Ceftaroline for Suspected or Confirmed Invasive Methicillin-Resistant *Staphylococcus aureus*: A Pharmacokinetic Case Series

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Objectives: To describe the ceftaroline pharmacokinetics in critically ill children treated for suspected or confirmed methicillin-resistant *Staphylococcus aureus* infections, including blood stream infection and describe the microbiological and clinical outcomes.

Design: Retrospective electronic medical record review.

Settings: Free-standing tertiary/quaternary pediatric children's hospital.

Patients: Critically ill children receiving ceftaroline monotherapy or combination therapy for suspected or confirmed methicillin-resistant *S. aureus* infections in the PICU.

Intervention: None.

Measurements and Main Results: Seven patients, three females (43%), and four males (57%), accounted for 33 ceftaroline samples for therapeutic drug management. A median of four samples for therapeutic drug management was collected per patient (range, 2–9 samples). The median age was 7 years (range, 1–13 yr) with a median weight of 25.5 kg (range, 12.6–40.1 kg). Six of seven patients (86%) demonstrated an increase in volume of distribution, five of seven patients (71%) demonstrated an increase in clearance, and 100% of patients demonstrated a shorter half-life estimate as compared with the package insert estimate. Six of seven patients (85.7%) had documented methicillin-resistant *S. aureus* growth from a normally sterile site with five of six (83.3%) having documented BSI, allowing six total patients to be evaluated for the secondary objective of microbiological and clinical response. All six patients achieved a positive microbiological and clinical response for a response rate of 100%.

Conclusions: These data suggest the pharmacokinetics of ceftaroline in PICU patients is different than healthy pediatric and adult patients, most notably a faster clearance and larger volume of distribution. A higher mg/kg dose and a more frequent dosing interval for ceftaroline may be needed in PICU patients to provide appropriate pharmacodynamic exposures. Larger pharmacokinetic, pharmacodynamic, and interventional treatment trials in the PICU population are warranted. (*Pediatr Crit Care Med* 2018; XX:00–00)

Key Words: ceftaroline; methicillin-resistant *Staphylococcus aureus*; pediatric; pharmacodynamic; pharmacokinetics

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major public health concern causing an estimated 80,000 invasive infections and 11,000 deaths annually in adults (1). Although mortality may not be as substantial in children as compared to adults, treatment failures with vancomycin and infection-related complications are frequent and estimated to occur in greater than or equal to 30% of infected children (2). Musculoskeletal infections, endovascular infections, and critical illness were all associated with an increased risk of treatment failure and each additional day of MRSA bacteremia in children was associated with a 50% increase in the odds of bacteremia-related complications (2). With the concern of vancomycin treatment failures and perception of increased nephrotoxicity, linezolid and daptomycin are often employed as second line agents for MRSA (3–11). Due to the nature of critical illness and immune suppression commonly seen in pediatric and adult ICU patients, the need

for a bactericidal drug against MRSA is vital. With an increasing frequency of extracorporeal life support including extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT), and infections relating to MRSA, research targeted toward optimizing dosing regimens and options to treat MRSA in adults and pediatrics is essential (12).

Ceftaroline is a novel cephalosporin initially approved in 2010 for the treatment of acute bacterial skin and skin structure infections (ABSSIs) and community-acquired bacterial pneumonia (CABP) in adults and children (13, 14). Ceftaroline fosamil is the prodrug of ceftaroline and has demonstrated excellent in vitro activity against common clinical isolates encountered in the pediatric population (15). Ceftaroline binds to penicillin-binding proteins (PBPs) and has a high affinity for PBP2a which confers activity to MRSA and PBP2x which is associated with penicillin resistant *Streptococcus pneumoniae* (13–15). While ceftaroline does not have a Food and Drug Administration (FDA) approved indication for invasive *S. aureus* infections, there is significant interest in exploring its utility for this indication considering ceftaroline is the only beta-lactam in the United States with activity against MRSA. In general, beta-lactams usually have favorable safety profiles and better clinical outcomes when compared with other classes of antiinfectives for methicillin-sensitive *S. aureus* (16). Therefore, the primary objective of this investigation was to describe the ceftaroline pharmacokinetics in critically ill children treated for suspected or confirmed MRSA infections, including blood stream infection (BSI). The secondary objective was to describe the microbiological and clinical outcomes associated with ceftaroline usage for suspected or confirmed MRSA infections.

