a determination of supratherapeutic levels. Additional pharmacodynamic targets analyzed were 1) ƒT greater than MIC for 40% of the dosing interval and 2) a trough concentration greater than MIC, as previously described (13). A noncompartmental pharmacokinetic analysis was conducted on each patients' individual drug concentrations to determine pharmacokinetic variables including elimination rate constant, Vd, half-life, and clearance. Equations used included: 1) elimination rate constant (k_e) = (ln [C1/C2])/time difference, 2) half-life = 0.693/ k_e, 3) Vd = dose/initial concentration, 4) Clearance = k_e × Vd, and 5) Dose (mg/kg/hr) = concentration at steady state (μg/mL) × clearance, where clearance = k_e (/hr) × Vd (L/kg). If an organism was obtained, the MIC of the infecting organism was used for the pharmacodynamic calculation. If an organism was not obtained, the highest Clinical and Laboratory Standards Institute (CLSI) MIC breakpoint was used for each drug for the pharmacodynamic calculation. To calculate free drug concentrations, the protein binding estimate documented in the drugs' respective package insert was used (24–31). Three pediatric drug dosing references (32–34) were then used to determine if "standard, published" dosing recommendations would have resulted in the desired pharmacodynamic targets. Demographic, clinical, and microbiological data were collected in addition to clinical outcome data. Descriptive statistics were used to describe patient drug concentrations, with data presented as the mean ± SD or median and range; additionally, percentages were used to describe the data, when appropriate.

Microbiological and Clinical Response

Patients eligible for evaluation of the secondary objectives for microbiological and clinical response needed to have a proven bacterial infection documented by growth of an identified pathogen from a normally sterile site in addition to having β-lactam TDM with drug concentration results for interpretation and analysis. Microbiological response was defined as sterilization of the site from which the documented pathogen was obtained. A positive clinical response was defined as completion of the antimicrobial treatment course without escalation (i.e., addition of a drug with a broader spectrum of activity) or addition of an antimicrobial agent. Patients were also assessed for reinitiation of antimicrobials within 48 hours of the primary course ending and reinfection within 28 days. A negative clinical outcome was defined as any clinical outcome other than a positive clinical outcome and/or death within 28 days from initiation of the primary antimicrobial course. Additionally, 28-day all-cause mortality from initial receipt of a β-lactam was evaluated in both cohorts.

RESULTS

A total of 82 patients, 41 females (50%) and 41 males (50%), met inclusion criteria for this study accounting for 248 samples for TDM and represent the total cohort (TC). A median of three samples for TDM was collected per patient (range two to eight samples). The median age was 1 year (range, 4 d to 18 yr) with a mean weight of 19.7 ± 22.3 kg (range, 2.7–116 kg). Of the 82 patients, 23 (28%) had growth of an identified pathogen from a normally sterile site and compose the infected cohort (IC). Patient demographics for the TC and IC are listed in **Table 1**. Of the 82 patient TC, 16 patients received extracorporeal therapy with 14 (17%) receiving ECMO and two (2.4%) receiving CRRT as compared to five patients receiving extracorporeal therapy with three of 23 patients (13%) and two of 23 (8.7%) patients in the IC receiving ECMO and CRRT, respectively.

Regarding the primary outcome, 78 of 82 patients (95%) had subtherapeutic anti-infective concentrations and did not attain the primary pharmacodynamic endpoint of

TABLE 1. Patient Demographic Data for the 82-Patient Total Cohort and the 23-Patient Infected Cohort Groups

Variables	Total Cohort	Infected Cohort
No. of patients	82	23
Mean age (yr), SD	4.1, 5.3	3, 4.4
Median age (yr), range	1, 4 d to 18 yr	1, 10 d to 16 yr
Mean weight (kg), SD	19.7, 22.3	19, 23.5
Median weight (kg), range	10, 2.7–116	13, 2.7–116
Male patients, *n* (%)	41 (50)	12 (52)
Female patients, *n* (%)	41 (50)	11 (48)
Total no. of levels	248	74
Median no. of levels, range	3, 2–8	3, 2–8
Median Pediatric RISk of Mortality score, range	17, 2–39	21, 5–32
Number of extracorporeal membrane oxygenation patients, *n* (%)	14 (17)	3 (13)
Number of continuous renal replacement therapy patients, *n* (%)	2 (2.4)	2 (8.7)
No. of deaths, *n* (%)	10 (12.2)	1 (4.3)

