JPPT | Retrospective Study

# Occurrence of Hyperbilirubinemia in Neonates Given a Short-term Course of Ceftriaxone versus Cefotaxime for Sepsis

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**OBJECTIVE** Ceftriaxone and cefotaxime are appealing options for the treatment of neonatal infections. Guidelines recommend cefotaxime as the cephalosporin of choice in neonates because of ceftriaxone's potential to cause hyperbilirubinemia. Unfortunately, due to cefotaxime discontinuation, providers must choose between alternative antibiotics. Clinicians at our institution adopted a protocol allowing for the utilization of cefepime and ceftriaxone for the management of neonatal sepsis. The objective of this study was to compare the incidence of hyperbilirubinemia between ceftriaxone and cefotaxime in the treatment of neonatal infections beyond the first 14 days of life.

**METHODS** This was a retrospective chart review of patients receiving ceftriaxone or cefotaxime for the treatment of neonatal infections. Patients were 15 to 30 days old at the time of antimicrobial administration and received at least 1 dose of ceftriaxone or cefotaxime during hospital admission. Patient characteristics and bilirubin levels were compared between ceftriaxone and cefotaxime.

**RESULTS** The analysis included 88 patients. There was no statistically significant difference between groups in age, gestational age, weight, and baseline total calcium and bilirubin levels. Normal baseline bilirubin levels increased to an abnormal level after antibiotic administration in 2 patients in the cefotaxime group and 1 patient in the ceftriaxone group. The median number of doses of cefotaxime and ceftriaxone were 3 and 2, respectively.

**CONCLUSION** Patients who received a short-term course of ceftriaxone did not have a higher likelihood of developing hyperbilirubinemia compared with those who received a short-term course of cefotaxime during their hospital stay.

**ABBREVIATIONS** ED, emergency department; ICU, intensive care unit; IV, intravenous; LOS, length of stay; Q1, first quartile; Q3, third quartile

**KEYWORDS** adverse drug effect; albumin; cefotaxime; ceftriaxone; hyperbilirubinemia; neonatal sepsis

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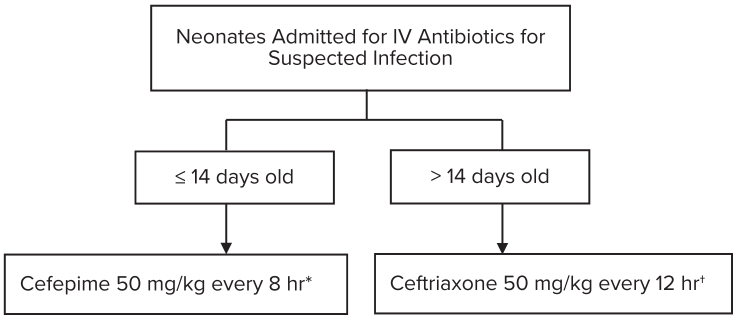
## Introduction

Neonatal sepsis is a life-threatening infection responsible for significant morbidity and mortality worldwide. The number of neonates who experience neonatal sepsis varies depending on setting and definition. The incidence of neonatal bacterial sepsis ranges from 1 to 4 infections per 1000 live births.[1] Common causative organisms associated with this infectious process include *Streptococcus agalactiae* (group B Streptococcus), *Escherichia coli*, *Listeria monocytogenes*, and other Gram-negative aerobes.[1] Due to the non-specific signs and symptoms and potential for severe consequences with untreated neonatal sepsis, the American Academy of Pediatrics recommends the initiation of broad spectrum antimicrobial therapy consisting of ampicillin plus either a third-generation cephalosporin or gentamicin until infectious etiology can be ruled out.[2]