MATERIALS AND METHODS

Patient Population and Study Design

Critically ill patients, including those receiving extracorporeal therapy with either ECMO or CRRT, that are prescribed β-lactams routinely undergo active therapeutic drug management (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 receiving ceftaroline in our 33-bed PICU from a single free-standing children's hospital (St. Christopher's Hospital for Children, Philadelphia, PA). This was an electronic medical record review of patients undergoing ceftaroline TDM for clinical management between January 1, 2016, and January 31, 2017. Patients admitted to the PICU who received ceftaroline for empiric or definitive monotherapy or combination therapy with an expected duration of greater than or equal to 48 hours were 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 using the modified Schwartz (17) 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. Demographic, clinical, and microbiological data were collected in addition to clinical outcome data.

Blood Sampling and Pharmacokinetic/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. 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. 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. A free time above the minimum inhibitory concentration for at least 40% of the dosing interval ($fT > 4–6 \times$ minimum inhibitory concentration [MIC]) is the target most commonly used internally at our institution in this patient population when designing and adjusting dosing regimens. Additionally, the site of infection is taken into account using penetration ratios into epithelial lining fluid (ELF) and cerebrospinal fluid, for example, when available to achieve the target exposures at the site of infection (18–20). While the minimum volume of blood required for concentration determination is 0.5 mL, most commonly 1–2 mLs per sample was obtained. Blood samples for ceftaroline determination 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 cryovial 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. Ceftaroline concentrations were determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS) (U.S. FDA guidelines: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf) at Atlantic Diagnostic Laboratories (Bensalem, PA). The LC-MS/MS method was accurate and precise at a linearity range of 0.1–60 mg/L with a correlation coefficient (r) of greater than or equal to 0.99 and an interday assay variability that was less than 4% across all control samples.

A noncompartmental pharmacokinetic analysis was conducted on each patients' individual drug concentrations to determine pharmacokinetic variables including elimination rate constant (k_e), volume of distribution (Vd), half-life ($t_{½}$),

TABLE 1. Patient Demographics and Ceftaroline Dosing Information for Seven PICU Patients Treated for Suspected or Confirmed Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

Patient	Age (yr)	Gender	Weight (kg)	Ceftaroline Dose (mg)	Ceftaroline Dose (mg/kg)	Interval (hr)
1	1	Male	12.6	200	15	6
2	10	Female	40.1	600	15	6
3	5	Male	22.2	300	13.5	6
4	5	Male	17.6	264	15	6
5	13	Female	38.6	600	15	6
6	7	Female	25.5	380	15	6
7	7	Male	27	405	15	6

and clearance. Equations used included 1) k_e = (ln [C1/C2])/time difference, where C = concentration, 2) $t_{½} = 0.693/k_e$, 3) Vd = dose/initial concentration (real or extrapolated peak), and (4) clearance = $k_e \times$ Vd. To calculate free drug concentrations, the protein binding estimate of 20% documented in the package insert (PI) was used (13).

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 ceftaroline 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 ceftaroline. Additionally, 28-day all-cause mortality from initial receipt of antiinfective(s) was evaluated.

