

JPPT | Single System Multi-Hospital Retrospective Study

Comparing the Frequency of Culture-Positive Late Onset Sepsis With the Use of Ceftazidime Versus Cefotaxime in the NICU

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OBJECTIVE As broader spectrum antibiotics have been associated with adverse effects, our study evaluated whether the frequency of culture-positive late-onset sepsis (LOS) and multidrug resistant (MDR) infections were increased with the use of ceftazidime as compared with cefotaxime in the neonatal intensive care unit (NICU).

METHODS This was a multihospital, retrospective chart review of patients who received at least 24 hours of ceftazidime or cefotaxime in the NICU between December 1, 2012 and August 31, 2021. Patients were excluded from analysis if they expired during the admission, had an incomplete history, positive cultures for an MDR infection prior to receiving either antibiotic, or received the alternate antibiotic within the same treatment course.

RESULTS A total of 334 patients were included for analysis (ceftazidime, n = 147; cefotaxime, n = 187). The average birth weight was lower in the ceftazidime cohort compared with the cefotaxime cohort [1.46 kg (95% CI, 1.29–1.63 kg) versus 1.93 kg (95% CI, 1.75–2.11 kg), p = 0.0002] with a corresponding lower gestational age [28.9 weeks (95% CI, 28.0–29.9 weeks) versus 31.7 weeks (95% CI, 30.8–32.6 weeks), p = 0.0001]. Adjusting for baseline differences showed a protective effect for ceftazidime (OR = 0.32; 95% CI, 0.16–0.62; p = 0.0009). There was no statistically significant difference in the frequency of MDR infections between the cohorts (OR = 0.25; 95% CI, 0.053–1.14; p = 0.07), however this study was underpowered to detect the difference noted.

CONCLUSIONS Ceftazidime appears to be a safe and effective alternative treatment option compared with cefotaxime in the NICU with no increase in the risk of culture-positive LOS or MDR infections.

ABBREVIATIONS EOS, early-onset sepsis; ELBW, extremely low birth weight; ESBL, extended spectrum beta-lactamase; LOS, late-onset sepsis; MDR, multidrug resistant; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PNA, postnatal age; VLBW, very low birth weight

KEYWORDS cefotaxime; ceftazidime; neonates; multidrug resistance; necrotizing enterocolitis

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Introduction

The incidence of culture-positive early-onset sepsis (EOS), occurring within the first 72 hours of life in neonates, is estimated to be between 0.8 to 1 per every 1000 live births, with the highest rates of mortality occurring in very low birth weight (VLBW) infants weighing less than 1000 grams.¹ Empiric management of suspected EOS in the neonatal intensive care unit (NICU) requires coverage of the most common organisms responsible for infection such as *Streptococcus agalactiae* (group B Streptococcus), *Escherichia coli*, and *Listeria monocytogenes*.¹ Ampicillin combined with an aminoglycoside is typically the initial empiric therapy of choice for suspected EOS. A third-generation cephalosporin may be used as part of the antimicrobial

regimen for EOS when dual coverage is desired (e.g., MDR infections), for central nervous system involvement (e.g., meningitis), or in cases of severe renal impairment to avoid the nephrotoxicity of aminoglycosides.² With activity against many organisms likely to cause EOS, in addition to proven safety and efficacy, cefotaxime has historically been the third-generation cephalosporin of choice in neonates for the empiric treatment of EOS. However, cefotaxime has been on a national shortage since 2015 due to manufacturer discontinuation.³ The lack of cefotaxime availability due to the national shortage has warranted the alternative use of ceftazidime or cefepime, both of which provide broader Gram-negative coverage including antipseudomonal coverage.³

