JPPT | Single-Center Retrospective Study

Comparison of Outcomes in Neonates Receiving Cefepime or Ceftazidime

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OBJECTIVES Cefepime and ceftazidime are alternatives to cefotaxime for management of Gram-negative infections in neonates. The objective was to evaluate neonatal outcomes when receiving cefepime or ceftazidime.

METHODS This was a single center, retrospective analysis of neonates exposed to at least 24 hours of cefepime or ceftazidime between June 1, 2018, and June 1, 2021. The primary outcome was incidence of culture-positive, late-onset sepsis after initial exposure. Secondary outcomes included culture-negative, respiratory, urinary tract, and resistant infections; necrotizing enterocolitis; length of stay; age at discharge; mortality; and adverse effects.

RESULTS A total of 105 neonates were included (cefepime, n = 50; ceftazidime, n = 55). Baseline characteristics were similar except more cumulative days of antibiotics (25.0 [IQR, 9.3–47.0] versus 9.0 [IQR, 4.0–23.5], p = 0.01), central line days (11.0 [IQR, 6.0–40.0] versus 6.5 [IQR, 0.0–11.5], p = 0.001), and ventilator days (13.0 [IQR, 2.3–48.0] versus 4.0 [IQR, 0.0–25.0], p = 0.02) were found in the cefepime group than in the ceftazidime group. There was no difference in culture-positive sepsis after the initial antibiotic course (8.0% versus 3.6%, p = 0.42). Statistical differences were seen in select secondary outcomes including treated respiratory infections (16.0% versus 1.8%, p = 0.01), length of stay greater than 30 days (72.0% versus 50.9%, p = 0.03), and mortality (26.0% versus 9.1%, p = 0.02). These differences were not observed in analyses adjusted for ventilator days.

CONCLUSIONS This analysis found no difference in culture-positive sepsis in neonates exposed to cefepime versus ceftazidime. Moreover, there were no differences in secondary outcomes in adjusted analyses. Further research is needed to assess neonatal outcomes in a larger analysis.

ABBREVIATIONS APGAR, appearance, pulse, grimace, activity, and respiration; CNS, central nervous system; FDA, US Food and Drug Administration; MDRO, multidrug-resistant organism; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit

KEYWORDS bacterial resistance; cefepime; ceftazidime; cephalosporin; neonate; outcome; sepsis

J Pediatr Pharmacol Ther 2023;28(5):439–445

DOI: 10.5863/1551-6776-28.5.439

Introduction

There is an estimated global incidence of approximately 22 cases of neonatal sepsis per 1000 live births, which translates to about 3 million neonatal sepsis cases per year.[1] The rate of neonatal sepsis is inversely related to gestational age and may lead to an increased risk of morbidity and mortality within this patient population.[1] Neonatal sepsis is classified as early-onset sepsis if clinical presentation occurs within the first 72 hours of life, compared with late-onset sepsis presenting at 72 hours or more of life.[2] Early-onset sepsis often occurs through vertical transmission with common pathogens including group B streptococci, *Escherichia coli*, and *Listeria monocytogenes*.[2] In contrast, late-onset sepsis can occur via vertical or horizontal transmissions with common pathogens including coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterobacter* spp, *Klebsiella* spp, and *Candida albicans*.[2]

When late-onset sepsis is suspected in a neonate, the recommended empiric management includes obtaining blood culture(s), complete blood count with differential, and inflammatory markers before initiating antibiotics.[3,4] In patients who are critically ill or have suspected central nervous system (CNS) infection, either ampicillin, nafcillin/oxacillin, or vancomycin plus a third-generation cephalosporin, most commonly cefotaxime, is recommended for empiric treatment.[4] Cefotaxime is a third-generation cephalosporin with bactericidal activity against Gram-negative organisms, an ability to penetrate the CNS, decreased nephrotoxic potential, and moderate plasma protein binding.[5]

Given the national shortage of cefotaxime, health care institutions have been challenged to select alternative antibiotics to manage infections caused by Gram-negative organisms such as *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella* spp, and more.[6,7] Ceftazidime and cefepime are cephalosporin agents currently used as substitutions for cefotaxime.[6,7] Both agents have been shown to be safe and effective for use in the neonatal population.[8,9] Additionally, both agents have bactericidal activity against Gram-negative organisms and can readily penetrate the CNS.[7,10] Ceftazidime is a third-generation cephalosporin that is approved by the US Food and Drug Administration (FDA) for neonates.[11] In contrast, cefepime is a fourth-generation cephalosporin that is FDA approved for pediatric patients 2 months and older.[12] When comparing the 2 agents, cefepime has a broader spectrum of activity against Gram-positive and Gram-negative organisms than ceftazidime.[13] While both agents are considered weak inducers of ampC beta-lactamase, cefepime possesses a net neutral charge that allows for more rapid penetration of the bacterial outer cell membrane, enhanced access to its enzymatic target, and ability to overcome beta-lactamase inactivation from ampC organisms, compared with other cephalosporins.[13,14]