RESULTS

A total of seven patients, three females (43%), and four males (57%) met inclusion criteria for this investigation and accounted for 33 ceftaroline samples for TDM. All patients met criteria for sepsis and no patients received any form of extracorporeal therapy (CRRT or ECMO) or were excluded based on a creatinine clearance estimate less than 60 mL/min/1.73 m^2 (21). A median of four samples for TDM was collected per patient (range, 2–9 samples). The median age was 7 years (range, 1–13 yr) with a median weight of 25.5 kg (range, 12.6–40.1 kg). Patient demographics and ceftaroline dosing information are presented in **Table 1**. The individual patient pharmacokinetic variable estimates are presented in **Table 2**. **Table 3** displays the pharmacokinetic variable estimates for pediatric patients published in the PI. Six of seven patients (86%) demonstrated an increase in Vd as compared with the PI estimate. Five of seven patients (71%) demonstrated an increase in clearance as compared with the PI estimate and 100% of patients demonstrated a shorter half-life estimate as compared with the PI estimate. All of the patients had adjustments made to their dosing regimens to meet the pharmacodynamic endpoint of at least 40% ƒT greater than 4–6 × MIC or were initially started on a nonstandard dose (non-FDA approved dose) based on internal pharmacokinetic monitoring data and experience and subsequently met the pharmacodynamic target. The ceftaroline concentration versus time data for each of the seven patients is presented in **Figure 1**.

The clinical and microbiological data for the seven patients are presented in **Table 4**. Six of seven patients (85.7%) had documented MRSA growth from a normally sterile site with five of six (83.3%) having documented BSI. The patient without documented growth of MRSA was initiated on ceftaroline monotherapy due to a history of MRSA infections and concern for acute kidney injury on presentation. Therefore, six of seven total patients (85.7%) could be evaluated for the secondary objective of microbiological and clinical response. Six of seven patients (85.7%) received greater than or equal to 72 of active MRSA combination therapy, including vancomycin with troughs in the range of 15–20 µg/mL, as noted in Table 4 and were deemed clinical failures due to persistent positive blood or other (i.e., cerebrospinal fluid [CSF], wound) cultures prior to the addition of ceftaroline. Of the six patients with documented MRSA growth, five of six (83.3%) had repeat cultures after adding ceftaroline and demonstrated sterilization of their blood from MRSA. Patient number 1 had two CSF cultures positive for MRSA prior to adding ceftaroline and did have a repeat CSF culture demonstrating no growth of MRSA after the addition of ceftaroline and negative blood cultures after adding ceftaroline as well. For the five patients with MRSA bacteremia, all patients achieved sterilization of their blood

TABLE 2. Individual Pharmacokinetic Variable Estimates for Ceftaroline for Seven PICU Patients Treated for Suspected or Confirmed Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

Patient	Regimen	Elimination Rate Constant	Half-life (hr)	Volume of Distribution (L/kg)	Clearance (mL/min/kg)
1	1	0.4	1.7	0.72	4.76
1	2	0.44	1.57	0.83	6.11
1	3	0.39	1.7	0.84	5.38
2	1	0.5	1.3	0.61	5.09
3	1	0.53	1.3	0.41	3.63
4	1	0.7	0.98	0.44	5.2
5	1	0.33	2	0.28	1.57
6	1	0.64	1.07	0.17	1.87
6	2	0.46	1.5	0.32	2.44
7	1	0.39	1.7	0.29	1.89
7	2	0.33	2	0.3	1.66

TABLE 3. Ceftaroline Pharmacokinetic Variable Estimates for Pediatric Patients[a]

Pharmacokinetic Variable	Values
Half-life (hr)	2.7
Volume of distribution (L/kg)	0.28
Clearance (mL/min/kg)	2.3

[a]Package insert data (13).

within 24 hours of adding ceftaroline. Patient number 5 did not have repeat cultures obtained from the surgical site abscess, so patient number 5 could not be included in the microbiological outcome; therefore, the microbiological response rate was 100%. Patient number 3 was admitted with respiratory failure and concern for pneumonia due to a history of MRSA and was initiated on ceftaroline. No invasive cultures such as a bronchoalveolar lavage or sputum culture were obtained and MRSA was not documented in this patient. As such, patient number 3 was not eligible for inclusion in the microbiological or clinical response outcome. Regarding the outcome of clinical response, all six patients achieved a positive clinical response as a result of adding ceftaroline to their regimen for a response rate of 100%.