Various studies have noted potential risks associated with utilizing third-generation cephalosporins, including cefotaxime and ceftazidime, in the NICU.^{4–8} To date, Patel et al⁵ is the only published study that compares NICU clinical outcomes specifically after the use of ceftazidime ($n = 58$) compared with cefotaxime ($n = 43$). The use of ceftazidime in neonatal patients receiving treatment for EOS was associated with an increase in stage II and III necrotizing enterocolitis (NEC) when compared with cefotaxime (22.4% versus 2.3%, $p = 0.04$). Additionally, they observed a trend toward increased rates of culture-positive late-onset sepsis (LOS) (17.2% versus 2.3%, $p = 0.09$) and MDR infections (5.2% versus 0%, $p = 0.26$) with the use of ceftazidime compared with cefotaxime. The authors concluded that ceftazidime was associated with increased rates of culture-positive LOS, MDR infections, and culture-negative presumed sepsis compared with cefotaxime. However, this single center small study was underpowered to detect many statistical differences in outcomes.

The objective of our study was to examine similar trends or increased adverse events in our NICU population using a larger sample size. Once the national cefotaxime shortage began in 2015, ceftazidime became the predominant alternative agent, in alignment with American Academy of Pediatrics recommendations.³

Materials and Methods

This was a single institution, multihospital, retrospective chart review of patients admitted to the NICU at any of 4 hospitals within the same health system in Northern Virginia between December 1, 2012 and August 31, 2021. Three facilities were level III NICUs with 1 level IV NICU totaling 187 NICU beds. Neonatal subjects were included in the study if they had received cefotaxime or ceftazidime for at least 24 hours. Subjects were excluded if they expired during the admission, had an incomplete history with unavailable documentation (e.g., transferred to outside hospital with no further access to their electronic medical record), had a positive culture for an MDR infection prior to receiving one of the antibiotics, or received both cefotaxime and ceftazidime for their initial antibiotic treatment course (inclusive of EOS and LOS).

Baseline data collected on all neonatal subjects included birth weight, birth weight classification, gestational age, postnatal age (PNA) at cephalosporin initiation, indication for treatment, duration of therapy, and concomitant antimicrobials. Primary outcomes were frequency of culture-positive LOS and of MDR infections after treatment. Culture-positive was defined as a positive culture from any source obtained after the first 72 hours of life. Multidrug resistant was defined as a positive culture for an isolate resistant to at least 3 antimicrobial classes.⁹ Secondary outcomes assessed the frequency of any sepsis evaluation following treat-

ment with cefotaxime or ceftazidime, the total number of sepsis evaluations per patient, hospital length of stay, the frequency of fungal infections following treatment, and the frequency of stage II or III NEC. Data regarding outcomes was collected only from the specific admission during which neonatal subjects received either cefotaxime or ceftazidime. There was no *a priori* sample size/power calculation performed for the study. Rather, all eligible patient charts over the approximately 8.75-year interval of interest were reviewed. Nominal and ordinal measures were evaluated with categorical statistical techniques, and data were reported as frequency (%). Interval measures were evaluated with parametric and nonparametric 2-sample tests, and data were reported as mean (95% CI). When appropriate, these data were reported as median (IQR). Correlation coefficients were used to evaluate the association of the predictor variable with the outcome variables, as well as the association among potential predictor variables. Data were reported as Spearman or Pearson correlation coefficients (ρ). Logistic regression was used to adjust for statistically significant differences between drug cohorts at baseline. Outcomes were reported as odds ratios (95% CI). All statistical tests were 2-sided and $p < 0.05$ was considered to indicate statistical significance. All analyses were conducted using SAS software (v9.4, SAS Institute).

Results

The patient chart selection process is shown in the Supplemental Figure. A total of 437 neonates were identified within the prespecified timeframe that had received at least 24 hours of cefotaxime or ceftazidime. All subjects had cultures drawn prior to antibiotic administration. Of the 437 subjects, 103 were excluded for various reasons resulting in 147 subjects in the ceftazidime cohort and 187 patients in the cefotaxime cohort.

