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Comparison of Neonatal Outcomes With the Use Cefotaxime Versus Ceftazidime in a Neonatal Intensive Care Unit

Payal D. Patel, PharmD; Palak Bhagat, PharmD; Allison H. Bartlett, MD; and Deborah S. Bondi, PharmD

OBJECTIVES There is a national drug shortage of cefotaxime, and ceftazidime is recommended as an alternative to cefotaxime for neonates. This study evaluated culture-positive late-onset sepsis (LOS), multidrug resistant organisms (MDROs), and other neonatal outcomes with the use of ceftazidime compared with cefotaxime in neonates.

METHODS This was a single-center, retrospective cohort study of neonatal subjects who received at least 24 hours of ceftazidime or cefotaxime between April 1, 2015, and August 1, 2017. Subjects were excluded if they received the alternate antibiotic for more than 24 hours.

RESULTS A total of 101 subjects were included (ceftazidime, n = 58; cefotaxime, n = 43). Median gestational ages were significantly different between groups (28.1 [IQR, 25.0–36.6] weeks versus 32.3 [IQR, 26.9–37.4] in the ceftazidime and cefotaxime groups, respectively, $p < 0.05$). Results showed a non-statistically significant increased incidence of culture-positive LOS (17.2% versus 2.3%, respectively, adjusted OR 6.51 [95% CI, 0.78–55.23], $p = 0.09$) and MDRO infections (5.2% versus 0%, respectively, $p = 0.26$) with the use of ceftazidime compared with cefotaxime. There was a statistically significant increased risk of stage II to III necrotizing enterocolitis (NEC) with the use of ceftazidime (22.4% versus 2.3%, respectively, adjusted OR 9.68 [95% CI, 1.18–79.45], $p = 0.04$).

CONCLUSIONS This study found a statistically significant increase in stage II to III NEC with the use of ceftazidime compared with cefotaxime. There was a higher rate of culture-positive LOS and MDRO infections with ceftazidime, but this was not significant. Further research is warranted to assess the implications ceftazidime use in neonates.

ABBREVIATIONS DOL, day of life; EOS, early-onset sepsis; ESBL, extended spectrum beta-lactamase; LOS, late-onset sepsis; MDROs, multidrug resistant organisms; NEC, necrotizing enterocolitis

KEYWORDS cefotaxime; ceftazidime; multi-drug resistant organisms; neonatal outcome; neonatal sepsis

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Introduction

The empiric management of sepsis in the NICU includes the use of antibiotics targeting the most common organisms seen in early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS occurs in the first 72 hours of life, whereas LOS occurs after the first 72 hours of life. These targeted organisms include group B *Streptococcus*, *Escherichia coli*, and other Gram-negative organisms for EOS and LOS, as well as coagulase-negative *Staphylococcus* for LOS.[1] The most common empiric regimens used in our NICU include ampicillin plus gentamicin for EOS and vancomycin plus gentamicin for LOS.

A third generation cephalosporin may be added or substituted for gentamicin in cases where patients are severely ill, renal function is poor, or meningitis attributable to Gram-negative organisms is suspected. The third generation cephalosporin often used in the neonatal population is cefotaxime.[1] However, there is a national drug shortage of cefotaxime with intermittent availability since 2015 due to discontinuation by one of its manufacturers. During the shortage, the American Academy of Pediatrics has recommended the use of ceftazidime in place of cefotaxime for neonates and infants < 2 months old. Ceftazidime is FDA-approved for all pediatric age groups and achieves therapeutic concentrations in various tissues and cerebrospinal fluid.[1,2] A notable difference between these 2 agents is ceftazidime has a broader spectrum of Gram-negative coverage and a narrower spectrum of Gram-positive coverage when compared with cefotaxime. Currently, there are no studies comparing clinical outcomes after use of ceftazidime compared with cefotaxime in neonates.

Rapid development of resistance can occur when

cefotaxime is routinely used for EOS.[2] Additionally, prolonged use of a third-generation cephalosporin in general has shown to be an independent risk factor for worse neonatal outcomes. One study found that previous antibiotic exposure to a third-generation cephalosporin was associated with the development of multidrug resistant Gram-negative bacteremia.[3] Another study found that neonates had increased mortality when treated with ampicillin plus cefotaxime when compared with ampicillin plus gentamicin.[4]

The association between prolonged broad-spectrum antibiotic therapy and worse neonatal outcomes, especially in relation to third-generation cephalosporins, led our investigators to research differences in neonatal outcomes between NICU subjects who received cefotaxime and ceftazidime. The primary objective of this study was to determine if the incidence of culture-positive LOS was increased with the use of ceftazidime compared with cefotaxime in the NICU. The secondary objective of this study was to determine if the incidence of multidrug resistant organisms (MDROs) and other neonatal outcomes were increased within the same comparison groups.

