Concurrent Bloodstream Infections in Infants with Necrotizing Enterocolitis

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Objective To determine the incidence, microbiology, risk factors, and outcomes related to bloodstream infections (BSIs) concurrent with the onset of necrotizing enterocolitis (NEC).

Study design We performed a retrospective review of all cases of NEC in a single center over 20 years. BSI was categorized as "NEC-associated" if it occurred within 72 hours of the diagnosis of NEC and "post-NEC" if it occurred >72 hours afterwards. Demographics, hospital course data, microbiologic data, and outcomes were compared via univariate and multivariate analyses.

Results NEC occurred in 410 infants with mean gestational age and birth weight of 29 weeks and 1290 g, respectively; 158 infants were diagnosed with at least one BSI; 69 (43.7%) with NEC-associated BSI, and 89 (56.3%) with post-NEC BSI. Two-thirds of NEC-associated BSI were due to gram-negative bacilli compared with 31.9% of post-NEC BSI (OR: 4.27; 95% CI: 2.02, 9.03) and 28.5% of all BSI in infants without NEC (OR: 5.02; 95% CI: 2.82, 8.96). Infants with NEC-associated BSI had higher odds of requiring surgical intervention (aOR: 3.51; 95% CI: 1.98, 6.24) and death (aOR: 2.88; 95% CI: 1.39, 5.97) compared with those without BSI.

Conclusions BSI is a common, underappreciated complication of NEC occurring concurrent with the onset of disease and afterwards. The microbiologic etiology of NEC-associated BSI is different from post-NEC and late-onset BSI in infants without NEC with a predominance of gram-negative bacilli. Infants with NEC-associated BSI are significantly more likely to die than those with post-NEC BSI and NEC without BSI. *(J Pediatr 2014;164:61-6)*.

Necrotizing enterocolitis (NEC) is a multifactorial disease process of the gastrointestinal tract. It occurs primarily in preterm infants and is associated with significant risk of death and long-term morbidity in survivors.[1-4] Although the precise cause of NEC is unknown, infection has been suspected to play a major role in the onset and extension of disease.[1,2,5-8] Reports linking NEC to various aerobic and anaerobic bacteria, fungi, and viruses have been well documented, primarily in individual case series and clustered outbreaks.[9-17]

Longitudinal data on concurrent bloodstream infections (BSIs) in infants diagnosed with NEC are limited. The overall incidence, associated risk factors, specific microbiology, and outcome of NEC-associated BSI are poorly defined. To address this deficiency, we performed a retrospective review of all cases of NEC in a single level IV neonatal intensive care unit (NICU) over a 20-year period. Based on clinical observations, we hypothesized that the majority of NEC-associated BSI would be due to enteric flora and, reflecting a more severe disease process, infants with NEC-associated BSI would have a higher incidence of surgical NEC, prolonged hospitalization, and death than NEC patients without associated BSI.

Methods

The Yale-New Haven Children's Hospital NICU is a 54-bed, level IV tertiary care referral center for infants with complex medical and surgical conditions. There are approximately 4000 to 4500 live births per year at Yale-New Haven Hospital, with 800 to 900 NICU admissions, both inborn and outborn.

The NICU at Yale-New Haven Children's Hospital has maintained an electronic database of all long-term (ie, >24 hours) admissions. These data include demographics, information related to the hospital course, and outcomes. Utilizing this database, all cases of NEC (irrespective of gestational age [GA] and birth weight [BW]), were identified from January 1, 1991 to December 31, 2010 and cross-referenced with a second database of BSI in the NICU over the same time period. Additional information was obtained from the medical record. Data collection included GA, BW, small for GA status, sex, race, whether the infants was inborn or outborn, the presence or absence of several major morbidities, the total duration of mechanical ventilation, total parenteral nutrition (TPN), length of hospital stay, and death. This study was approved by the Human Investigation Committee of the Yale University School of Medicine.

BPD	Bronchopulmonary dysplasia	GA	Gestational age
BSI	Bloodstream infection	*K pneumoniae*	*Klebsiella pneumoniae*
BW	Birth weight	NEC	Necrotizing enterocolitis
CoNS	Coagulase-negative staphylococci	NICU	Neonatal intensive care unit
E coli	*Escherichia coli*	ROP	Retinopathy of prematurity
		TPN	Total parenteral nutrition
		VLBW	Very low BW

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Small for GA was defined as those neonates with BW <10th percentile for GA. Respiratory distress syndrome was defined by characteristic appearance on chest radiograph and requiring intubation and the administration of exogenous surfactant. Bronchopulmonary dysplasia (BPD) was defined as the need for supplemental oxygen at 36 weeks postmenstrual age in association with characteristic radiographic changes.[18] Intraventricular hemorrhage was graded based on the classification system developed by Papile et al and included grades I-IV.[19] Retinopathy of prematurity (ROP) was determined over the entire study period by a single experienced pediatric ophthalmologist and staged according to the criteria established by the International Committee for Classification of ROP.[20] All stages were included. Mechanical ventilation was defined as intubation and support with synchronized intermittent mandatory ventilation and/or high frequency oscillatory ventilation. Mortality included death from any cause.

