Characterization of the Clinical Outcomes With Cefepime in a Neonatal Intensive Care Unit: A Retrospective Cohort Study

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OBJECTIVES The objective of this study was to characterize clinical outcomes when cefepime was used in a neonatal intensive care population.

METHODS Data were extracted from the medical records of all full-term (40 weeks gestational age) patients up to 2 months of age and preterm patients up to 48 weeks postmenstrual age admitted to the neonatal intensive care unit (NICU) at a freestanding children's hospital between January 1, 2010, and December 31, 2013, who received at least 48 hours of cefepime. The primary outcome measure was a positive clinical response as defined by a normalization of white blood cell count and/or culture clearance.

RESULTS Final analysis included 74 patients. Clinical response was evaluable in 43.2% (32 of 74) of courses. Of these, positive clinical response was observed in 81.3% (26 of 32). Overall patient mortality was 16.2% (12 of 74). Adverse effects (AEs) occurred in 14.9% (11 of 74) of courses.

CONCLUSIONS Cefepime can be used safely with reasonable clinical response in a NICU population, but additional studies are needed to further determine cefepime-associated clinical outcomes.

ABBREVIATIONS AE, adverse effect; AKI, acute kidney injury; NICU, neonatal intensive care unit; WBC, white blood cell

KEYWORDS adverse effects; cefepime; intensive care; neonatal; outcomes

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Introduction

Neonates admitted to neonatal intensive care units (NICUs) face a significant risk of developing nosocomial infections. An immature immune system coupled with extreme prematurity, congenital abnormalities, metabolic disorders, and invasive medical procedures may predispose neonates to a variety of infections, including catheter-related bloodstream infections, pneumonia, urinary tract infections, surgical wound infections, and early- as well as late-onset sepsis.^{1–3} The typical implicated pathogens include the Gram-negative enteric bacilli *Escherichia coli* and *Klebsiella* species, as well as the non-enteric Gram-negative bacillus *Pseudomonas aeruginosa*.³ Several hospital-acquired strains of *P aeruginosa* are resistant to commonly used antibiotics, and *Klebsiella* species and *E coli* can harbor extended-spectrum β -lactamases, which confer resistance to third-generation cephalosporins and demonstrate variable susceptibility to inhibition by available β -lactamase inhibitors.^{3–5}

Cefepime is a broad-spectrum fourth-generation cephalosporin that may be added to empiric treatment for late-onset sepsis. Our NICU often uses cefepime

in addition to the standard regimen of vancomycin and gentamicin in hemodynamically unstable patients with sepsis or suspected Gram-negative infections, or in place of gentamicin for the treatment of suspected pneumonia or meningitis. Cefepime is used because of its activity against many Gram-positive organisms and antibiotic-resistant Gram-negative organisms, including *E coli*, *Klebsiella* species, *Pseudomonas* species, *Enterobacter* species, *Citrobacter* species, and *Serratia* species.^{3,6,7} Cefepime susceptibilities in our institution's NICU for *Enterobacter* species, *E coli*, and *Klebsiella pneumoniae* are 96%, 100%, and 100%, compared with 30% susceptibility to ampicillin for *E coli* isolates. Carbapenem antibiotics, specifically meropenem, are another option for Gram-negative infections, but their use in our institution is restricted. Meropenem requires approval by our pediatric antimicrobial stewardship team or the infectious diseases service. Use of meropenem is extremely rare in our NICU, with 0.07 days of therapy per 1000 patient days during the previous 12 months. Cefepime penetrates the cerebrospinal fluid, which is of critical importance when treating potential or proven central nervous system infections.⁸ Unlike third-generation cephalosporins, cefepime has not been

associated with an increased risk of fungal infections, induction of resistance, or necrotizing enterocolitis.⁹

Safety and efficacy of cefepime have been described in children older than 2 months, but no data currently exist to establish clinical outcomes with cefepime in newborns.⁸ Pharmacokinetic studies in neonatal populations are available, but studies evaluating dosing beyond the first few weeks are lacking.^{3,4,10} If cefepime is to be more widely used in neonates, particularly as antimicrobial resistance patterns dictate changes in preferred antibiotic choices and drug shortages with other commonly used antimicrobials persist, the need for studies characterizing cefepime-associated clinical and safety outcomes grows. The objective of this study was to characterize the clinical outcomes of cefepime in a neonatal intensive care population.