Materials and Methods

Subjects. This was a single-center, retrospective cohort study conducted in the NICU at the University of Chicago Medicine Comer Children's Hospital between April 1, 2015, and August 1, 2017. This was approved by our institutional review board on August 18, 2017, and written informed consent was not required. Neonates were included in the study if they received at least 24 hours of cefotaxime or ceftazidime within prespecified time frames in the NICU, as determined by our institutional drug shortage status. During the times of institutional cefotaxime shortage outlined below, ceftazidime was recommended in place of cefotaxime in the NICU, and the electronic medical record only allowed ordering of ceftazidime. Therefore, the predominant use in this study would be expected to be as a replacement for cefotaxime rather than a specific clinical decision by the medical team to use ceftazidime for antipseudomonal coverage. These prespecified time frames based on our institutional availability of cefotaxime were as follows: 1) Cefotaxime (non-shortage time frame): April 1, 2015 to November 2, 2015 and March 23, 2016 to October 25, 2016; 2) Ceftazidime (shortage time frame): November 3, 2015 to March 22, 2016 and October 26, 2016 to August 1, 2017.

Subjects were excluded if they received the alternative study antibiotic for more than 24 hours during the same admission. Each subject was included only once based on the first time the study antibiotic was received. Subjects were permitted to be on other concomitant antimicrobials.

Outcomes. The primary outcome evaluated was culture-positive LOS, defined as a positive blood culture after the first 72 hours of life, which was treated with at least 7 days of targeted antimicrobial therapy. The main secondary outcome evaluated was MDRO infections, which was defined as positive cultures (in blood, cerebrospinal fluid, urine, or tracheal aspirate) with a targeted treatment course of antimicrobials for at least 7 days. Patients were considered to have a MDRO if the isolate tested resistant to an agent in at least 3 antimicrobial classes.[5] If the subject had polymicrobial bacteremia from a single blood culture, only 1 of the isolates was required to be resistant for it to be considered an MDRO infection. Additional neonatal outcomes included the following: 1) Presumed culture-negative sepsis, defined as an antimicrobial therapy course for at least 7 days for presumed sepsis without positive cultures from any source; 2) Stage II to III necrotizing enterocolitis (NEC); 3) Urinary tract infection, defined as a positive urine culture with at least 7 days of targeted antimicrobial therapy; 4) Mortality; 5) Length of stay; 6) Postmenstrual age at discharge; and 7) Adverse events identified by providers in the medical chart as attributable to cefotaxime or ceftazidime.

Data Collection. Baseline data collected on all neonates included gestational age, birthweight, gender, race, mode of delivery, small for gestational age, maternal chorioamnionitis, Apgar scores, day of life (DOL) therapy started, previous duration of exposure to other antibiotics, positive blood cultures or NEC prior to the use of ceftazidime or cefotaxime, duration of the initial course and cumulative days of ceftazidime or cefotaxime, the number of courses during the entire admission, and concomitant antimicrobials.