TABLE 2. β-Lactam Agents for Which Therapeutic Drug Management was Conducted for the 82-Patient Total Cohort and the 23-Patient Infected Cohort Groups

	Total Cohort				Infected Cohort			
Anti-Infectives	*n* (%)	Number With Nonstandard Dose to Start, *n* (%)	Number With Dosing Change, *n* (%)	Number Receiving Initial Combination Therapy, *n* (%)	*n* (%)	Number With Nonstandard Dose to Start, *n* (%)	Number With Dosing Change, *n* (%)	Number Receiving Definitive Combination Therapy, *n* (%)
Ampicillin	4 (4.9)	0	4 (100)	4 (100)	–	–	–	–
Cefazolin	3 (3.7)	0	3 (100)	3 (100)	–	–	–	–
Cefepime	24 (29.3)	21 (87.5)	12 (50)	24 (100)	2 (8.7)	2 (100)	2 (100)	1 (50)
Cefotaxime	13 (15.9)	2 (15.4)	11 (84.6)	13 (100)	–	–	–	–
Ceftaroline	7 (8.5)	7 (100)	1 (14.3)	7 (100)	6 (26.1)	6 (100)	1(16.7)	6 (100)
Doripenem	1 (1.2)	1 (100)	1 (100)	1 (100)	–	–	–	–
Piperacillin/tazobactam	14 (17.1)	0	14 (100)	14 (100)	9 (39.1)	0	9 (100)	3 (33.3)
Meropenem	16 (19.5)	16 (100)	10 (62.5)	16 (100)	6 (26.1)	6 (100)	6 (100)	3 (50)

ƒT > 4–6 × MIC for 40% of the dosing interval with current published pediatric β-lactam dosing recommendations. Of the 78 patients with subtherapeutic anti-infective concentrations, five (6.4%) had supratherapeutic concentrations (i.e., levels exceeding 4–6 × MIC) and 73 (93.6%) had subtherapeutic concentrations. Four of 82 patients (5%) had anti-infective concentrations within the pharmacodynamic target range of ƒT > 4–6 × MIC for 40% of the dosing interval current published pediatric β-lactam dosing recommendations. Therefore, 95% of the patients in the TC did not meet the primary pharmacodynamic target using current published pediatric β-lactam dosing recommendations. In the IC, no patient met the primary pharmacodynamic endpoint of ƒT > 4–6 × MIC for 40% of the dosing interval with current published pediatric β-lactam dosing recommendations. The five patients with supratherapeutic concentrations had reductions in their dosing regimens. For the 73 patients with subtherapeutic concentrations, all of them had adjustments made to their dosing regimens to meet the pharmacodynamic endpoint of ƒT > 4–6 × MIC for 40% of the dosing interval or were initially started on a nonstandard dose (i.e., cefepime 50 mg/kg/dose IV every 6 hr, meropenem 40 mg/kg/dose IV every 6 hr, or ceftaroline 15 mg/kg/dose IV every 6 hr) and subsequently met the pharmacodynamic endpoint of ƒT > 4–6 × MIC for 40% of the dosing interval. All initial dosing adjustments were made within 48 hours of β-lactam initiation, with the majority, 50 of 56 (89.3%) being made within 18–24 hours after β-lactam initiation. All changes made to the dosing regimens were done in regards to the interval. For the patients with supratherapeutic concentrations, the interval was lengthened (i.e., e.g., every 8 hr to every 12 hr), and for the patients with subtherapeutic concentrations the intervals were shortened or infusion times were prolonged (i.e., change from a 30-min infusion to a 3-hr infusion or conversion to a continuous infusion). The anti-infectives subject to TDM for the TC and IC are presented in **Table 2**, and the complete pharmacodynamic analyses for the anti-infectives are presented in **Table 3**.