Despite the increasingly widespread use of ceftazidime and cefepime, neonatal outcomes and potential collateral damage from early exposure to these broad-spectrum antibiotic therapies remain unclear. Early and prolonged exposure to broad-spectrum antibiotics is thought to be associated with negative outcomes such as increased development of multidrug-resistant Gram-negative bacteria and mortality.[15,16] However, there are currently no studies, to our knowledge, directly comparing neonatal outcomes when either of the 2 broad-spectrum antibiotics are used and it is unknown whether one agent possesses an advantage over the other. In a recent study by Patel et al,[16] comparing neonatal outcomes with the use of cefotaxime (n = 43) or ceftazidime (n = 58), there was a statistically significant increase in stage 2 and 3 necrotizing enterocolitis (NEC) with use of ceftazidime (adjusted OR, 9.68 [95% CI, 1.18–79.45], p = 0.04). Additionally, the study found a greater incidence of culture-positive late-onset sepsis, multidrug-resistant organism (MDRO), and culture-negative presumed sepsis in the ceftazidime cohort.[16] Our single center, retrospective chart review aimed to assess similar neonatal outcomes from the study of Patel et al[16] when comparing cefepime with ceftazidime, with the ultimate goal to evaluate if findings could provide guidance in antibiotic selection at our institution.

Materials and Methods

Subjects. This was a single center, retrospective chart review conducted at a level 4 neonatal intensive care unit (NICU) of a children's hospital between June 1, 2018, and June 1, 2021. The analysis period was selected on the basis of anticipated transition away from cefotaxime owing to a long-standing drug shortage. Neonates were included if they had been exposed to at least 24 hours of either cefepime or ceftazidime. Those who received both cefepime and ceftazidime during the same hospital admission, had a complex hospital stay, were readmitted to the NICU, had missing baseline information, were transferred from outside hospital with a missing medical history, or were transferred from an outside hospital at greater than 7 days of life were excluded. A complex hospital stay was defined as neonates with multiple comorbidities or neonates with multiple transfers to different units within the children's hospital during admission. Missing baseline information included neonates with unidentifiable maternal characteristics or neonatal APGAR (appearance, pulse, grimace, activity, and respiration) scores. Neonates were permitted to have received other antibiotics prior to receiving cefepime or ceftazidime. Moreover, neonates were permitted to be on concomitant antimicrobial agents while receiving cefepime or ceftazidime. If individuals received multiple courses of cefepime or ceftazidime during the same admission, only the first course was included in the analysis.

Outcomes. The primary outcome of this analysis was the incidence of culture-positive sepsis after the first 72 hours of life, requiring treatment for at least 7 days with targeted antibiotics following the use of cefepime or ceftazidime. Secondary outcomes included 1) treatment for MDRO infection with at least 7 days of targeted antimicrobial therapy, defined as a positive culture (in blood, cerebrospinal fluid, urine, or tracheal aspirate) with the isolated organism resistant to at least 3 antimicrobial classes; 2) presumed culture-negative sepsis with at least 7 days of antimicrobial therapy without positive culture from any source; 3) respiratory infection with at least 7 days of targeted antimicrobial therapy; 4) stage 2 or 3 NEC; 5) urinary tract infection with at least 7 days of targeted antimicrobial therapy; 6) length of hospital stay greater than 30 days; 7) postmenstrual age at discharge; 8) all-cause mortality; and 9) reported adverse events associated with cefepime or ceftazidime.

Data Collection. Baseline characteristics collected in all neonates included gestational age, birth weight, race, sex, cesarean delivery, small for gestational age (Fenton growth chart for preterm birth and World Health Organization growth chart for term birth), maternal chorioamnionitis, APGAR scores at 1 minute and 5 minutes of life, day of life at analysis, positive blood culture prior to analysis, diagnosis of NEC prior to analysis, duration of antibiotic exposure, cumulative days of all antibiotic agents during admission, central line days, ventilator days, and concomitant antimicrobials.