Materials and Methods

This was a retrospective, single-center cohort study. A pharmacy computer system-generated report was used to identify all patients, both full-term and preterm, up to 48 weeks postmenstrual age admitted to the NICU of a freestanding children's hospital between January 1, 2010, and December 31, 2013, who received a course of cefepime. A course of cefepime was defined as at least 48 consecutive hours of cefepime receipt. Only the first cefepime course was included if patients received multiple courses during an admission, to avoid duplicating data. No additional exclusion criteria were identified for this study.

Demographic and outcome data from 72 hours prior to cefepime initiation, during cefepime treatment, and for 72 hours after discontinuation were extracted from patients' medical records. Mortality from any cause at any time was also extracted from each patient's medical record, if available.

Cefepime-associated clinical outcomes evaluated in this study included clinical response, all-cause mortality, and adverse effects (AEs) during cefepime administration. Potential cefepime-related hypophosphatemia was defined as hypophosphatemia that occurred during receipt of cefepime or within 72 hours following discontinuation. Hypophosphatemia was defined as a serum phosphorus concentration less than 4.8 mg/dL, as per the hospital pathology laboratory's age-based reference range. Clinical response was evaluated in patients who had an elevated white blood cell (WBC) count based on the hospital pathology laboratory's age-based reference ranges and/or a positive culture growing cefepime-susceptible bacteria. Patients were categorized as having positive clinical response to the course of cefepime if, while on cefepime, the patient experienced normalization of a previously elevated WBC count and/or negative follow-up cultures. In instances where follow-up WBC count or cultures were not obtained or documented, patients were categorized as non-responders. Acute kidney injury (AKI) was de-

fined as a serum creatinine increase of 50% or greater above baseline or a urine output of less than 1 mL/kg/hr.¹¹ Late-onset sepsis was defined as infection that occurred more than 3 days after birth.²

Descriptive statistics were conducted using Statistical Package for Social Sciences version 23.0 (SPSS Inc, Chicago, IL). Mean and SD were used for reporting of normally distributed data, and median and IQR were used for non-normally distributed data. The study was approved by the Indiana University and Butler University Institutional Review Boards.

Results

A total of 74 patients who received cefepime treatment were included. Patients were born at a mean $\pm$ SD gestational age of 29.7 ± 5.8 weeks. The mean postmenstrual age at cefepime initiation was 33 ± 6.2 weeks, and 63.5% (47 of 74) were male. The mean empiric cefepime dose was 36 ± 12.6 mg/kg per dose every 12 hours; however, dosing was based on postmenstrual age and renal function, and it varied widely among patients. The median (IQR) cefepime treatment duration was 5 days (3–8 days). Cefepime was most commonly used for late-onset sepsis (42%). Table 1 summarizes the indications for cefepime therapy in the study population. Concomitant antibiotics were used during all courses. Specifically, gentamicin was used in 91.9% (68 of 74) of those courses.

An initial WBC count was obtained in 89.2% (66 of 74) of courses, with 22.7% (15 of 66) of those being elevated. The median (IQR) maximum WBC count (cells $\times 10^3/\mu\text{L}$) in the 66 courses with an available WBC count was 14 (10.7–21.2), with a minimum and maximum of 5.1 and 69.9, respectively. Positive bacterial cultures were observed in 29.7% (22 of 74) of courses. There were 2 instances where results of cultures from multiple sites were positive. In 1 cefepime course, bacteria were isolated from blood, urine, and a wound. In another cefepime course, bacteria were isolated from blood and urine cultures. Blood was the most common culture site, observed in 86.4% (19 of 22) of patients (Table 2). Follow-up cultures were obtained in 95.5% (21 of 22) of patients with an initial positive culture and were negative in all instances. The median (IQR) time to negative cultures was 1 day (1–3 days) following cefepime initiation.