Tables 4 and **5** display the sites from which the pathogens were isolated and the categorization of infecting pathogens and their respective MIC for the β-lactam used during treatment, respectively. In the IC, 100% of patients achieved a microbiological response, and 22 of 23 (95.7%) had a positive clinical response with an overall mortality rate of 4.3% in the IC compared with a 12.2% mortality rate (10/82 patients) in the TC. The IC patient who did not achieve clinical response was a neonate on ECMO withdrawn from technological support as a result of an ECMO sequelae, intracranial hemorrhage. The patient did achieve microbiological response after eradication of *Pseudomonas aeruginosa* from the blood for a period of 5 days prior to withdrawal.

DISCUSSION

In this investigation, we observed a high percentage, 95%, of critically ill children did not achieve the a priori primary pharmacodynamic endpoint with current published pediatric β-lactam dosing recommendations. This is a significant number and promotes the need to 1) describe innovative, individualized approaches to anti-infective dosing that can enhance the achievement of therapeutic concentrations and 2) supports the demand for clinical investigations that evaluate whether achieving target concentrations with β-lactam dose optimization results in improved patient outcomes.

Initially, new anti-infectives are evaluated in vitro and tested in animal models for toxicity and efficacy. Afterward, dosing regimens are derived based on these in vitro or animal in vivo pharmacokinetic/pharmacodynamic studies (13). The next phase of drug development involves evaluating the

TABLE 3. Pharmacodynamic Analysis for the 82-Patient Total Cohort and the 23-Patient Infected Cohort Evaluating ƒt > 4–6 × Minimum Inhibitory Concentration for 40% of the Dosing Interval, ƒt > Minimum Inhibitory Concentration for 40% of the Dosing Interval, and Trough Concentrations Above the Minimum Inhibitory Concentration

		Total Cohort				Infected Cohort		
Groups	*n*	4-6 × Time > MIC, *n* (%)	Time > MIC, *n* (%)	Trough > MIC, *n* (%)	*n*	4-6 × Time > MIC, *n* (%)	Time > MIC, *n* (%)	Trough > MIC, *n* (%)
All	82	9 (10.9)	31 (37.8)	23 (28)	23	0	4 (17.4)	0
Extracorporeal membrane oxygenation	14	4 (28.5)	6 (42.9)	5 (35.7)	3	0	0	0
Continuous renal replacement therapy	2	0	0	0	2	0	0	0

dosing regimens in healthy human volunteers for tolerability and then clinical efficacy studies in a noncritically ill population. Eventually, these dosing regimens are then used in the ICU population which can result in suboptimal outcomes (13). Similarly, pediatric pharmacokinetic studies are done on a smaller scale as compared to their adult counterparts, if they are done at all. Critically ill adult patients have been shown to exhibit altered Vd for anti-infectives and commonly need larger initial doses to rapidly achieve therapeutic concentrations (13, 35). Further complicating the situation is the proportion of patients displaying augmented renal clearance necessitating even higher doses and/or more frequent dosing intervals to overcome increased drug elimination to allow for therapeutic concentrations and exposures (9, 36). Dosing regimens are reliant on an equation, simplified here, where dose = desired concentration × Vd × clearance value. As can be seen with a simple manipulation of the above equation, if the Vd or clearance changes, the desired target concentration will not be obtained following administration of a "standard dose." For example, if a "standard" cefepime dose is given and the clearance estimate is doubled, the actual concentration will be reduced in comparison to the target concentration. This relationship is rarely used when selecting and designing dosing regimens in the PICU (32–34). Frequently, the site of infection and ex vivo treatment devices (i.e., ECMO and CRRT) are rarely considered when designing drug dosing regimens, which is a paradigm that must be amended as ongoing anti-infective pharmacokinetic and pharmacodynamic research is conducted considering 95% of the TC needed a dosage modification based on current published pediatric β-lactam dosing recommendations (32–34).