DISCUSSION

Currently, ceftaroline is FDA approved in children greater than or equal to 2–18 years old for ABSSIs and CABP and has not been extensively evaluated for infections caused by MRSA. The FDA approved ceftaroline dose is 8–12 mg/kg/dose with an interval ranging from every 8 to 12 hours. Table 4 displays the pharmacokinetic variable estimates for pediatric patients published in the PI (13). These data suggest the pharmacokinetics of ceftaroline differ significantly in PICU patients with invasive MRSA infections as compared with the pharmacokinetic estimates reported in the PI from pediatric patients treated for ABSSIs and CABP excluding MRSA. These findings are not surprising considering pharmacokinetic alterations are known to occur in a dynamic setting such as the PICU (22–28). The current FDA approved dosing recommendations use the pharmacokinetic estimates from the PI where dose = desired concentration × clearance and the clearance= ke × Vd. Therefore, if either the clearance or Vd estimate changes, the desired target concentration will not be obtained following administration of a "standard dose" as can be demonstrated with simple manipulation of the above equation(s). If the clearance and Vd estimates both increase, as was seen in this cohort of seven patients, for example, then the dose would need to be increased and the dosing interval would most likely also have to be shortened (i.e., change from an every 8-hr to an every 6-hr administration). In this cohort, a ceftaroline dosing regimen of 15 mg/kg/dose every 6 hours was successful, when added to other MRSA active agents including vancomycin, in treating invasive infections due to MRSA and obtaining good clinical outcomes.

In addition to the growing public health concern with MRSA, there is a larger concern with multidrug resistant organisms (MDROs), in general, due to a lack of novel therapeutic antiinfective agents to treat the growing number of MDROs. Antimicrobial stewardship is one initiative targeted toward using antiinfectives more appropriately across different practice settings. Since 1997, the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (IDSA) have published guidelines to prevent antimicrobial resistance arguing that "… appropriate antimicrobial stewardship, that includes optimal antiinfective selection,

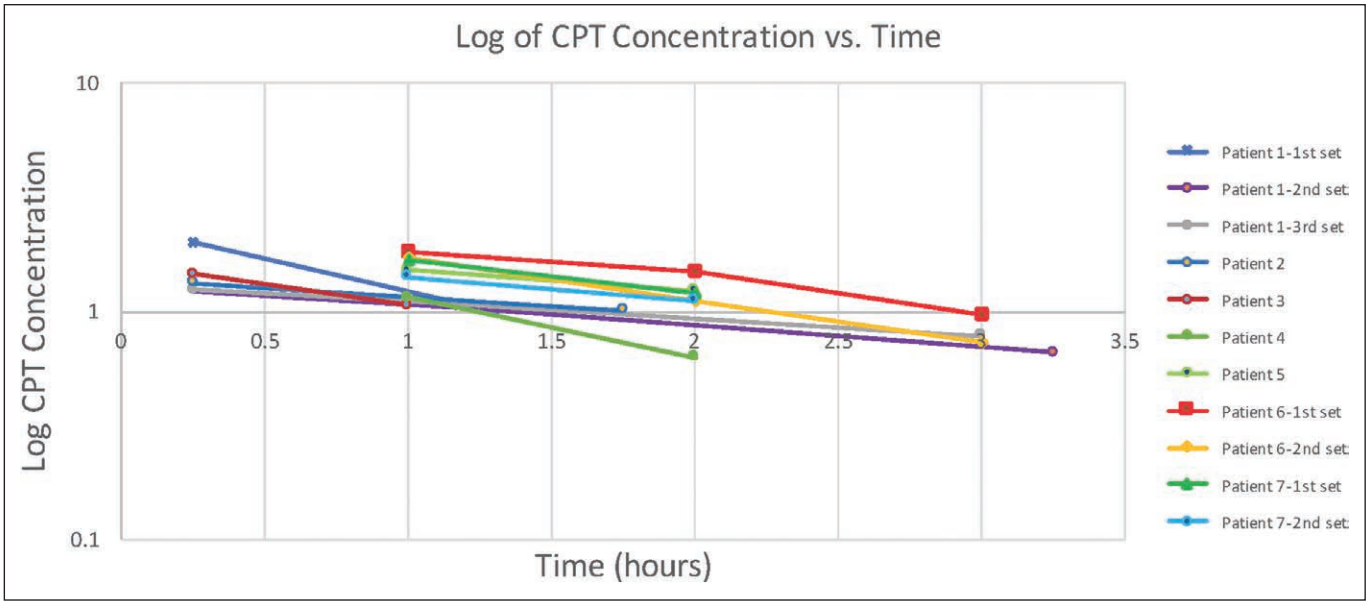

Figure 1. Log of ceftaroline (CPT) concentrations versus time for seven PICU patients treated with CPT for suspected or confirmed invasive methicillin-resistant *Staphylococcus aureus* infections.

