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Association between positive urine cultures and necrotizing enterocolitis in a large cohort of hospitalized infants

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ABSTRACT

Objective: We used a large research database to examine the association between urinary tract infections and necrotizing enterocolitis (NEC) in premature infants.
Methods: This retrospective data analysis included infants ≤32 week gestational age and ≤1500 g at birth who had urine cultures obtained at one of 322 neonatal intensive care units managed by the Pediatrix Medical Group from 1997 to 2012. The primary outcome was a diagnosis of NEC within 7 days after urine culture. We used multivariable conditional logistic regression conditioned on postnatal age and controlling for gestational age, inotropic support on the day of culture, and mechanical ventilation on the day of culture to evaluate the association between urine culture result and NEC.
Results: We identified 25,816 infants who had 43,556 urine cultures obtained; 6586 (15.1%) of the cultures were positive. A diagnosis of NEC within 7 days after culture was made in 334 (5.1%) of the 6586 positive cultures versus 1582 (4.3%) of the 36,970 negative cultures ($p < 0.01$). On multivariable analysis, infants with any positive urine culture had increased risk of NEC (odds ratio [OR] 1.16, 95% confidence interval [CI] 1.02–1.31); the risk was higher when limited to Gram-negative organisms (OR 1.37, 95% CI 1.17–1.59). The risk of surgical NEC was increased in infants with any positive urine culture (OR 1.46, 95% CI 1.18–1.81) and was also higher when limited to Gram-negative organisms (OR 1.99, 95% CI 1.53–2.59).
Conclusion: Positive urine cultures were associated with increased risk of NEC within 7 days of culture.

1. Introduction

Necrotizing enterocolitis (NEC) occurs in 5% to 11% of very low birth weight (VLBW; <1500 g) infants [1,2]. NEC likely results from a combination of several factors, including genetic predisposition, intestinal immaturity, excessive intestinal inflammatory response, and inappropriate microbial colonization [3,4]. NEC mortality ranges from 16% to 42% [5]. Survivors are at high risk of severe growth delay and poor neurodevelopmental outcomes [6,7].

NEC has previously been associated with preceding gastrointestinal, respiratory, and bloodstream infections [8–10]. Outbreaks of NEC have been described, suggesting a transmissible infectious factor. Despite these reports, no single pathogen has been identified. A shift in the intestinal microbial ecology is thought to contribute to NEC risk in premature infants. This shift is preceded and marked by a loss of overall diversity and an increase in the proportion of bacterial families such as the *Enterobacteriaceae* [11–13]. *Enterobacteriaceae* includes *Escherichia coli*, *Klebsiella spp.*, and *Enterobacter spp.*, which are among the most commonly isolated organisms in urinary tract infections (UTIs) affecting infants in the neonatal intensive care unit (NICU) [14,15]. We examined the association between UTIs and NEC using a large research database.

2. Methods

2.1. Study cohort

We identified a cohort of all infants discharged from 322 NICUs managed by the Pediatrix Medical Group from 1997 to 2012. The data were obtained from an electronic medical record that prospectively captured data from admission notes, daily progress notes, procedure notes, and discharge summaries. Information was collected regarding maternal history and demographics, medications, laboratory results, culture results, and diagnoses.

Abbreviations: CoNS, coagulase-negative staphylococci; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; UTIs, urinary tract infections; VLBW, very low birth weight.

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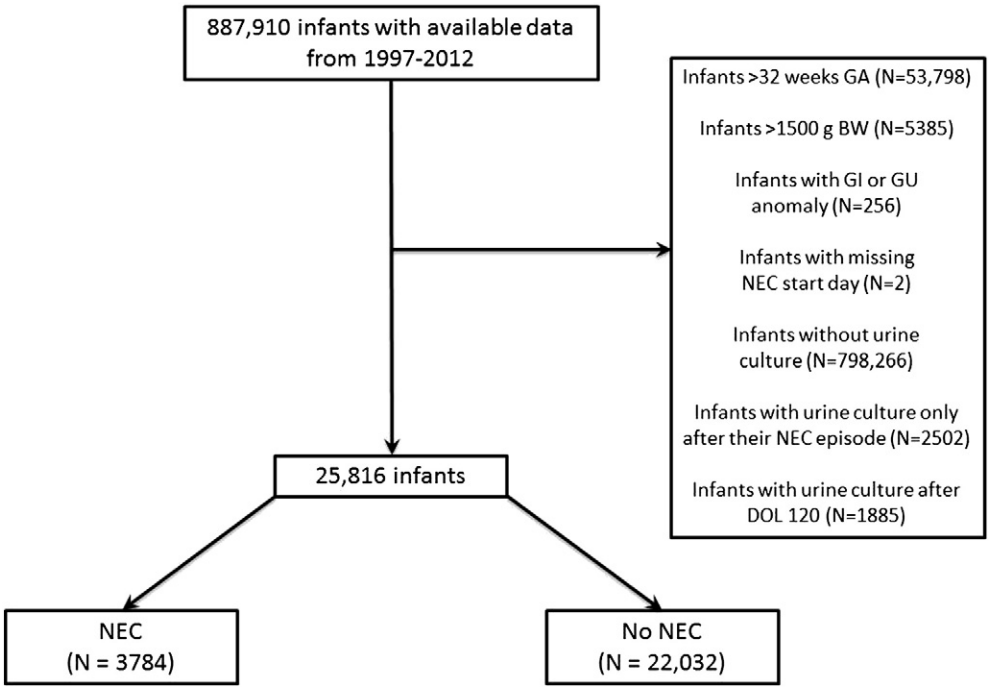