Ceftriaxone and cefotaxime are third-generation parenteral cephalosporins with broad-spectrum activity against Gram-positive and Gram-negative organisms. Favorable pharmacokinetic and pharmacodynamics properties (long serum half-life, tissue and central nervous system penetration, and simple dosing regimen) make these agents appealing options in neonatal infections.[3] Cefotaxime is recommended over ceftriaxone because ceftriaxone may cause bilirubin displacement, potentially leading to serious adverse events associated with unconjugated hyperbilirubinemia such as kernicterus. An additional concern with ceftriaxone use is that high drug concentrations in the biliary system can result in ceftriaxone-calcium complexation, thereby increasing concerns for cholestasis, pseudolithiasis, and biliary sludging.[4] Likewise, coadministration of IV calcium-containing solutions may result in precipita-

**Figure.** Protocol overview.




* Dosage demonstrates cephalosporin treatment protocol and does not represent a complete algorithm for the management of neonatal sepsis.
† Per institutional protocol, patients would not receive ceftriaxone if they had known, active hyperbilirubinemia (jaundice) or if they were extremely premature (born before 28 weeks).

tion of these complexes, increasing the risk of these complications.[4] Current literature suggests the use of an alternative antimicrobial option when feasible for patients 28 days or younger to reduce the risk of developing hyperbilirubinemia and other complications associated with ceftriaxone.[3–5] Conversely, the American Academy of Pediatrics recommends the use of ceftazidime for patients up to 2 months of age when cefotaxime is unavailable.[6]

Due to a national drug shortage beginning in 2015, cefotaxime is no longer available. Consequently, treatment of neonatal infections has become increasingly complex.[5] In response to this shortage and discontinuation, clinicians at our institution adopted the following institutional-wide protocol for management of neonatal sepsis (Figure): neonates ≤14 days old can receive ampicillin plus cefepime, and neonates ≥15 days old can receive ampicillin plus ceftriaxone. Per institutional protocol, patients would not receive ceftriaxone if they had known, active hyperbilirubinemia (jaundice) or if they were extremely premature (defined as a gestational age < 28 weeks).

The primary objective of this study was to compare the incidence of hyperbilirubinemia between ceftriaxone and cefotaxime in the treatment of neonatal infections beyond the first 14 days of life. Secondary objectives included the comparison of hospital LOS and ICU.

## Materials and Methods

This was a single-center retrospective chart review of patients receiving ceftriaxone or cefotaxime for the treatment of neonatal infections between January 1, 2013 and August 31, 2018. Subjects were identified based on pharmacy charges for ceftriaxone or cefotaxime. Patients were included if they were 15 to 30 days old at the time of antimicrobial administration and must have received at least 1 dose of ceftriaxone or cefotaxime. Patients could be admitted from the emergency department or directly admitted to the neonatal ICU, pediatric ICU, or general pediatric floor unit. Exclusion criteria included incomplete medical records, administration of both ceftriaxone and cefotaxime during hospital admission, documented history of hyperbilirubinemia, and lack of subsequent total bilirubin levels beyond the baseline result.

Manual chart review was performed, and data were entered into a RedCap database (Vanderbilt University, Nashville, TN). The following information was extracted from the medical record: age at initial hospital admission, sex, gestational age, history of hyperbilirubinemia, total LOS, ICU LOS, administration of IV calcium-containing fluids or drugs, ursodiol use, positive culture results, administration of other systemic antibiotics, and laboratory values for total calcium, ionized calcium, total bilirubin (serum), albumin, and serum creatinine. Only laboratory values above the upper limit of normal were documented as abnormal. Laboratory values below normal limits were not documented as abnormal. Upper and lower limits were defined according to the institutional electronic health record's range. Patients included in the study with bilirubin levels 0.1 to 1.0 mg/dL were defined as normal. Bilirubin levels > 1.0 mg/dL were defined as abnormal. History of hyperbilirubinemia was determined by chart review and documented past medical history. The following medication-related information was extracted during data collection: weight at time of first dose, initial dose received (mg/kg), maintenance dose received (mg/kg/day), and initial antimicrobial course duration in days. Patient characteristics, dosing regimen, laboratory values, and patient outcomes were compared between those in the cefotaxime group and those in the ceftriaxone group.