NEC was defined according to the modified Bell staging criteria and included only those cases with greater than or equal to stage IIA.[21] NEC was further classified as surgical or medical according to final treatment/intervention. In cases of surgical NEC, intestinal perforation was identified by pathology report (preferable when available), operative report, and/or the presence of pneumoperitoneum on abdominal radiograph. Cases of spontaneous intestinal perforation (ie, without pathologic evidence of NEC) were excluded from the investigation. Standard evaluation and treatment for NEC in our NICU during this time was to obtain at least 1 but ideally 2 blood cultures and to initiate broad spectrum antimicrobial therapy with ampicillin, gentamicin, and clindamycin (although prescription of clindamycin was variable).

All BSI identified were "late-onset," which was defined as a positive blood culture occurring at >72 hours of life and meeting the Center for Disease Control and Prevention criteria for a laboratory confirmed BSI.[22] Although the definition for a commensal species-related BSI was modified in 2008, the previous definition was utilized to maintain consistency throughout the study period. A BSI was categorized as "NEC-associated" if the blood culture was drawn within 72 hours (before or after) of the diagnosis of NEC and "post-NEC" if it occurred >72 hours after the diagnosis of NEC. For comparison, the category "BSI without NEC" included only late-onset cases over the same 20-year study period and excluded any BSI that occurred in an infant with documented or suspected NEC.

All blood cultures were assessed using a fluorescent-detection system for the presence of CO_2 production (Bactec II or 9240; Becton Dickinson, Sandy, Utah), and species were identified using standard procedures.

Statistical Analyses

The IBM SPSS Statistics v. 19.0 software package (Armonk, New York) was utilized for data analyses. Descriptive data for the entire patient cohort was expressed as mean and SD or median and range, where appropriate, for continuous data and absolute number and percentage for dichotomous data; results presented in Table I. Trends in cases of NEC, NEC-associated BSI, post-NEC BSI, and death were assessed over the study period via univariate linear regression.

Infecting organisms responsible for BSI in infants with NEC-associated BSI, post-NEC BSI, and BSI without NEC over the study period were compared via χ^2 analysis and presented as unadjusted OR with 95% CI. If an infant had multiple episodes of sepsis, only the first was included in the analyses.

All infants with NEC were next compared and contrasted. Infants with NEC-associated BSI, post-NEC sepsis, and NEC without BSI were compared utilizing both univariate and multivariate analyses. In the univariate analyses, continuous data were analyzed using the Kruskal–Wallis and Mann–Whitney U tests, where appropriate. Dichotomous data were analyzed using χ^2 analysis and Fisher exact test, where appropriate. A P value $< .05$ was considered statistically significant.

All-cause mortality in infants with NEC was assessed as the dependent variable in a multivariate logistic regression model. This model incorporated variables identified in a univariate regression model with a P-value of <.10 and included GA, BW, race, BPD, surgical NEC, and NEC-associated BSI, post-NEC BSI, and NEC without BSI as a categorical variable. Results were presented as aOR and 95% CI.

Results

A total of 410 cases of NEC were identified in 410 infants (Table I) with no statistically significant trend in the

Table I. Characteristics of 410 neonates with NEC, 1991-2010

GA (wk)*	29.1 ± 4.3
BW (g)*	1290 ± 753
Male†	235 (57.3)
Race†	
White	158 (38.5)
African American	161 (39.3)
Hispanic	80 (19.5)
Outborn†	229 (55.9)
Small for GA†	60 (14.6)
RDS†	168 (41.0)
BPD†	163 (39.8)
IVH†	25 (6.1)
ROP†	124 (30.2)
Ventilator d*	29.8 ± 35.7
NEC†	
Medical	166 (40.5)
Surgical	244 (59.5)
DOL NEC*	20.1 ± 16.1
Duration of TPN use (d)*	42.7 ± 39.1
Any late-onset BSI†	158 (38.5)
NEC associated‡	69 (43.7)
Post-NEC‡	89 (56.3)
Multiple (>1) episodes	30 (7.3)
Length of stay (d)*	64.6 ± 49.2
Death†	111 (27.1)

DOL, day of life; *IVH*, intraventricular hemorrhage; *RDS*, respiratory distress syndrome.
*Mean ± SD.
†N (%).
‡Denominator is infants with late-onset BSI.