Baseline patient characteristics are described in Table 1. Mean birth weight was lower in the ceftazidime cohort (1.46 kg; 95% CI, 1.29–1.63 kg) versus the cefotaxime cohort (1.93 kg; 95% CI, 1.75–2.11 kg); $p = 0.0002$. In terms of birth weight intervals, the ceftazidime cohort had a higher frequency of extremely low birth weight (ELBW) neonates (54% versus 36%, $p = 0.001$) and a lower frequency of normal birth weight neonates (22% versus 37%, $p = 0.004$). The ceftazidime cohort had a lower mean gestational maternal age than the cefotaxime cohort (28.9 weeks; 95% CI, 28.0–29.9) versus (31.7 weeks; 95% CI, 30.8–32.6), $p = 0.0001$.

Concomitant antimicrobial use is described in Table 1. Ampicillin and gentamicin were the most common concomitant antimicrobials administered. The ceftazidime cohort had a lower frequency of concomitant ampicillin (81% versus 92%, $p = 0.003$). Other antibiotics utilized in the assessed patients included vancomycin, metronidazole, piperacillin-tazobactam, azithromycin, ceftazolin,

Table 1. Baseline Patient Characteristics

Parameter	Ceftazidime (n = 147)	Cefotaxime (n = 187)	p value
Birth weight, mean [95% CI], kg	1.46 [1.29–1.63]	1.93 [1.75–2.11]	0.0002
ELBW (<1 kg), n (%)	79 (54)	68 (36)	0.001
VLBW (1–1.49 kg), n (%)	16 (11)	24 (13)	0.59
LBW (1.5–2.49 kg), n (%)	19 (13)	26 (14)	0.81
Birth weight ≥2.5 kg, n (%)	33 (22)	69 (37)	0.004
Gestational maternal age, mean [95% CI], wk	28.9 [28–29.9]	31.7 [30.8–32.6]	0.0001
PNA at cephalosporin initiation, median [IQR], days	1 [0–6]	0 [0–1]	0.02
Indication			
Early onset sepsis, n (%)	116 (79)	171 (91)	0.0001
Tracheitis, n (%)	10 (7)	4 (2)	0.05
Bacteremia, n (%)	7 (5)	3 (2)	0.11
Necrotizing enterocolitis, n (%)	3 (2)	3 (2)	1.00
Pneumonia, n (%)	4 (3)	1 (1)	0.17
Cellulitis, n (%)	1 (1)	0 (0)	0.44
Urinary tract infection, n (%)	2 (1)	1 (1)	0.58
Other,* n (%)	4 (3)	4 (2)	0.73
Duration of therapy, mean [95% CI], days	5.22 [4.35–6.10]	3.88 [3.45–4.31]	0.007
Concomitant antimicrobials administered			
Gentamicin, n (%)	129 (88)	176 (94)	0.10
Ampicillin, n (%)	119 (81)	172 (92)	0.003
Acyclovir, n (%)	6 (4)	6 (3)	0.15
Antifungals, n (%)	3 (2)	0 (0)	0.50
Other antibiotics, [†] n (%)	26 (18)	21 (11)	0.16

ELBW, extremely low birth weight; LBW, low birth weight; PNA, postnatal age; VLBW, very low birth weight

*Other indications include clinical manifestations of neonatal sepsis without a determined source of infection.

[†]Other antibiotics administered include vancomycin, metronidazole, piperacillin-tazobactam, azithromycin, cefazolin, nafcillin, and sulfamethoxazole-trimethoprim.

nafcillin, and sulfamethoxazole-trimethoprim. There were no statistically significant differences between cohorts for their administration. The median PNA at cephalosporin initiation was higher in the ceftazidime cohort (1 day; IQR, 0–6 days) versus (0 days; IQR, 0–1 days), $p = 0.02$. The ceftazidime cohort had a lower frequency of antibiotic therapy for early onset sepsis (79% versus 91%, $p = 0.0001$), but higher mean duration of therapy days (5.22 days; 95% CI, 4.35–6.10 days) versus (3.88 days; 95% CI, 3.45–4.31 days), $p = 0.007$. No other indications for antimicrobial use were statistically significantly different between cohorts.