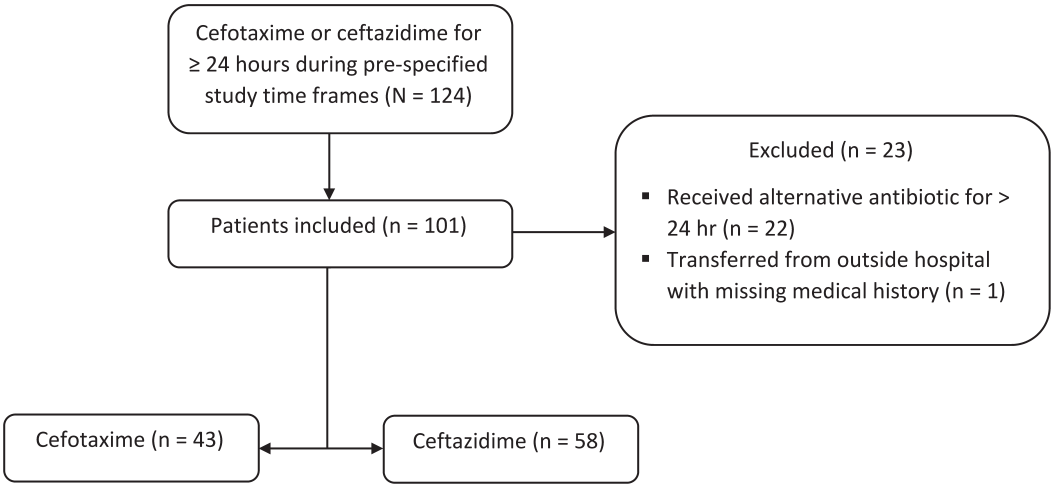
Statistical Analysis. Statistical analyses were performed with STATA version 15.1 for Windows. Categorical variables were analyzed with χ^2 and Fisher exact tests, as appropriate. Continuous variables were analyzed using the Wilcoxon rank sum test and Student *t* test, as appropriate. Multiple logistic regression models adjusting for significant baseline demographics were performed. A p value of < 0.05 was considered statistically significant. Post hoc subgroup analyses were conducted for 2 different gestational age groups: less than 30 weeks' gestation and 30 weeks' gestation or more.

Results

The medical records of 124 neonates who received cefotaxime or ceftazidime within the prespecified time frames were reviewed. Of these, 23 patients were excluded from our analysis (Figure 1), leaving a total of 101 subjects included in the final analysis (ceftazidime, n = 58; cefotaxime, n = 43).

The median gestational ages were significantly different between the ceftazidime and cefotaxime groups (28.1 [IQR, 25–36.6] weeks versus 32.3 [IQR, 26.9–37.4] weeks, respectively, $p < 0.05$). The birth weights were also significantly different between the

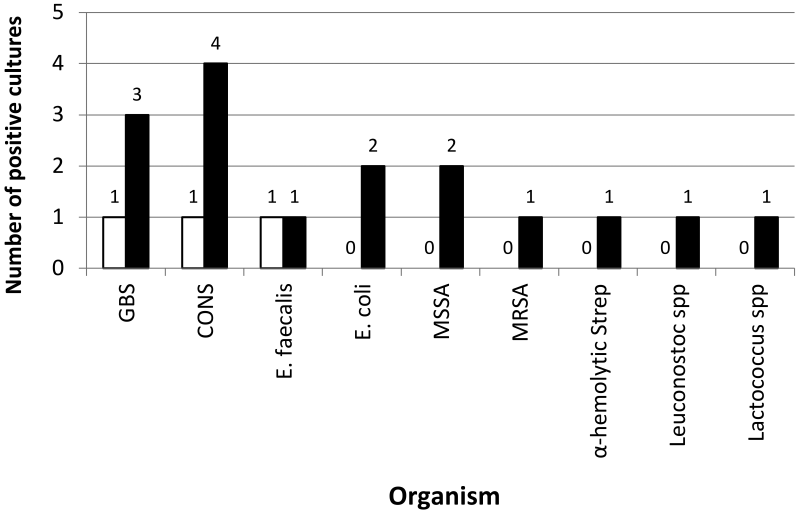
Figure 1. Inclusion and exclusion flow diagram.



groups (990 [IQR, 716.3–2318.8] grams versus 1670 [IQR, 972–3057.5] grams, respectively, p = 0.03). All other baseline demographics were similar between the 2 groups (Table 1). The most common concomitant antimicrobials were gentamicin, ampicillin, and vancomycin. The median time to initiation of ceftazidime versus cefotaxime was 4 (IQR, 1–24.5) days versus 2 (IQR, 1–13) days, respectively (p = 0.4). There was no difference in median initial course duration of antibiotics between the ceftazidime and cefotaxime groups (5 [IQR, 2–11] days versus 3 [IQR, 2–10] days, respectively, p = 0.52). Additionally, the cumulative days of study drug throughout hospital admission were 6 (IQR, 3–11) days versus 3 days (IQR, 2–10.5), respectively (p = 0.29).

There were 11 cases (10.9%) of culture-positive LOS in the total population (Table 2). Of these, 10 were in the ceftazidime group (17.2% of 58 subjects) versus 1 in the cefotaxime group (2.3% of 43 subjects). When adjusting for gestational age, the primary outcome was not statistically significant (adjusted OR, 6.51 [95% CI,

Figure 2. Positive blood culture organisms* after the initiation of cefotaxime or ceftazidime.