Clinical response could be evaluated based on the predetermined criteria in 43.2% (32 of 74) of courses. Positive clinical response was observed in 26 of the 32 evaluable courses (81.3%). Of the 6 patients who were classified as non-responders, 5 were due to either no available follow-up or persistently elevated WBC count, and 1 was because of a lack of follow-up cultures ($n = 1$). Overall all-cause patient mortality was 16.2% (12 of 74).

There were 12 AEs potentially attributable to cefepime, and these occurred in 14.9% (11 of 74) of courses. Hypophosphatemia was the most frequent AE (75%; 9

Table 1. Indications for Cefepime Initiation (N = 74)

Indication	n (%)
Late-onset sepsis	31 (42)
Early-onset sepsis	13 (17.6)
Multiple indications	12 (16.2)
Pneumonia	6 (8.1)
Urinary Tract Infection	4 (5.4)
Necrotizing enterocolitis	3 (4.1)
Peritonitis	2 (2.7)
Wound infection	1 (1.3)
Infected incision site	1 (1.3)
Unclear	1 (1.3)

of 12) and was observed in 12.2% of overall courses (9 of 74). Other documented AEs were seizures (n = 2) and hyponatremia (n = 1). Development of AKI was observed in 16.2% (12 of 74) of courses. In 7 of these courses, the AKI definition was met based on urine output alone, 3 courses met AKI definition with serum creatinine and urine output, and 2 courses met the definition with serum creatinine values alone. A concomitant nephrotoxin was used in all courses, with gentamicin and vancomycin being used in 100% (12 of 12) and 66.7% (8 of 12), respectively.

Discussion

In this cohort of NICU patients, cefepime was safely used for a variety of indications and resulted in positive clinical outcomes in approximately 81% of evaluable courses, with possible cefepime-associated AEs observed in 14.9% of courses. This is the largest known characterization of cefepime use in a NICU population.

The clinical response rate of 81.3% in our study was generally lower than what has been reported in other populations as well as in other antibiotics of similar mechanism and class. A number of studies found responses of 90% to 98% with cefotaxime, ceftazidime, and meropenem in similar populations, albeit for some different indications.^{12–14} A study of ceftazidime in newborns with meningitis/septicemia found that ceftazidime monotherapy resulted in a 70% positive clinical response, and response increased to 100% in patients receiving combination therapy of ceftazidime plus ampicillin.¹⁵ This study noted a majority of Gram-positive organisms, which calls into question extrapolation of the authors' efficacy findings to treatment of infections caused by Gram-negative organisms.¹⁵ Although nearly all of the patients in our cohort were administered cefepime concurrently with gentamicin, all isolated pathogens were Gram-negative organisms. Patients in our NICU frequently receive an empiric combination of vancomycin and gentamicin, with the addition of ce-

fepime in patients deemed to have a higher severity of illness or likelihood of Gram-negative infections. Such patients may include those with ventriculoperitoneal shunts, ventricular reservoirs, mechanically ventilated patients with pneumonia, and newly hypotensive patients already receiving vancomycin and an aminoglycoside. Thus, our mortality and response rates are likely biased, because our sickest patients are most likely to receive cefepime. It is also impossible to separate the impacts of cefepime versus gentamicin.