Statistical Analysis. Continuous data are presented as medians with IQRs and compared between antibiotic groups by using Mann-Whitney *U* tests. Categorical data are presented as counts with frequencies and

compared between groups by using chi-square or Fisher exact tests. Logistic regression adjusting for ventilator days was performed. Analyses were conducted in SPSS (Statistical Package for the Social Sciences) version 27. p values <0.05 were considered significant.

Results

A total of 132 neonatal medical records were reviewed and 105 neonates were included in the final analysis (cefepime, n = 50; ceftazidime, n = 55). Reasons for exclusion are outlined in the Supplemental Figure.

Baseline characteristics were mostly similar between the 2 groups (Table 1). The median gestational age was 32 weeks, with a birth weight of 1740 g. Most neonates were male, Black or African American, and delivered via cesarean delivery. The median APGAR score was 4 at 1 minute after birth and 7 at 5 minutes after birth. About 19% of neonates were small for gestational age, 11% were born to mothers with chorioamnionitis, and 40% had positive blood cultures prior to cefepime or ceftazidime exposure. The most common species identified from positive cultures were *Staphylococcus* spp, *Escherichia* spp, *and Streptococcus* spp (Figure 1). The most common concomitant antimicrobials included ampicillin, gentamicin, and vancomycin (Table 2). The median day of life at initiation of either cefepime or ceftazidime was 8 days. The cefepime group, when compared with the ceftazidime group, had more cumulative days of all antibiotics (25.0 days [IQR, 9.3–47.0] versus 9.0 days [IQR, 4.0–23.5], p = 0.01), greater need for central lines (43 [88.0%] versus 37 [67.3%], p = 0.02) and for a longer period of time (11.0 days [IQR,

Table 1. Baseline Characteristics

	Cefepime (n = 50)	Ceftazidime (n = 55)	p value
Gestational age, median (IQR), wk	31.7 (26.4–37.1)	33.1 (27.4–37.4)	0.50
Birth weight, median (IQR), g	1509 (757–2645)	1920 (887–2820)	0.37
Sex, male, n (%)	30 (60.0)	28 (50.9)	0.35
Race, n (%)			0.86
Black or African American	27 (54.0)	29 (52.7)	
White or Caucasian	17 (34.0)	18 (32.7)	
Hispanic or Latino	4 (8.0)	3 (5.5)	
Asian	0 (0.0)	1 (1.8)	
Other	2 (4.0)	4 (7.3)	
Cesarean delivery, n (%)	36 (72.0)	35 (63.6)	0.36
Small for gestational age, n (%)	9 (18.0)	11 (20.0)	0.79
Chorioamnionitis, n (%)	6 (12.0)	6 (10.9)	0.86
Apgar score at 1 min, median (IQR)	5 (3.0–6.8)	4 (2.0–6.0)	0.75
Apgar score at 5 min, median (IQR)	7 (5.3–8.0)	7 (5.0–9.0)	0.96
Day of life therapy started, median (IQR)	16.5 (1.0–40.8)	5 (1.5–17.5)	0.09
Positive blood culture prior to initiation, n (%)	22 (44.0)	20 (36.4)	0.43
NEC prior to initiation, n (%)	4 (8.0)	3 (5.5)	0.71
Prior exposure to other antibiotics, median (IQR), days	3.5 (1.0–9.0)	2 (1.0–7.0)	0.20
Duration of initial course of antibiotics, median (IQR), days	3 (2.0–7.0)	3 (2.5–4.0)	0.83
Cumulative days of all antibiotic agents during admission, median (IQR), days	25 (9.3–47.0)	9 (4.0–23.5)	0.01
Central line, n (%)	43 (86.0)	37 (67.3)	0.02
Number of days with central line during admission, median (IQR), days	11.0 (6.0–40.0)	6.5 (0.0–11.5)	0.001
Ventilator, n (%)	44 (88.0)	38 (69.1)	0.02
Number of days on ventilator during admission, median (IQR), days	13.0 (2.3–48.0)	4.0 (0.0–25.0)	0.02

NEC, necrotizing enterocolitis

Figure 1. Positive blood culture prior to cefepime or ceftazidime antibiotic initiation by species.