Fig. 1. Patient flow chart. GA, gestational age; BW, birth weight; GI, gastrointestinal; GU, genitourinary; NEC, necrotizing enterocolitis; DOL, day of life.

We included all infants who were ≤32 week gestational age and weighed ≤1500 g at birth and who had urine cultures obtained via supra-pubic tap, in-and-out catheterization, or bag in the first 120 days of life. We excluded infants whose only urine cultures were obtained after developing NEC, as well as those with congenital gastrointestinal or urogenital defects. All urine cultures obtained prior to a diagnosis of NEC or 120 days of life were included in the analysis (Figure 1). We included definite and probable episodes of coagulase-negative staphylococci (CoNS) infection as defined using previously reported criteria: a definite CoNS infection was defined as two positive cultures on the same day; a probable CoNS infection as two positive cultures within a 4-day period, three positive cultures within a 7-day period, or four positive cultures within a 10-day period; and a possible CoNS infection as a culture positive for CoNS that did not meet criteria for definite or probable CoNS sepsis [16–18]. The diagnosis and severity of NEC were assigned at each site by the attending neonatologist and included either medical NEC or surgical NEC. NEC severity was defined on the first day of the course of NEC regardless of change in severity thereafter.

2.2. Statistical analysis

The unit of observation for this study was a urine culture. The primary outcome was a diagnosis of NEC occurring within 7 days after the urine culture was obtained. Infant-level categorical variables were compared between patients with and without NEC following the urine culture using chi-square tests and Wilcoxon rank sum tests. We used multivariable conditional logistic regression conditioned on postnatal age in days at the time of urine culture to evaluate the association between urine culture and NEC. In the final model, we included the following covariates: gestational age, inotropic support on the day of culture, and mechanical ventilation on the day of culture. All analyses were performed using Stata 12 (College Station, TX) and assumed a significance limit of $\alpha = 0.05$. The study was approved by the Duke University Institutional Review Board without the need for written informed consent as the data were collected without identifiers.

3. Results

We identified 25,816 infants with 43,556 urine cultures. The median gestational age and birth weight were 27 weeks (interquartile range [IQR] 25–29) and 915 g (IQR 720–1154), respectively. Infants who developed NEC had a lower median birth weight compared to those who did not develop NEC (880 g, IQR 700–1106, vs. 920 g, IQR 725–1160, respectively; $p < 0.001$) (Table 1).

There were 6586/43,556 (15.1%) positive urine cultures in 5675 infants. Among those with positive urine cultures, the median postnatal age at the time of urine culture was 16 days (IQR 7–30) in those who did not develop NEC and 19 days (IQR 12–29) in those who developed NEC within 7 days. The organism most commonly cultured from the urine was *E. coli* (1079/6586, 16.4%), followed by *Klebsiella* (940/6586, 14.3%) and *Enterococcus* (917/6586, 13.9%). Among infants with positive urine cultures who subsequently developed NEC within 7 days ($N = 334$), the most common organism cultured from the urine was *Klebsiella* (62/334, 18.6%) (Table 2). Infants with positive urine cultures who did not develop NEC ($N = 6252$) most commonly had urine cultures growing *E. coli* (1028/6252, 16.4%). We identified 1916 cases of NEC within 7 days of a urine culture. NEC was diagnosed more frequently within 7 days of a positive culture than a negative culture (334/6586 [5.1%] vs. 1582/36,970 [4.3%], $p < 0.01$). Of the 334 NEC cases following a positive urine culture, 108 (32.3%) were surgical NEC, and 226 (67.7%) were medical NEC. Using multivariable analysis, odds of NEC were increased in infants with any positive urine culture (OR 1.16, 95% CI 1.02–1.31), and the odds were higher when limited to urine cultures with Gram-negative organisms (OR 1.37, 95% CI 1.17–1.59). Odds of surgical NEC were increased in infants with any positive urine culture (OR 1.46, 95% CI 1.18–1.81), and the odds were higher when limited to urine cultures with Gram-negative organisms (OR 1.99, 95% CI 1.53–2.59). We did not observe an association between NEC and Gram-positive urinary tract infections (OR 1.00, 95% CI 0.80–1.27) (Table 3).

4. Discussion

We identified UTI as a risk factor in the development of NEC. An NEC diagnosis within 7 days was made more frequently after positive than