In a study of NICU patients with late-onset sepsis receiving cefotaxime and gentamicin, 72% of patients were subsequently discharged from the hospital, which was a surrogate for positive clinical outcomes.¹⁶ However, in that same study 26% of the patients had a prolonged NICU stay and 22% had to be hospitalized again at a later date.¹⁶ This clinical response is lower than our study's clinical response rate of 81.3%, although it is difficult to discern true clinical response in the absence of a clear definition. Dajani and Pokowski¹⁷ reported microbiologic cure of 97.1% in pediatric patients with *Haemophilus influenzae* meningitis who were treated with cefotaxime. Similarly, in our cohort, microbiologic cure was 100% in cases where follow-up cultures were available. Inherent differences between *H influenzae* and the enteric Gram-negative organisms observed in our study may muddle comparison of these 2 studies.

We expected a positive clinical response similar to those previously reported, but our lower rate may have been due in part to a heterogeneous population and our study's definition of clinical response. Our definition included WBC normalization, but of the 6 courses categorized as non-response, 5 were because of no follow-up WBC count or persistently elevated WBC count, which categorized these courses as non-response. One of the 6 non-response courses was due to lack of a follow-up culture, but all of the Gram-negative organisms encountered (Table 2) were susceptible to cefepime. It is unclear why follow-up cultures were not obtained, but continued infectious symptoms would likely have resulted in additional cultures. The overall mortality and time to culture clearance in our cohort are similar to those in previous reports. Kent et al.¹⁸ reported 31% all-cause mortality and a time to negative culture of 5 days in 116 patients compared with the overall mortality of 16.2% and a time to negative culture of 1 day in our cohort.¹⁸ Our positive clinical response rate of 81.3% should be considered a very conservative finding because of our response definition and categorization.

The most commonly reported cefepime-attributed AEs in the literature have been rash and diarrhea, although neither was documented in our neonatal cohort. Rash has been reported in the range of 1.5% to 6.4%, but this is less likely in neonates because of underdeveloped immune systems.^{9,19,20} Diarrhea appears to occur more frequently and has been reported in the range of 6.4% to 13%.^{9,19} Diarrhea was not noted

Table 2. Culture Site and Bacteria Distribution of Positive Cultures

Culture site*	n (%)	Organisms	n (%)
Blood	17 (77.3)	<i>Enterobacter</i> species	1 (5.9)
		<i>Escherichia coli</i>	6 (35.2)
		<i>Klebsiella</i> species	5 (29.4)
		<i>Haemophilus influenzae</i>	2 (11.8)
		<i>Pseudomonas aeruginosa</i>	2 (11.8)
		<i>Serratia</i> species	1 (5.9)
Blood and urine†	1 (4.5)	<i>E coli</i> and <i>Klebsiella</i> species	1 (100)
Blood, urine, and wound	1 (4.5)	<i>E coli</i>	1 (100)
Urine	2 (9.1)	<i>E coli</i>	1 (50)
		<i>Serratia</i> species	1 (50)
Wound	1 (4.5)	<i>Klebsiella</i> species	1 (100)

* There were 22 patients with positive cultures.

† Multiple bacteria isolated.

in our population, but we were unable to evaluate the consistency of all stools given the retrospective nature of this study. In non-neonates, the frequency of adverse effects observed with cefepime is similar to that with ceftazidime, which has a long record of NICU use.²¹ In a study that compared cefepime with ceftazidime treatment of urinary tract infections, clinical adverse events occurred in 28% of cefepime patients and 25% of ceftazidime patients.¹⁴ The incidence of AEs in our study was almost half of that, potentially due to differences in age, indication, or concomitant illnesses. It could also be due to the retrospective nature of the study and low recognition or documentation of potential association with antibiotic therapy at the time of care.

Of the AEs in our study, hypophosphatemia was the most common (75%), followed by seizures and hyponatremia. Because we did not use an adverse drug reaction probability scale and because of the retrospective nature of this study, we cannot determine causality of the AEs our population experienced. Our population had many possible explanations for hypophosphatemia, but we were unable to evaluate each specifically. A common cause of hypophosphatemia in premature patients is nutritional deficiency, which can be due to the inability to provide phosphorus in the same amounts as would be accrued in utero.²² Many premature patients and term patients with illnesses severe enough to warrant the use of cefepime will also require parenteral nutrition. Our institution uses total parenteral nutrition with lipids, dextrose, and amino acids mixed together in the same bag. Many medications, including cefepime, are incompatible with total parenteral nutrition. As a result, patients will often not receive the entire amount of phosphorus ordered, which can easily add up to a deficit. In addition, some medications, like loop diuretics, can cause increased wasting of phosphorus, and immature renal function in premature neonates can lead to decreased reabsorption of phosphorus.