TABLE 4. Clinical and Microbiological Data for Seven PICU Patients Treated With Ceftaroline for Suspected or Confirmed Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

Patient Number	Organism	Ceftaroline Minimum Inhibitory Concentration (μg/mL)	Infection Site	Days of (+) Cultures Before Ceftaroline Addition	Days to Sterile Culture	Drug Regimen Before Adding Ceftaroline	Drug Regimen After Adding Ceftaroline
1	MRSA	0.5	BSI, cerebrospinal fluid, pericardial fluid	9	1	Vancomycin/ rifampin/ gentamicin	Vancomycin/ rifampin/ gentamicin/ ceftaroline
2	MRSA	0.38	BSI, tibial bone culture	5	1	Vancomycin/ clindamycin/ gentamicin	Vancomycin/ clindamycin/ ceftaroline
3	NA	NA	Lung	NA	NA	Started on ceftaroline	NA
4	MRSA	1	BSI, ankle bone	5	1	Vancomycin/ clindamycin/ gentamicin	Vancomycin/ clindamycin/ ceftaroline
5	MRSA	0.5	Back wound (linezolid scapular abscess, surgical site, spinal rods)	7	NA	Vancomycin/ linezolid	Vancomycin/ ceftaroline
6	MRSA	0.5	BSI, pyomyositis, osteomyelitis	4	1	Vancomycin/ clindamycin/ gentamicin	Vancomycin/ clindamycin/ gentamicin/ ceftaroline
7	MRSA	0.5	BSI, osteomyelitis	3	1	Vancomycin/ clindamycin/ gentamicin	Vancomycin/ clindamycin/ ceftaroline

BSI = blood stream infection, MRSA = methicillin-resistant *Staphylococcus aureus*, NA = not applicable.

dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms." (29) One of the hallmarks of stewardship is identifying the optimal dose. To determine the optimal dose, additional research and investigations with newer antiinfectives, such as ceftaroline in a critically ill pediatric population, need to be conducted in order to ensure delivery of an optimal dose, reduction of resistance emergence, and superior clinical outcomes. For the first time, the Society of Critical Care Medicine in conjunction with IDSA recently recommended dosage optimization for patients with hospital acquired and ventilator-associated pneumonia in addition to patients with sepsis and septic shock (30, 31). The respective guidelines suggest dosing be determined using pharmacokinetic and pharmacodynamic data, rather than manufacturers' prescribing information and they place a high value on improving clinical outcomes by optimization of therapy. The guidelines state optimized dosing refers to the use of blood concentrations, extended, and/or continuous infusion modalities (30, 31).