Primary outcomes are described in Table 2. An adjusted odds ratio was calculated to account for the differences noted in baseline characteristics. The frequency of culture-positive LOS was lower in the ceftazidime cohort but did not reach statistical significance (15% versus 21%, $p = 0.13$). However, the adjusted odds ratio favored ceftazidime use (OR = 0.32; 95% CI, 0.16–0.62; $p = 0.0009$). The number needed to treat was approximately 17. There was no significant difference in the frequency of MDR infections between the cohorts, but the total number of cases were few (2% versus 5%, $p = 1.00$). The adjusted odds ratio favored

ceftazidime use (OR = 0.25; 95% CI, 0.053–1.14; $p = 0.07$), but the difference was not statistically significant and the cases were few (3 versus 9).

Multidrug resistant infections noted in the cefotaxime cohort included *Pseudomonas aeruginosa* tracheitis ($n = 1$), conjunctivitis ($n = 1$), and cellulitis ($n = 1$); methicillin-resistant *S epidermidis* bacteremia ($n = 1$), methicillin-resistant *S aureus* pneumonia ($n = 1$), *Stenotrophomonas maltophilia* pneumonia ($n = 1$), and extended spectrum beta-lactamase (ESBL)-producing *E coli* urinary tract infection ($n = 1$). MDR infections noted in the ceftazidime cohort included methicillin-resistant *S epidermidis* bacteremia ($n = 2$) and ESBL-producing *E coli* urinary tract infection ($n = 1$).

Secondary outcomes are described in Table 3. There was no significant difference in the frequency of sepsis evaluations following treatment between the cohorts (28% versus 32%, $p = 0.47$). The median total number of sepsis evaluations in patients with at least 1 evaluation was the same, but the IQR was narrower in the ceftazidime cohort (1 [IQR, 1–2] versus 1 [IQR, 0–6], $p = 0.41$). The frequency of total fungal infections was lower in the ceftazidime cohort (5% versus 9%, $p = 0.25$). Most of the fungal infections were characterized as a

Table 2. Primary Outcomes After Treatment With Cephalosporins

Outcomes	Ceftazidime (n = 147)	Cefotaxime (n = 187)	Unadjusted p value	Adjusted OR (95% CI)* p value
Cases of culture-positive LOS, n (%)	22 (15)	40 (21)	0.13	0.32 (0.16–0.62), 0.0009
Cases of MDR infection after treatment with cephalosporin, n (%)	3 (2)	9 (5)	1.00	0.25 (0.053–1.14), 0.07

LOS, late-onset sepsis; MDR, multidrug resistant

*ORs adjusted for birth weight, gestational maternal age, early onset sepsis, postnatal age at cephalosporin initiation, duration of therapy, length-of-stay.

monial rash in both cohorts, but the frequency was lower among ceftazidime neonates (63% versus 75%, $p = 0.87$). Other sources of fungal infections noted in the ceftazidime cohort included 2 subjects with candidemia and 1 subject with peritoneal candidiasis. Other sources of fungal infections noted in the cefotaxime cohort included 2 subjects with candidemia; 1 subject with congenital cutaneous candidiasis; and 1 subject with *Candida* tracheitis. Three patients in the ceftazidime cohort had stage II or III NEC, while there were no cases in the cefotaxime cohort (7% versus 0%, $p = 0.10$). Mean length of stay was longer in the ceftazidime cohort (88.3 days [95% CI, 79.4–97.2 days] versus 65.1 days [95% CI: 57.2–73.0 days], $p = 0.0001$).