TABLE 4. The Sites of Pathogen Isolation for the 23-Patient Infected Cohort Group

Site of Pathogen Isolation	*n*	Percent
Blood	14	46.7
Bone	5	16.7
Urine	3	10
Peritoneal fluid	2	6.7
Cerebrospinal fluid	2	6.7
Wound	2	6.7
Bronchoalveolar lavage fluid	1	3.3
Pericardial fluid	1	3.3

Underdosing and low exposures have been linked to the development of anti-infective resistance which was first discovered with fluoroquinolones and more recently shown to develop with β-lactams (37, 38). Low exposures have also been linked to morbidity and mortality, and active management of anti-infective concentrations and exposures has been associated with improved outcomes (14). Depending on the specific organism and disease state, infection and sepsis mortality estimates in the pediatric population are greater than or equal to 25% (1–3). The mortality rate in our TC was 12.2% and in the IC was 4.3% suggesting there may also be morbidity and mortality reduction in the pediatric population as a result of active management of anti-infective concentrations and exposures. Further, our inability to determine an infecting organism and its' MIC could have had an impact on the mortality rate difference between the TC and IC. Although the highest CLSI MIC breakpoint was used for the pharmacodynamic calculations, the dosing adjustments made based on that presumed MIC may, in fact, not have been optimal. The organism may have had an MIC in the intermediate or resistant range of susceptibilities to the β-lactam the patient was being treated with. Additionally, there are other factors independent of the anti-infective and dosing change(s) that could have contributed to mortality such as host factors that were not measured or accounted for with this investigation. Most of the literature describing pharmacokinetic alterations with ECMO and CRRT are with older equipment and devices. This is another area of research and literature that must be revised to incorporate contemporary devices and treatment modalities considering infection rates and mortality estimates increase when extracorporeal therapies are used (39, 40). Even though the number of patients in the IC that received extracorporeal therapies was small, they also had a high rate

TABLE 5. Infecting Pathogens and Anti-Infective Minimum Inhibitory Distribution

Organisms	Total No. of Isolates	Drug	MIC (μg/mL)	No. of Isolates With MIC
Pseudomonas aeruginosa	4	Piperacillin/tazobactam	16	4
	3	Meropenem	0.25	2
		Meropenem	8	1
	1	Cefepime	2	1
Methicillin resistant *Staphylococcus aureus*	6	Ceftaroline	0.38	1
		Ceftaroline	0.5	4
		Ceftaroline	1	1
Escherichia coli	3	Piperacillin/tazobactam	4	3
	1	Meropenem	0.25	1
Acinetobacter species	2	Piperacillin/tazobactam	8	1
		Piperacillin/tazobactam	16	1
	1	Meropenem	1	1
Klebsiella pneumoniae	1	Piperacillin/tazobactam	4	1
	1	Meropenem	2	1
Enterobacter species	1	Cefepime	1	1
Serratia species	1	Meropenem	0.25	1

MIC = minimum inhibitory concentration.

of microbiological response, clinical response, and lower rate of mortality as compared to the literature, again suggesting benefit of active management of anti-infective concentrations and exposures. In general, β-lactam antimicrobials are generally well tolerated (41). In an adult ICU population, Beumier et al (42) found a correlation between elevated β-lactam trough concentrations and neurologic deterioration in patients receiving meropenem and piperacillin, but not in patients receiving cefepime. Not surprisingly, the patients with diminished renal function were most likely to have elevated β-lactam trough concentrations. While the majority of patients in the TC had subtherapeutic concentrations, 6.4% of the TC had supratherapeutic concentrations for which dosing adjustments were made. Monitoring of renal function is essential in any ICU population and dosage adjustments should be made based on renal function and drug levels, when available, to minimize the possibility of adverse events occurring from elevated anti-infective concentrations.