The suggested pharmacodynamic target for ceftaroline is a free ceftaroline (*f*T) concentration above the MIC of the infecting organism for 25% of the dosing interval (*f*T > MIC) for gram-positive organisms (13). One challenge in identifying optimal doses and dosing regimens is determining if the pharmacodynamic target associated with success in animal models and relatively healthy volunteers is the same in populations such as the critically ill. For example, Ariano et al (32) demonstrated in adult patients with fever and neutropenia that an 80% *f*T greater than MIC for the dosing interval was the pharmacodynamic target predictive of efficacy for meropenem as opposed to the 40% *f*T greater than MIC suggested in the PI (33). Additionally, investigations in adult ICU patients receiving beta-lactams demonstrate improved outcomes as the pharmacodynamic %*f*T greater than MIC increases, which is logical considering the state of critical illness is known to make patients functionally immune suppressed such that they would need higher exposures to achieve optimal clinical outcomes (34). Tamma et al (35) evaluated the piperacillin MIC for *Pseudomonas aeruginosa* isolates on outcomes in children with bacteremia. The authors concluded that elevated piperacillin MICs were associated with higher mortality, increasing from 9% to 24%, in children with higher MICs (i.e., > 16 μg/mL), and they supported the Clinical and Laboratory Standards Institute (CLSI) recommendation to lower the breakpoint for piperacillin against *P. aeruginosa* to less than or equal to 16 μg/mL. Interestingly, the majority of children in that investigation received 300 mg/kg/d of piperacillin (interval unknown). Pharmacodynamic data in critically ill children demonstrate intermittent doses of 300 mg/kg/d as a standard 30-minute infusion do not achieve an appropriate target attainment (27). Based on our previously published pharmacokinetic and pharmacodynamic data, 100 mg/kg of piperacillin every 6 hours as a 3-hour infusion and 400 mg/kg/d as a continuous infusion were the only regimens to provide optimal exposures at the CLSI breakpoint of 16 μg/mL (27). Therefore, the increased mortality from the investigation by Tamma et al (35) could partly have been the result of using suboptimal doses of piperacillin. The dilemma of choosing an optimal dose plagues clinicians worldwide and if suboptimal doses continue to be used, the antiinfective armamentarium could perceivably be depleted.

Drug penetration into sites of potential infection outside of the bloodstream also poses a challenge when creating optimal dosing regimens. Rabbit models of meningitis suggest a ceftaroline CSF penetration ratio of ~15% with inflamed meninges (18, 19). Data from a five-patient adult case series, success was associated with a ceftaroline dosing regimen of 600 mg IV q8h, which is higher than the current highest FDA approved dose of 600 mg IV every 12 hours (36). The one patient who did not achieve clinical success received a dosing regimen of 600 mg IV q12h. When comparing the dosing regimen interval of every 8 hours associated with success in the adult meningitis cases to the data presented here, a ceftaroline dosing regimen using an interval of every 6 hours would be needed in pediatric patients. Adult data suggest that ELF penetration is ~23% (20). Additionally, adult data using ceftaroline for BSI also suggest success is linked to an every 8-hour dosing regimen (37). Therefore, when creating and using ceftaroline for indications such as BSI, pneumonia, and meningitis when MRSA is a concern, our data would support ceftaroline being dosed at an interval of every 6 hours. Furthermore, if there is a scenario when a patient's Vd would be expected to be increased as well, the higher 15 mg/kg/dose would also be suggested, based on the data presented here, which provided for at least a *f*T greater than 4–6 × MIC of 40%.

There are several limitations regarding this case series. First, this is a single-center experience using ceftaroline primarily as add-on therapy to other active MRSA therapy including vancomycin for invasive infections with confirmed or suspected MRSA. As such, conclusions regarding ceftaroline use as monotherapy cannot be made. Second, the combination of vancomycin and ceftaroline has been shown to be successful in treating persistent bacteremia in adults (38). Considering all patients were on active MRSA therapy for at least 72 hours with clinical failure in this investigation, the addition of ceftaroline to vancomycin was associated with clinical success in this population but the effect of ceftaroline alone or any synergism between the other active MRSA antimicrobials and ceftaroline cannot be evaluated. Third, although each patient had a good clinical outcome, a sample size of seven patients is a relatively small sample size. Fourth, a single pharmacodynamic target was used when designing/adjusting the dosing regimens and 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 patients and all indications. Fifth, the blood concentrations used for the pharmacodynamic analysis serve as a surrogate marker and do not necessarily reflect the ceftaroline 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. Sixth, 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 total number of samples collected for each child may not have been ideal to fully characterize the pharmacokinetics of ceftaroline 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.

CONCLUSIONS

These data suggest the pharmacokinetics of ceftaroline in PICU patients is different than healthy pediatric and adult patients, most notably a faster clearance and larger Vd. A higher mg/kg dose and a more frequent dosing interval for ceftaroline may be needed in PICU patients to provide appropriate pharmacodynamic exposures. Larger pharmacokinetic, pharmacodynamic, and interventional treatment trials in the PICU population are warranted.

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