CONS, coagulase-negative Staphylococcus; GBS, Group B Streptococcus; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; spp, species; Strep, Streptococcus

* Cultures may be polymicrobial.

☐ Cefotaxime; ■ Ceftazidime

Table 1. Baseline Demographics

Parameter	Ceftazidime (n = 58)	Cefotaxime (n = 43)	p value
Gestational age, wk, median (IQR)	28.1 (25–36.6)	32.3 (26.9–37.4)	< 0.05
Birthweight, g, median (IQR)	990 (716.3–2318.8)	1670 (972– 3057.5)	0.03
Male, n (%)	32 (55.2)	25 (58.1)	0.77
Race, black, n (%)	44 (75.9)	24 (55.8)	0.15
Cesarean section, n (%)	34 (58.6)	20 (46.5)	0.23
Small for gestational age, n (%)	14 (24.1)	8 (18.6)	0.51
Chorioamnionitis, n (%)	18 (31.0)	15 (34.9)	0.68
Apgar score at 1 min, median (IQR)	5 (2–7)	3 (1–7)	0.48
Apgar score at 5 min, median (IQR)	7 (6–8)	7 (6–8)	0.73
Day of life therapy started, median (IQR)	4 (1–24.5)	2 (1–13)	0.4
Positive blood culture prior to initiation, n (%)	11 (19.0)	9 (20.9)	0.81
NEC prior to initiation, n (%)	6 (10.3)	3 (7.0)	0.73
Prior exposure to other antibiotics, days, median (IQR)	4.5 (1–13.8)	3 (2–13)	0.3
Duration of initial course of study antibiotic, days, median (IQR)	5 (2–11)	3 (2–10.5)	0.52
Cumulative days of study antibiotic during admission, days, median (IQR)	6 (3–11)	3 (2–10.5)	0.29
Concomitant antimicrobials, n (%)			
None	1 (1.7)	1 (2.3)	0.83
Ampicillin	36 (62.1)	34 (79.1)	0.07
Gentamicin	48 (82.8)	40 (93.0)	0.15
Vancomycin	28 (48.3)	13 (30.2)	0.07
Metronidazole	7 (12.1)	4 (9.3)	0.46
Piperacillin/tazobactam	0 (0)	1 (2.3)	0.43
Cefepime	1 (1.7)	0 (0)	1
Meropenem	0 (0)	1 (2.3)	0.43
Acyclovir	5 (8.6)	6 (14.0)	0.52
Antifungal	9 (15.5)	6 (14.0)	0.83
Other	2 (3.4)	2 (4.6)	1

NEC, necrotizing enterocolitis

0.78–55.23], p = 0.09). All cases of culture-positive LOS were related to bacterial organisms. The most common positive blood cultures seen were coagulase-negative *Staphylococcus* and group B *Streptococcus* (Figure 2). The secondary outcome of MDRO infections was not significantly different between groups, with 3/58 (5.2%) cases in the ceftazidime group versus 0/43 (0%) cases in the cefotaxime group (p = 0.26). Four MDRO were found in 3 subjects: 1) extended spectrum beta-lactamase (ESBL)-producing *E coli* in the blood; 2) *Pseudomonas aeruginosa* in the urine; and 3) ESBL-producing *E coli* in the urine in addition to *P aeruginosa* in a tracheal aspirate.

There were 13 cases (22.4%) of stage II to III NEC in the ceftazidime group versus 1 case (2.3%) in the cefotaxime group. This outcome remained statistically significant when adjusted for gestational age (adjusted OR, 9.68 [95% CI, 1.18–79.45], p = 0.04). Results also showed a non-significant increased incidence of presumed culture-negative sepsis in the ceftazidime group versus the cefotaxime group (37.9% versus 20.9%, respectively, p = 0.07). No differences were noted for mortality, postmenstrual age at discharge, incidence of urinary tract infections, hospital length of stay, or adverse events.