This investigation has several limitations. First, these data are from a single center and may not be generalizable to other pediatric institutions. Second, pathogens were only isolated in 28% of the population which prevented evaluation of microbiological and clinical response in the entire cohort. Third, as is common in pediatric sepsis and septic shock, all of our patients were started on anti-infective regimens with at least two drugs. Without identifying an organism, it is not possible to determine the impact of each particular anti-infective for each patient in the TC. TDM routinely occurs in our institution for vancomycin targeting troughs of 15–20 μg/mL and for gentamicin/tobramycin targeting peaks of at least 8–12 μg/mL and troughs less than 2 μg/mL, depending on the clinical scenario. Therefore, we could not accurately determine the impact of combination therapy in the TC and IC. However, active TDM with vancomycin and aminoglycosides is commonplace across most pediatric institutions. Therefore, the morbidity and mortality estimates to date have included patients undergoing TDM with vancomycin and aminoglycosides. Fourth, for the pharmacodynamic analysis, when an organism was not obtained, the CLSI MIC breakpoint was used and may not reflect the MIC of the actual infecting pathogen(s), if the underlying cause of disease was in fact bacterial in origin. Fifth, a single pharmacodynamic target was used for the primary outcome analysis. There is still debate regarding what the clinical pharmacodynamic target(s) should be and it is unlikely that a single pharmacodynamic target would be appropriate for all drugs, all pathogens, and all indications. Sixth, the blood concentrations used for the pharmacodynamic analysis serve as a surrogate marker and do not necessarily reflect the anti-infective concentration at the site of infection. However, blood samples are more readily available and analyzable and are likely to correlate with the concentrations at the site of infection. Seventh, drug concentration measurements were performed as total drug and not unbound drug concentrations and in critically ill patients, the assumption of static protein binding values may not be accurate when interpreting total drug

concentrations. Finally, we employed an opportunistic sampling strategy to minimize accessing central catheters, bundle specimens, and inflict minimal pain on the child contributing blood samples when they could not be obtained via a central line. While convenient for the child, sampling times as well as the sparse number of samples collected for each child may not have been ideal to fully characterize the pharmacokinetics of each antimicrobial in each individual child. We believe, however, that the use of individual variable estimates is capable of providing a reasonable pharmacokinetic profile for each patient and mimics the sampling strategy commonly employed in clinical practice for aminoglycosides and vancomycin.

CONCLUSION

Overall, 95% of patients had subtherapeutic anti-infective concentrations and did not achieve the requisite pharmacodynamic exposure with current published pediatric β-lactam dosing recommendations. All patients with a documented pathogen achieved a microbiological response, and 95.7% achieved clinical response with active β-lactam TDM. These data suggest β-lactam TDM is a potentially valuable intervention to optimize anti-infective pharmacokinetics and the pharmacodynamic exposure. Further, these data also suggest the need for additional research in specific pediatric populations and assessing clinical outcomes associated with β-lactam TDM in a larger cohort of pediatric patients.