For categorical variables, frequencies and column percentages were reported and p values were calculated using $\chi^2$ and Fisher exact tests. Continuous variables were tested for normality using Shapiro-Wilk normality test, and p values were calculated using Welch 2-sample *t* test. Otherwise, medians and first

**Table 1.** Patient Characteristics

| | All Patients (N = 88) | Cefotaxime (n = 43) | Ceftriaxone (n = 45) | p value |
|---|---|---|---|---|
| Age at initial visit, median (Q1, Q3), days | 21.0 (17.0, 26.0) | 21.0 (18.0, 24.0) | 22.0 (15.0, 27.0) | 0.983 |
| Gestational age, median (Q1, Q3), wk | 38.2 (36.4, 40.0) | 39.0 (36.5, 39.2) | 38.0 (36.5, 40.0) | 0.688 |
| Sex, n (%), male | 59 (67.0) | 29 (67.4) | 30 (66.7) | 1.000 |
| Weight, median (Q1, Q3), kg | 3.5 (3.0, 4.1) | 3.3 (2.9, 4.1) | 3.6 (3.0, 4.2) | 0.545 |
| Total calcium at baseline, median (Q1, Q3), mg/dL | 9.9 (9.5, 10.2) | 9.9 (9.4, 10.3) | 9.8 (9.6, 10.2) | 0.837 |
| Albumin at baseline, median (Q1, Q3), g/dL | 3.1 (2.8, 3.3) (N = 86) | 3.1 (2.7, 3.2) (n = 42) | 3.2 (2.9, 3.3) (n = 44) | 0.036 |
| Serum creatinine at baseline, median (Q1, Q3), mg/dL | 0.3 (0.2, 0.4) (N = 87) | 0.3 (0.2, 0.4) (n = 43) | 0.3 (0.2, 0.4) (n = 44) | 0.865 |
| Number of antibiotic doses, median (Q1, Q3) | 3.0 (2.0, 3.0) | 3.0 (3.0, 3.0) | 2.0 (2.0, 3.0) | — |
| Antibiotic dose, median (Q1, Q3), mg/kg | 50.1 (49.1, 51.4) | 50.1(49.3, 51.0) | 50.3 (49.0, 51.4) | — |
| Antibiotic dose, median (Q1, Q3), mg/kg/day | 147.1 (100.0, 193.5) (N = 72) | 186.1 (150.0, 200.1) (n = 40) | 100.0 (95.1, 102.0) (n = 32) | — |
| Calcium supplementation, n (%) | 22 (25.0) | 9 (20.9) | 13 (28.9) | 0.538 |
| Lactated Ringer, n (%) | 15 (17.0) | 6 (14.0) | 9 (20.0) | 0.638 |
| Total parenteral nutrition, n (%) | 7 (8.0) | 3 (7.0) | 4 (8.9) | 1.000 |
| Calcium gluconate, n (%) | 2 (2.3) | 2 (4.7) | 0 (0.0) | 0.236 |
| Calcium chloride, n (%) | 3 (3.4) | 2 (4.7) | 1 (2.2) | 0.612 |

*Q1, first quartile; Q3, third quartile*

and third quartiles (Q1, Q3) were reported, and p values were calculated using Mann-Whitney *U* tests. P values under 0.05 were considered statistically significant. Missing observations were reported and excluded on an analysis-by-analysis basis. All analyses were done in R programming language, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

A total of 88 patients were included in the analysis after meeting inclusion and exclusion criteria. The main reason for exclusion was lack of laboratory values pertinent to the study. There was no statistically significant difference in patient age, baseline total calcium levels, administration of IV calcium-containing fluids or drugs, or gestational age between the cefotaxime and ceftriaxone groups. The median number of doses of cefotaxime and ceftriaxone were 3 and 2, respectively. Additional patient characteristics and results can be found in Table 1.

Patient outcomes and bilirubin levels are listed in Table 2. There was no statistically significant difference between the 2 groups in hospital LOS or ICU LOS. After initiation of antibiotic therapy, baseline bilirubin levels increased from a normal to an abnormal level in 2 patients in the cefotaxime group and in 1 patient in the ceftriaxone group (p = 0.601). Patients who received ceftriaxone did not have a larger mean increase in bilirubin levels between baseline and abnormal compared with those who received cefotaxime (p = 0.243). Of the 88 patients analyzed, no patients died.