Due to the significant difference in median gestational age between groups, post hoc subgroup analyses were performed for 2 cohorts: infants born

Table 2. Clinical Neonatal Outcomes

Outcome	Ceftazidime (n = 58)	Cefotaxime (n = 43)	Unadjusted p value	Adjusted* Odds Ratio (95% CI), p value
Culture-positive LOS after initial course of study antibiotic, n (%)	10 (17.2)	1 (2.3)	0.02	6.51 (0.78–55.23), 0.09
MDRO infection† after initial course of study antibiotic, n (%)	3 (5.2)	0 (0)	0.26	
Presumed culture-negative sepsis after initial course of study antibiotic, n (%)	22 (37.9)	9 (20.9)	0.07	
Stage II–III NEC after initial course of study antibiotic, n (%)	13 (22.4)	1 (2.3)	< 0.01	9.68 (1.18–79.45), 0.04
Medical, n (%)	12 (20.7)	1 (2.3)		
Surgical, n (%)	1 (1.7)	0 (0)		
Urinary tract infection† after initial course of study antibiotic, n (%)	7 (12.1)	6 (14.0)	0.07	
Hospital length of stay, days, median (IQR)	78 (32–120)	43 (18– 97)	0.05	
Postmenstrual age at discharge, wk, median (IQR)	41.4 (38.6–45)	40.9 (37.9–47.4)	0.9	
Death, n (%)	4 (6.9)	5 (11.6)	0.49	
Adverse events, n (%)	0 (0)	0 (0)	—	

LOS, late-onset sepsis; MDRO, multidrug resistant organism; NEC, necrotizing enterocolitis

* Adjusted for gestational age. Odds ratio reflects odds of occurrence with ceftazidime compared with cefotaxime.

† Infection = positive cultures with a targeted treatment course of antibiotics.

at less than 30 weeks' gestational age or infants born at 30 weeks' gestational age or more. The median gestational age in the less than 30 weeks' gestational age subgroup (n = 52) was similar for ceftazidime compared with cefotaxime (25 [IQR, 24.6–27.4] weeks versus 26.3 [IQR, 25–28.7] weeks, respectively, p = 0.34). For those born less than 30 weeks' gestational age, there was a significant increase in culture-positive LOS in the ceftazidime group versus the cefotaxime group [10/35 cases (28.6%) versus 0/17 cases (0%), respectively (p = 0.021)]. Additionally, for those born at 30 weeks' gestational age or more (n = 49), there was an increase in presumed culture-negative sepsis in the ceftazidime group versus the cefotaxime group (11/23 cases [47.8%] versus 5/26 cases [19.2%], respectively, p = 0.033). There were no other significant differences found in the subgroup analyses.

A multiple logistic regression analysis was performed adjusted for significant baseline demographics. When adjusted for gestational age at birth, cumulative duration (days) of third-generation cephalosporin (either ceftazidime or cefotaxime) was found to increase the odds of a MDRO infection (adjusted OR, 1.13 [95% CI, 1–1.26], p = 0.04). Cumulative duration of third-generation was not found to be a statistically significant risk factor for culture-positive LOS, presumed culture-negative sepsis, or NEC. When adjusted for other significant baseline demographics, increasing gestational age was found to decrease the odds of culture-positive LOS (adjusted OR, 0.81 [95% CI, 0.67–0.99], p = 0.04). No other significant associations were found.

Discussion

The prolonged use of antibiotics in the neonatal population, especially preterm neonates, has been repeatedly found to be associated with negative long-term outcomes. A study by Kuppala et al[6] determined that prolonged empiric antibiotic therapy was associated with an increased odds of LOS (OR, 2.45 [95% CI, 1.28–4.67]) and the combined outcomes of LOS, NEC, or death (OR, 2.66 [95% CI, 1.12–6.3]). Another study by Cotten et al[7] suggested an association with prolonged antibiotic therapy (5 or more days) in extremely low birth weight neonates and an increased odds of NEC or death. Specifically, they found an approximate 4% increase in the odds of NEC or death with each additional day of initial empirical antibiotic treatment in these infants.

Additional concerns have been placed specifically on the use of cephalosporins in neonates. Bryan et al[8] demonstrated a rapid development of cefotaxime-resistant *Enterobacter cloacae* within 10 weeks when cefotaxime was used in place of gentamicin for empiric therapy of neonatal sepsis. When used empirically for EOS, Clark et al[4] found that neonates had increased mortality when treated with ampicillin plus cefotaxime compared with ampicillin plus gentamicin (adjusted OR, 1.5 [95% CI, 1.4–1.7]). This evidence led our investi-

gators to further explore the use of cephalosporins in neonates, specifically a comparison between agents due to the cefotaxime shortage.