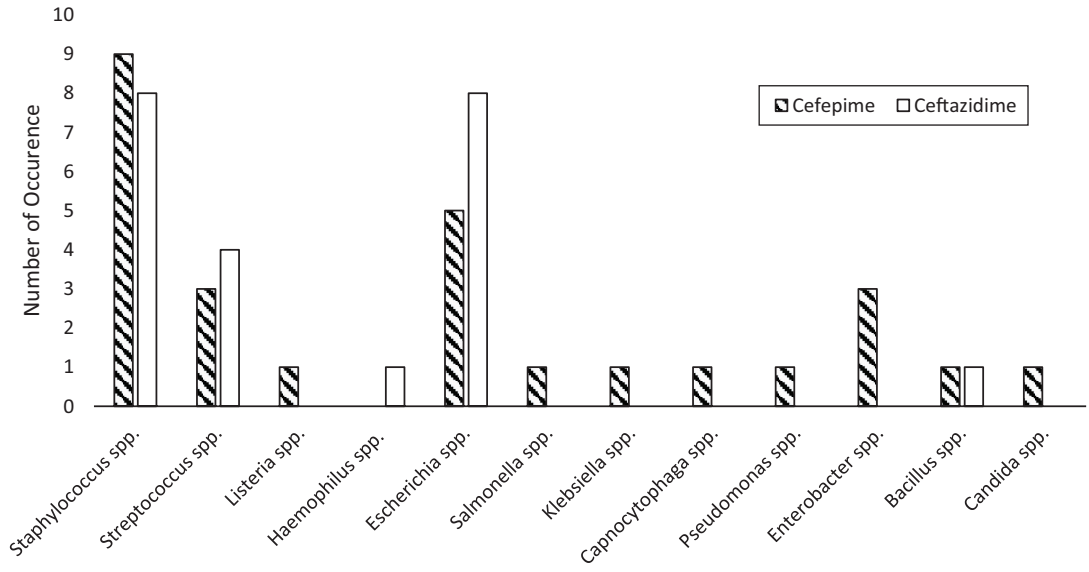


Table 2. Concomitant Antimicrobials Used With Cefepime and Ceftazidime

	Cefepime (n = 50)	Ceftazidime (n = 55)
Concomitant antimicrobials, n (%)		
None	2 (4.0)	0 (0.0)
Acyclovir	6 (12.0)	14 (25.5)
Ampicillin	22 (44.0)	32 (58.2)
Cefazolin	8 (16.0)	4 (7.3)
Fluconazole	5 (10.0)	4 (7.3)
Gentamicin	19 (38.0)	21 (38.2)
Nafcillin	8 (16.0)	14 (25.5)
Piperacillin/tazobactam	15 (30.0)	6 (10.9)
Vancomycin	18 (36.0)	15 (27.3)
HIV agents	2 (4.0)	2 (3.6)
Others	10 (20.0)	8 (14.5)

HIV, human immunodeficiency virus

6.0–40.0] versus 6.5 days [IQR, 0.0–11.5], p = 0.001), and more neonates requiring mechanical ventilation (44 [88.0%] versus 38 [69.1%], p = 0.02) also for a longer duration (13.0 days [IQR, 2.3–48.0] versus 4.0 days [IQR, 0.0–25.0], p = 0.02).

There were 6 neonates with culture-positive sepsis cases after initial exposure to cefepime or ceftazidime. Of those, 4 (8.0%) were in the cefepime group and 2 (3.6%) were in the ceftazidime group (p = 0.42; Table 3). Of all culture-positive sepsis cases, the most common identified organism was *Staphylococcus* spp (3 [6.0%] versus 1 [1.8%]), of which 3 of 4 were coagulase-negative staphylococci (Figure 2). One patient in the cefepime group grew both *Enterobacter* spp and coagulase-negative staphylococcus in their blood culture. There were no statistical differences identified in secondary outcomes including MDRO infection (1 [2.0%] versus 2 [3.6%], p > 0.99), presumed culture-negative sepsis after initial antibiotic exposure (4 [8.0%] versus 0 [0.0%], p = 0.05), stage 2 or 3 NEC after initial exposure (2 [4.0%] versus 0 [0.0%], p = 0.22), urinary tract infection (6 [12.0%] versus 4 [7.3%], p = 0.51), and post-menstrual age at discharge (41.9 weeks [IQR, 37.1–47.5] versus 39.3 weeks [IQR, 37.0–42.5], p = 0.05). Moreover, there were no reported adverse events related to antibiotics in either group. Statistical differences between neonates receiving cefepime compared with ceftazidime were identified in treated respiratory infections (8 [16.0%] versus 1 [1.8%], p = 0.01), length of hospital stay greater than 30 days (36 [72.0%] versus 28 [50.9%], p = 0.03), and all-cause mortality (13 [26.0%] versus 5 [9.1%], p = 0.02), respectively. However, statistical differences were not observed in adjusted analyses for ventilator days (Table 3).