## Discussion

In this single-center, retrospective chart review of patients receiving ceftriaxone or cefotaxime for empiric treatment of neonatal infections, patients receiving ceftriaxone did not have a higher likelihood of developing hyperbilirubinemia compared with those who received cefotaxime during their hospital stay. The median age of patients on their initial day of visit who received ceftriaxone was 22.0 days.

These results are consistent with previously published studies.[3,6,7] Van Reempts et al[3] evaluated the safety of ceftriaxone in combination with either ampicillin or vancomycin in 80 neonates. Direct hyperbilirubinemia (>2 mg/dL) occurred in 2 cases during treatment, and no neonates had serum bilirubin levels that required exchange transfusions. Although our study measured total bilirubin levels rather than direct bilirubin levels, these results question the clinical significance of ceftriaxone's ability to elevate bilirubin levels in this population. Also, the use of ceftriaxone as outpatient therapy after discharge has been evaluated in neonates with an infectious process or presumed sepsis.[6] In a cohort of 95 neonates, 20 received ceftriaxone. Upon discharge, the mean bilirubin level was 8.1 ± 0.4 mg/dL. There were 4 patients who developed bilirubin levels >8 mg/dL that required ceftriaxone to be switched to

**Table 2.** Patient Outcomes and Bilirubin Levels

| | All Patients (N = 88) | Cefotaxime (n = 43) | Ceftriaxone (n = 45) | p value |
|---|---|---|---|---|
| LOS, median (Q1, Q3), days | 3.0 (2.0, 5.0) | 2.0 (2.0, 5.5) | 3.0 (2.0, 4.0) | 0.484 |
| <3, n (%), days | 38 (43.2) | 22 (51.2) | 16 (35.6) | — |
| 3, n (%), days | 20 (22.7) | 5 (11.6) | 15 (33.3) | — |
| 4–25, n (%), days | 9 (10.2) | 5 (11.6) | 4 (8.9) | — |
| ≥26, n (%), days | 21 (23.9) | 11 (25.6) | 10 (22.2) | — |
| ICU LOS, median (Q1, Q3), days | 3.0 (1.0, 5.0) (N = 29) | 3.0 (1.5, 4.5) (n = 15) | 3.0 (1.2, 6.5) (n = 14) | 0.842 |
| Baseline bilirubin, median (Q1, Q3), mg/dL | 2.3 (1.3, 4.0) | 2.7 (1.4, 3.8) | 2.3 (1.3, 4.1) | 0.867 |
| Abnormal bilirubin, n (%), mg/dL | 76 (86.4) | 36 (83.7) | 40 (88.9) | 0.693 |
| Abnormal bilirubin, median (Q1, Q3), mg/dL | 2.8 (1.4, 4.2), (N = 76) | 3.4 (1.5, 4.4) (n = 36) | 2.3 (1.4, 4.1) (n = 40) | 0.482 |
| Peak abnormal bilirubin, median (Q1, Q3), mg/dL | 2.8 (1.4, 4.2) (N = 76) | 3.4 (1.5, 4.4) (n = 36) | 2.3 (1.4, 4.1) (n = 40) | 0.476 |
| Resolved abnormal bilirubin, median (Q1, Q3), mg/dL | 0.9 (0.8, 2.1) (N = 7) | 0.9 (0.8, 3.0) (n = 4) | 0.9 (0.8, 2.1) (n = 3) | 0.858 |
| Increase in bilirubin: baseline to abnormal, n (%) | 3 (3.9) | 2 (5.6) | 1 (2.5) | 0.601 |
| Difference in bilirubin values abnormal versus baseline, mean ± SD | 0.2 ± 1.4 (N = 76) | 0.4 ± 2.1 (n = 36) | 0.0 ± 0.2 (n = 40) | 0.243 |