In this study, we found a statistically significant increased incidence of stage II to III NEC and non-statistically significant increases in culture-positive LOS, MDRO infections, and presumed culture-negative sepsis with the use of ceftazidime versus cefotaxime. We found that lower gestational ages and lower birth weights were more likely to be found in the ceftazidime group versus the cefotaxime group; however, the cause of this difference is unclear. Our unit has seen an overall increased census of extremely low birth weight neonates in recent years, which may have contributed to the difference because the dates of the cefotaxime shortage were more recent.

Although our primary outcomes of culture-positive LOS and MDRO infections were non-significant after adjusting for gestational age and birth weight, it is possible that we were unable to detect a significant difference due to the limited sample size of the population. Of the culture-positive LOS cases, 10 of the 11 (91%) cases were in the ceftazidime group. Similarly, all 3 neonates (100%) with MDRO infections and 22 of the 31 (71%) presumed culture-negative sepsis cases were found in the ceftazidime group versus the cefotaxime group. Characteristics that were similar among the 3 neonates who developed MDRO infections included use of ceftazidime, younger gestational ages of 24.9 to 27 weeks, and lower birth weights of 700 to 900 grams. There was more variability among the 3 neonates with MDRO infections regarding DOL at ceftazidime initiation (1–127 DOL), duration of ceftazidime exposure (3–49 days), and total prior exposure to other antibiotics prior to ceftazidime initiation (1–44 days). Previous studies have found an increased risk of MDRO infections and worse neonatal outcomes with the use of third generation cephalosporins; however, data in the neonatal population regarding differences in outcomes between agents in this class are unknown. Our data suggest that further research regarding neonatal outcomes with the use of ceftazidime when compared with cefotaxime is warranted in a larger cohort of patients.

Previous studies have shown that being born with extremely low birth weight (< 1000 grams) and extremely preterm are independent risk factors associated with resistant *Enterobacteriaceae* and ESBL-producing *Klebsiella pneumoniae* infections in critically ill neonates.[9,10] Similarly, our study found an increased risk of culture-positive LOS in this same subgroup of neonates, and more specifically, in neonates who received ceftazidime instead of cefotaxime. A study by Tsai et al[3] has shown that previous antibiotic exposure to a third-generation cephalosporin is associated with the acquisition of MDRO Gram-negative bacteremia. We similarly found that cumulative duration of third-generation cephalosporin use was an independent risk factor for development of an MDRO infection.

Limitations of this study include the difference in gestational age between groups, single-centered study design, retrospective analysis, and a relatively small patient population resulting an inability to obtain 80% power. The actual indication for the use of ceftazidime was also unknown for most neonates. Although we attempted to control for this by using prespecified dates based on the cefotaxime shortage, it is possible that antipseudomonal coverage was actually desired. Additionally, due to the retrospective nature of the study, the definition of culture-positive LOS was limited to include patients who received an antibiotic course of at least 7 days, which targeted an organism on culture; however, this could have included cases in which the organism may have been a contaminant and the clinical decision to treat with antibiotics could vary by provider.

Conclusion

Overall, this study found a statistically significant increase in stage II to III NEC with the use of ceftazidime compared with cefotaxime. There was also a numerically higher rate of culture-positive LOS, MDRO infections, and culture-negative presumed sepsis in neonates who received ceftazidime. Although these findings were non-significant, the small sample size may have limited our ability to detect a difference in these neonatal outcomes. Similar to previous studies, we found that prolonged use of third-generation cephalosporins may be associated with the development of MDRO infections in neonates, and that gestational age and birth weight may increase the risk of culture-positive LOS. Further multicenter research is warranted to assess the effect of this drug shortage on the neonatal population and the implications of using ceftazidime for neonatal sepsis.

ARTICLE INFORMATION

Affiliations Department of Pharmacy (PDP), Baptist Hospital, Miami, FL, Department of Pharmacy (PB, DSB), University of Chicago Medicine Comer Children's Hospital, Chicago, IL, Section of Infectious Diseases (AHB), University of Chicago Medicine Comer Children's Hospital, Chicago, IL

Correspondence Deborah S. Bondi, PharmD; deborah.bondi@uchospitals.edu

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee did not require HIPAA Waiver of Authorization, Waiver of Assent, and Waiver of Parental Permission under Expedited criterion.

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