Discussion

This analysis compared neonatal outcomes with the use of cefepime or ceftazidime in approximately 100 individuals. No differences in culture-positive sepsis in neonates exposed to cefepime compared with ceftazidime were observed. Moreover, there were no differences in secondary outcomes in adjusted analyses for ventilator days. Of the 6 identified culture-positive sepsis cases after initial exposure to cefepime or ceftazidime in our cohort, there were twice the number of neonates with culture-positive sepsis in the cefepime group. Despite this, there were no statistical differences in primary outcome between the cefepime and ceftazidime groups. This could partly be due to the small sample size of the analysis, which limits the ability to detect statistical differences.

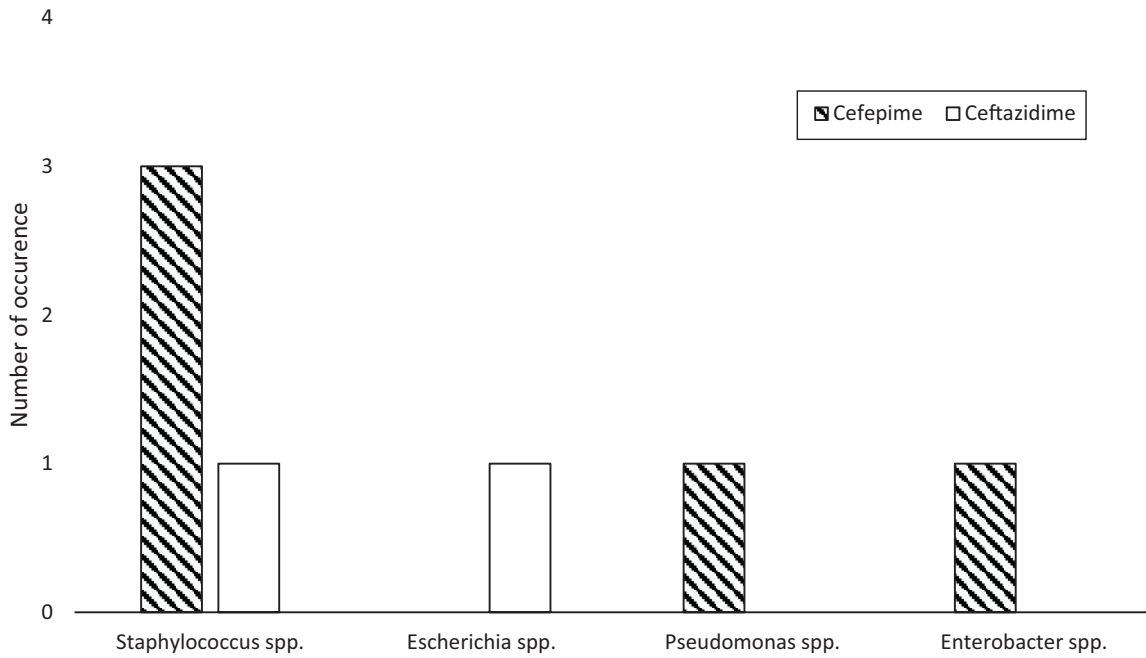
Table 3. Clinical Neonatal Outcomes Among Included Patients

	Cefepime (n = 50)	Ceftazidime (n = 55)	Unadjusted p value	Adjusted Odds Ratio* (95% CI), p value
Primary outcome				
Culture-positive sepsis after initial course of antibiotics, n (%)	4 (8.0)	2 (3.6)	0.42	—
Secondary outcomes				
MDRO infection developed after initial course of antibiotics, n (%)	1 (2.0)	2 (3.6)	>0.99	—
Presumed culture-negative sepsis after initial course of antibiotics, n (%)	4 (8.0)	0 (0.0)	0.05	—
Treated respiratory infection after initial course of antibiotics, n (%)	8 (16.0)	1 (1.8)	0.01	4.10 (0.42–40.56), 0.23
Stage 2 or 3 NEC after initial course of antibiotics, n (%)	2 (4.0)	0 (0.0)	0.22	—
Urinary tract infection after initial course of antibiotics, n (%)	6 (12.0)	4 (7.3)	0.51	—
Length of hospital stay >30 days, n (%)	36 (72.0)	28 (50.9)	0.03	1.89 (0.68–5.24), 0.22
All-cause mortality, n (%)	13 (26.0)	5 (9.1)	0.02	2.77 (0.87–8.83), 0.09
Reported adverse events associated with antibiotics, n (%)	0 (0.0)	0 (0.0)	—	—
Post-menstrual age at discharge, median (IQR), wk	41.9 (37.1–47.5)	39.3 (37.0–42.5)	0.05	—

MDRO, multidrug-resistant organism; NEC, necrotizing enterocolitis

* Adjusted for days on ventilator. Odds ratio is odds of occurrence with cefepime compared with ceftazidime.