REFERENCES

1. Balamuth F, Weiss SL, Neuman MI, et al: Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med* 2014; 15: 798–805
2. Tamma PD, Turnbull AE, Milstone AM, et al: Does the piperacillin minimum inhibitory concentration for *Pseudomonas aeruginosa* influence clinical outcomes of children with pseudomonal bacteremia? *Clin Infect Dis* 2012; 55:799–806
3. Weiss SL, Fitzgerald JC, Pappachan J, et al; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med* 2015; 191:1147–1157
4. Kearns GL, Abdel-Rahman SM, Alander SW, et al: Developmental pharmacology–drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349:1157–1167
5. Rowe JW, Andres R, Tobin JD, et al: The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. *J Gerontol* 1976; 31:155–163
6. Bartelink IH, Rademaker CM, Schobben AF, et al: Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet* 2006; 45:1077–1097
7. Chien S, Wells TG, Blumer JL, et al: Levofloxacin pharmacokinetics in children. *J Clin Pharmacol* 2005; 45:153–160
8. Carcillo JA, Doughty L, Kofos D, et al: Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. *Intensive Care Med* 2003; 29:980–984
9. Cies JJ, Shankar V, Schlichting C, et al: Population pharmacokinetics of piperacillin/tazobactam in critically ill young children. *Pediatr Infect Dis J* 2014; 33:168–173
10. Roberts JA, Lipman J: Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 2009; 37: 840–851; quiz 859
11. MacArthur RD, Miller M, Albertson T, et al: Adequacy of early empiric antibiotic treatment and survival in severe sepsis: Experience from the MONARCS trial. *Clin Infect Dis* 2004; 38:284–288
12. Weiss SL, Fitzgerald JC, Balamuth F, et al: Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med* 2014; 42:2409–2417
13. Roberts JA, Paul SK, Akova M, et al; DALI Study: DALI: Defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis* 2014; 58:1072–1083
14. Scaglione F, Esposito S, Leone S, et al: Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. *Eur Respir J* 2009; 34:394–400
15. Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009; 66:82–98
16. Moore RD, Smith CR, Lietman PS: The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J Infect Dis* 1984; 149:443–448
17. Roberts JA, De Waele JJ, Dimopoulos G, et al: DALI: Defining antibiotic levels in intensive care unit patients: A multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. *BMC Infect Dis* 2012; 12:152
18. Craig WA: Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; 26:1–10; quiz 11
19. Drusano GL: Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug.' *Nat Rev Microbiol* 2004; 2:289–300
20. Ariano RE, Nyhlén A, Donnelly JP, et al: Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. *Ann Pharmacother* 2005; 39:32–38
21. Turnidge JD: The pharmacodynamics of beta-lactams. *Clin Infect Dis* 1998; 27:10–22
22. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41:580–637
23. Schwartz GJ, Muñoz A, Schneider MF, et al: New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20:629–637
24. Ampicillin [package insert]. New Brunswick, NJ, Claris Lifesciences INB, 2010
25. Cefazolin [package insert]. Verona, Italy, GlaxoSmithKline, 2008
26. Cefepime [package insert]. Princeton, NJ, Sandoz IP, 2011
27. Cefotaxime [package insert]. Frankfurt, Germany, Aventis Pharma, 2001
28. Ceftaroline [package insert]. Teramo, Italy, Forest Pharmaceutical IT, 2015
29. Doripenem [package insert]. Raritan, NJ, Shionogi IFP, 2016
30. Meropenem [package insert]. Wilmington, DE, AstraZeneca Pharmaceuticals LP, 2007
31. Piperacillin/tazobactam [package insert]. Lake Forest, IL, Fresenius Kabi USA LLZ, 2016
32. Lexi-Comp Online™. Macedonia, OH. Lexi-Comp. Available at: http://online.lexi.com. Accessed March 16, 2016
33. Pediatric & Neonatal Lexi-Drugs Online™. Macedonia, OH, Lexi-Comp. Available at: http://online.lexi.com. Accessed March 16, 2016
34. Thomson Micromedex Web site: Micromedex (Columbia Basin College Library ed.) [Electronic version].Greenwood Village, CO: Truven Health Analytics. Available at: http://www.micromedexsolutions.com/. Accessed March 16, 2016
35. Roberts JA, Taccone FS, Udy AA, et al: Vancomycin dosing in critically ill patients: Robust methods for improved continuous-infusion regimens. *Antimicrob Agents Chemother* 2011; 55:2704–2709
36. Udy AA, Baptista JP, Lim NL, et al: Augmented renal clearance in the ICU: Results of a multicenter observational study of renal function

in critically ill patients with normal plasma creatinine concentrations*. *Crit Care Med* 2014; 42:520–527

37. Stamey TA, Bragonje J: Resistance to nalidixic acid. A misconception due to underdosage. *JAMA* 1976; 236:1857–1860
38. Gugel J, Dos Santos Pereira A, Pignatari AC, et al: beta-Lactam MICs correlate poorly with mutant prevention concentrations for clinical isolates of Acinetobacter spp. and *Pseudomonas aeruginosa. Antimicrob Agents Chemother* 2006; 50:2276–2277
39. Aubron C, Cheng AC, Pilcher D, et al: Infections acquired by adults who receive extracorporeal membrane oxygenation: Risk factors and outcome. *Infect Control Hosp Epidemiol* 2013; 34:24–30
40. Bizzarro MJ, Conrad SA, Kaufman DA, et al; Extracorporeal Life Support Organization Task Force on Infections, Extracorporeal Membrane Oxygenation: Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. *Pediatr Crit Care Med* 2011; 12:277–281
41. Gonçalves-Pereira J, Póvoa P: Antibiotics in critically ill patients: A systematic review of the pharmacokinetics of β-lactams. *Crit Care* 2011; 15:R206
42. Beumier M, Casu GS, Hites M, et al: Elevated β-lactam concentrations associated with neurological deterioration in ICU septic patients. *Minerva Anestesiol* 2015; 81:497–506