Discussion

Cotten et al⁴ showed use of third-generation cephalosporin in ELBW neonates ($n = 3702$), especially for a duration of therapy beyond 5 days, was associated with increased incidence of candidiasis ($r = 0.67$, $p = 0.017$). Another study conducted by Clark et al⁶ in 128,914 NICU patients showed use of cefotaxime with ampicillin was associated with an increased rate in mortality compared with the use of gentamicin with ampicillin (OR, 1.5; 95% CI, 1.4–1.7). Increased mortality was also reported with exposure to a third-generation cephalosporin or a carbapenem (28.6% versus 10.5%; $p < 0.001$) in a study conducted in 1106 neonates.⁷ Tsai et al⁷ also noted the risk for acquisition of MDR Gram-negative bacterial infections were increased more than 2-fold (95% CI, 2.37–15.08; $p < 0.001$) and was associated with increased infectious complications (21.4% versus 10.5%; $p = 0.011$). One retrospective study of 349 isolates ($n = 215$) from NICU patients exposed to ceftazidime noted each day of ceftazidime exposure was associated with 13% greater odds of *P aeruginosa* resistance (OR_{adj} 1.13; 95% CI, 1.03–1.23).⁸

Our findings contrast to other research that showed an increase in subsequent MDR infections and other adverse outcomes including NEC and culture-positive LOS when ceftazidime was used over cefotaxime.^{5–7}

Previously Mayes et al⁸ reported an increased risk for MDR infections in NICU patients following prolonged ceftazidime exposure compared with no ceftazidime exposure (adjusted OR for each additional day of cephalosporin therapy: 1.13; 95% CI, 1.03–1.23). Patel et al⁵ also performed a multivariate linear regression showing that cumulative days of exposure to cefotaxime or ceftazidime were associated with acquisition of MDR infections (adjusted OR, 1.13; 95% CI, 1.00–1.26; $p = 0.04$). Despite our ceftazidime cohort receiving antibiotic therapy for a significantly longer duration than the cefotaxime cohort, the likelihood of MDR infections was lower for the ceftazidime group, although not statistically significant (adjusted OR, 0.25; 95% CI, 0.53–1.14; $p = 0.07$). Possible explanations for our failure to observe an increase in MDR infections following ceftazidime use include regional differences in background MDR organism frequency compared to other studies and antimicrobial stewardship interventions at our study sites, which decreased overall selective pressure for MDR organisms. Additionally, the difference in duration of therapies noted in our study (5.22 versus 3.88 days) may not have been large enough to note a significant impact on the risk for MDR infections given Mayes et al⁸ reported an adjusted OR of 1.13 for each additional day of therapy. Nevertheless, our finding may challenge the notion that increased duration of therapy and the use of broader spectrum antibiotics, such as ceftazidime, always increases the risk for MDR infections in NICU patients.

Patel et al⁵ identified additional cautionary outcomes relating to the use of ceftazidime as an alternative agent to cefotaxime in the NICU including a significantly increased risk for stage II or III NEC. Cotten et al⁴ also demonstrated an increased risk for NEC in patients requiring prolonged antibiotic therapy. In our study we found no statistically significant increased risk of NEC following prolonged antibiotic exposure in the ceftazidime cohort. However, the absolute difference between NEC frequencies was too small to provide sufficient power to detect such a difference.

Table 3. Secondary Outcomes After Treatment With Cephalosporins

Outcomes	Ceftazidime (n = 147)	Cefotaxime (n = 187)	p value
Sepsis evaluation after treatment with cephalosporin, n (%)	41 (28)	59 (32)	0.47
Median total number of sepsis evaluations (in patients with ≥ 1 evaluations), median [IQR]*	1 [1–2]	1 [0–6]	0.41
Fungal infection after treatment with cephalosporin, n (%)	8 (5)	16 (9)	0.25
Mean length of stay, days [95% CI]	88 [79.4–54.5]	65 [57.2–73.0]	0.0001
Stage II or III NEC after treatment with cephalosporin, n (%)	3 (7) [†]	0 (0)	0.10

NEC, necrotizing enterocolitis

*Denominators for ceftazidime (n = 41) and cefotaxime (n = 59).

[†]Five total sepsis evaluations for stage II or III NEC occurred after administration of ceftazidime, 2 evaluations were in the same patient.