AKI was observed in 16.2% (12 of 74) of courses in

our study. Although cefepime has been associated with less nephrotoxicity than penicillin antibiotics, like nafcillin and piperacillin/tazobactam, cephalosporins have been reported to cause acute tubular necrosis in animals and humans.²³ However, one important consideration is a concomitant nephrotoxin was being used in all but one AKI occurrence in our study, with most of the patients receiving gentamicin and/or vancomycin. Although few studies regarding AKI in pediatric populations are available, a retrospective study found that vancomycin therapy lasting longer than 8 days resulted in AKI developing in 13% of patients.²⁴ Viswanathan and colleagues²⁵ examined risk factors for AKI in extremely low birth weight neonates during an 8-year period. The investigators found an overall incidence of AKI of 12.5% (59 of 472). When 46 neonates with AKI were matched with controls, it was found that exposure to cefotaxime was associated with development of AKI. In this study, there was no difference in the exposure to vancomycin or gentamicin between patients who developed AKI and those who did not.²⁵

In the study by Viswanathan et al.,²⁵ as well as in our study, it is likely that renal dysfunction was attributable to many other causes or more of a reflection of illness severity than a direct antibiotic effect. The single patient in our study with AKI who did not receive a concomitant nephrotoxin may have developed AKI secondary to the stress of the infectious process. It is not uncommon for critically ill neonates to develop adrenal insufficiency, and treatment of a significant patent ductus arteriosus with indomethacin or ibuprofen could result in rising creatinine and/or decreased urine output.²⁶ Regardless, it is important to monitor renal function during cefepime therapy to make dose adjustments if renal function deteriorates.

There are multiple limitations to this study. The retrospective manner limited control over study records and documentation. Repeat WBC count documentation was inconsistent, and assessment of clinical response could

vary based on disease state. A decreased WBC count can be as concerning as an elevated WBC count, but we did not account for potential positive clinical responses in the 2 patients with low initial WBC counts ($5.1 \times 10^3/\mu\text{L}$ and $6 \times 10^3/\mu\text{L}$, respectively). In these 2 patients, normalization of leukopenia would, from a clinical perspective, likely be characterized as improvement and response to medication.

An additional study limitation is the cefepime dosing encountered in this cohort. Commonly available dosing references include contrasting dosing recommendations for cefepime, and the ideal dosing regimens for premature neonates as they age have not yet been determined because of limited pharmacokinetic information. Our institution differentiates dosing recommendations by serum creatinine (<0.7 mg/dL and 0.7 – 1.3 mg/dL), postmenstrual age (≤ 30 weeks and >30 weeks), and whether or not meningitis is a concern. Most regimens at our institution are either 30 mg/kg or 50 mg/kg every 12 hours. Despite such dosing guidance and the availability of clinical pharmacy support in person or via phone 24 hours a day, it is possible that some patients received suboptimal doses because of the lack of data for dosing throughout the neonatal period.

This is the first report describing outcomes in neonates who were treated with cefepime. Neonates are a vulnerable population that will not be spared from infections with antibiotic-resistant bacteria, so more comprehensive studies regarding the safety and efficacy of newer antibiotics, such as cefepime, are needed. With few data on these newer agents in a vulnerable population like neonates, practitioners must make therapeutic decisions that potentially involve more risk. Prospective, comparative studies with carefully defined end points are needed. In this neonatal cohort, findings suggest that cefepime can be used safely with reasonable clinical response, but additional pharmacokinetic and outcome studies are needed.

ARTICLE INFORMATION

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