Figure 2. Positive blood culture after cefepime or ceftazidime initiation by species.



There remains a concern with excessive use of broad-spectrum antibiotics for a prolonged period of time within the neonatal population.[16,17] Specifically, both longer antibiotic duration of therapy and use of broad-spectrum antibiotics may increase the risk of adverse effects, alter intestinal microbiome colonization, and lead to the emergence of antibiotic-resistant bacteria.[16,17] Five of the 7 species identified from the culture-positive sepsis cases in this analysis were from the cefepime group. Of these 5 species, 1 was

a *Pseudomonas* spp and 1 was an *Enterobacter* spp, which are both Gram-negative organisms commonly associated with antibiotic resistance. It is important to note, however, that neonates in the cefepime group had more positive cultures for these Gram-negative bacterial organisms prior to receiving either cefepime or ceftazidime, which may have prompted the selection of cefepime later in the hospital stay. Additionally, neonates in the cefepime group had more invasive medical devices in place and for a longer period of time at baseline, which could have influenced both infection risk and antibiotic selection. This also may have contributed to more days on antibiotics during same hospital admission in comparison with those in the ceftazidime group, all of which can lead to an increased risk of developing more virulent bacterial infections.[18–20]

There are several limitations worth noting from our retrospective study. The small sample size, and the fact that the analysis was conducted at a single center, limits the generalizability of the results. Second, identification of adverse events was limited to what was reported in the patients' charts. In addition, neonates in the cefepime group possessed more risk factors, which may indicate a more critical clinical state at baseline than those in the ceftazidime group. Similarly, there was not a standardized process in selecting antibiotic agents, rather selection was at the discretion of the medical team. This could suggest that medical providers at our institution tend to favor initiating cefepime over ceftazidime for more clinically complicated neonatal patients and/or those with a history of ampC beta-lactamase–producing bacteria. The adjusted analyses for ventilator days attempted to account for this. Additionally, in reviewing the institution's antibiogram during the study period, it does not appear susceptibility data would have influenced cephalosporin selection. Finally, for the cases of MDRO infections, the 2 patients in the ceftazidime group did not have susceptibility results for ceftazidime and the patient in the cefepime group experienced an *Enterobacter cloacae* urinary tract infection, resistant to 3 antibiotic classes, but still susceptible to cefepime. These findings make it difficult to determine any events of treatment failure. Despite these limitations, the current analysis adds to the sparse data available comparing cefepime versus ceftazidime in neonates.

Conclusion

This is the first study, to our knowledge, comparing neonatal outcomes with use of cefepime or ceftazidime. Overall, our analysis did not identify any differences in neonatal outcomes when comparing use of cefepime or ceftazidime. Neonates in the cefepime group had a greater number of treated respiratory tract infections, longer lengths of hospital stay, and greater all-cause mortality. However, no differences were identified in adjusted analyses for ventilator days. Moreover, although not statistically significant, the cefepime group had numerically higher culture-positive sepsis, presumed culture-negative sepsis, stage 2 or 3 NEC, and urinary tract infection. However, it is important to note that the cefepime group possessed more risk factors at baseline, which may complicate the interpretation of outcomes observed in this study. Prospective multicenter studies with larger neonatal populations are needed to compare outcomes with use of cefepime or ceftazidime for neonatal sepsis.

Article Information

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Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

Acknowledgments. Authors would like to thank Casey Cummings, PharmD candidate, and Aubree Houston, PharmD candidate, for their assistance during the data collection process for this study. Preliminary results from this research were presented virtually at the Vizient University Health System Consortium Pharmacy Network resident poster session on December 2, 2021. Final results from this research were presented at the Pediatric Pharmacy Association 31st Annual Meeting poster session in Norfolk, VA, on May 4, 2022, and University of North Carolina at Chapel Hill Research in Education and Practice Symposium in Chapel Hill, NC, on May 17, 2022.

Submitted. August 24, 2022

Accepted. November 20, 2022

Supplemental Material. DOI: 10.5863/1551-6776-28.5.439.S1

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