Unlike Cotten et al,⁴ we did not observe a higher frequency of total fungal infections. Although the frequency of total fungal infections was lower in our ceftazidime cohort, there were no statistically significant differences between antimicrobial cohorts. When fungal infections occurred, they most frequently were related to fungal dermatitis with a low frequency of invasive candidiasis.

We also saw no difference in the frequency of sepsis evaluations between ceftazidime and cefotaxime cohorts (28% versus 32%, $p = 0.47$). However, in our study, the likelihood of culture-positive LOS was lower for ceftazidime (OR_{adj}, 0.32; 95% CI, 0.16–0.62; $p = 0.0009$). The longer duration of ceftazidime use compared with cefotaxime in our study may be due to cefotaxime typically being used as part of the empiric antimicrobial regimen for EOS evaluation, with transition to ceftazidime for definitive treatment of infections from organisms such as *P aeruginosa*. Lastly, there was a significantly increased length of stay noted in the ceftazidime cohort compared with the cefotaxime cohort. This was likely attributed to the lower gestational ages and birth weights noted in the ceftazidime cohort, similar to prior studies, as no other causes were identified.¹⁰ Though mortality can serve as a marker of antibiotic failure, this was not an outcome followed in our study to allow for a focus on the outcomes of length of stay and the frequency of LOS. Mortality in this patient population is also likely multifactorial making it difficult to correlate specifically to cephalosporin therapy chosen. Additionally, Patel et al¹⁵ noted no significant differences in mortality between the cefotaxime and ceftazidime cohorts in their study.

It is ultimately difficult to measure the potential confounding effect our antimicrobial stewardship program had on our results. Patients in the ceftazidime cohort were less likely to receive concomitant ampicillin, with no other significant differences in concomitant antimicrobial administration noted between the cohorts. This may be associated with changes in antimicrobial

stewardship practices within our health system since 2016 that have discouraged the use of unnecessary additional antibiotics.

Our study is not without limitations. This was a single institution, multihospital retrospective chart review, which is subject to bias, missing data, changes in definition of variables and processes of care over time, and unmeasured confounders. We attempted to address these by having 2 authors collect and review all data for consistency. Variables and processes were defined prior to data collection based on available literature and discussion with clinicians. There were many baseline differences between our cohorts on characteristics known to influence our study outcomes, including birth weight, gestational age, indication, and duration of therapy. While we were able to adjust for these confounders with a multivariate logistic model, this adjustment would not account for unmeasured confounders, such as changes in antimicrobial stewardship practices, including updates to unit policies and infection prevention bundles, that occurred within our health system within the timeframe of our study. It is difficult to measure what affect these stewardship interventions had on our observed outcomes. Additionally, we were not able to extrapolate how individual adjusted variables impacted adjusted odds ratios to reduce bias. Obtaining this information may have resulted in choosing risk factors that could sway statistical outcomes back in favor of the unadjusted odds ratios. Data such as average ventilator and central line days between the cohorts would have also been useful to collect as it may have influenced infection risk or choice of antibiotic therapy.

Caution should be exercised in the interpretation of our primary outcomes. Although our statistical model was well-fit and showed a highly statistically significant adjusted difference for culture-positive LOS in favor of ceftazidime, the variance explained was low ($R^2 = 0.30$), suggesting potential operating influences not captured in the model. Further, the MDR

analyses were underpowered to detect the empirical difference seen between cohorts. Finally, there is evidence to support underdetected bacterial growth in neonatal cultures due to low collected volumes.¹¹ Underdetection of bacterial growth in cultures may have led to a decreased frequency of culture-positive LOS noted. Lastly, neonatal subjects were only followed for the duration of the admission, therefore the true risk for future LOS or MDR infections was likely underestimated.

Conclusion

Ceftazidime appears to be a safe and effective alternative treatment option compared with cefotaxime in the NICU with no increase in the risk of culture-positive LOS. However, the lack of sufficient data does not allow us to make any determination about ceftazidime's effect on MDR infections. Continuing research efforts will be required to clarify the use of ceftazidime for the treatment of neonatal sepsis.

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the nature of our study, informed consent was not required.

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