*Q1, first quartile; Q3, third quartile*

ampicillin plus gentamicin therapy. However, none of these patients required exchange therapy.[6]

Additionally, *in vivo* bilirubin-albumin binding interactions were investigated in non-jaundice neonates between the gestation age of 33 and 43 weeks.[7] After administration of ceftriaxone (50 mg/kg), the total serum bilirubin concentrations decreased along with the reserve albumin concentration indicating drug-bilirubin-albumin interactions. It appears that the interaction is dependent on the rate of change of the plasma concentration of ceftriaxone and an extended infusion may lead to only minor changes. However, no adverse effects were recorded and clinical significance appears to be minimal.[7] Pharmacokinetic and pharmacodynamic studies in neonates suggest these adverse effects are limited to ceftriaxone and are not a concern with other oxyimino-cephalosporins such as cefotaxime.[8] However, *in vitro* studies have also suggested that ceftriaxone does not bind to the same albumin binding site as bilirubin and displacement of bilirubin is unlikely to occur.[3]

Thirteen patients received both ceftriaxone and IV calcium-containing solutions during their hospital admission. One patient received calcium chloride and the rest received either Lactated Ringer or total parenteral nutrition. However, for the purpose of this study coadministration timing was not documented, and patients may not have received both solutions simultaneously. Institutional strategies should be optimized to ensure coadministration of IV calcium-containing solutions and ceftriaxone is avoided where clinically appropriate to avoid complications associated with ceftriaxone-calcium complexation.

Given the single-center retrospective design of this study, inherent limitations such as cofounding factors and patient selection bias may exist. An additional limitation is that this study only included neonates 15 to 30 days old at the time of antimicrobial administration due to the nature of the institutional protocol detailed in the Figure. Also, several patients were excluded from our study due to lack of follow-up laboratory results after receiving ceftriaxone or cefotaxime. Therefore, not all patients could be included in our assessment of changes in bilirubin levels. Adjustments to institutional protocol to include follow-up laboratory requirements to monitor patients may be beneficial. Also, bilirubin reference ranges vary depending on institution electronic health records and should be considered when classifying bilirubin levels. Our institutional reference range changes at 15 days of life from 1.0 to 10.5 mg/dL to 0.1 to 1.0 mg/dL. Furthermore, none of the patients received ursodiol to manage hyperbilirubinemia. However, data for patients who received phototherapy were not collected and may potentially affect documented total bilirubin levels. Finally, the median number of doses of cefotaxime and ceftriaxone were 3 and 2, with ranges of 19 and 20, respectively. It is possible that this treatment duration was insufficient to see the increase in total bilirubin level, and these results should not be extrapolated to a full course of treatment of cefotaxime

and ceftriaxone. However, this study may serve as guidance for other institutions that are facing a similar issue surrounding cefotaxime.

The objective of this study was to compare the incidence of hyperbilirubinemia between ceftriaxone and cefotaxime in the treatment of neonatal infections beyond the first 14 days of life. These data suggest neonates at least 15 days old treated with a short-term course of ceftriaxone for suspected neonatal sepsis did not have a higher likelihood of developing hyperbilirubinemia compared with those receiving a short-term course of cefotaxime. Therefore, other institutions who are facing similar difficulties may consider implementing a protocol incorporating the use of ceftriaxone in neonates ≥15 days of age.

## Conclusion

In this single-center retrospective chart review, neonates at least 15 days old who were treated with a short-term course of ceftriaxone did not have a higher likelihood of developing hyperbilirubinemia compared with those who received a short-term course of cefotaxime during their hospital stay. Due to the national drug shortage and discontinuation of cefotaxime, other institutions who are facing difficulties in the management of neonatal sepsis may consider implementing a similar protocol. Future studies are warranted to assess the clinical and safety outcomes of neonates at least 15 days old receiving long-term course of ceftriaxone for the treatment of neonatal sepsis.

### Article Information

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**Ethical Approval and Informed Consent.** Given the nature of this study, the project was exempt from institution board/ethics committee review and informed consent was not obtained.

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