Bloodstream Infections in Very Low Birth Weight Infants with Intestinal Failure

Conrad R. Cole, MD, MPH, MSc[1], Nellie I. Hansen, MPH[2], Rosemary D. Higgins, MD[3], Edward F. Bell, MD[4], Seetha Shankaran, MD[5], Abbot R. Laptook, MD[6], Michele C. Walsh, MD, MS[7], Ellen C. Hale, RN, BS[8], Nancy S. Newman, RN[7], Abhik Das, PhD[9], and Barbara J. Stoll, MD[8], for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Neonatal Research Network*

Objective To examine pathogens and other characteristics associated with late-onset bloodstream infections (BSIs) in infants with intestinal failure (IF) as a consequence of necrotizing enterocolitis (NEC).

Study design Infants weighing 401-1500 g at birth who survived for >72 hours and received care at *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network centers were studied. The frequency of culture-positive BSI and pathogens were compared in infants with medically managed NEC, NEC managed surgically without IF, and surgical IF. Among infants with IF, the duration of parenteral nutrition (PN) and other outcomes were evaluated.

Results A total of 932 infants were studied (IF, n = 78; surgical NEC without IF, n = 452; medical NEC, n = 402). The proportion with BSI after diagnosis of NEC was higher in the infants with IF than in those with surgical NEC ($P = .007$) or medical NEC ($P < .001$). Gram-positive pathogens were most frequent. Among infants with IF, an increased number of infections was associated with longer hospitalization and duration of PN (median stay: 172 for those with 0 infections, 188 days for those with 1 infection, and 260 days for those with ≥2 infections [$P = .06$]; median duration of PN: 90, 112, and 115 days, respectively [$P = .003$]) and decreased achievement of full feeds during hospitalization (87%, 67%, and 50%, respectively; $P = .03$).

Conclusion Recurrent BSIs are common in very low birth weight infants with IF. Gram-positive bacteria were the most commonly identified organisms in these infants. *(J Pediatr 2012;160:54-9)*.

Bloodstream infections (BSI) are associated with increased morbidity and mortality in infants with short bowel syndrome (SBS) and intestinal failure (IF).[1] Very low birth weight (VLBW) infants (defined as birth weight ≤1500 g) are at increased risk for surgical SBS and subsequent IF because of their greater risk of developing necrotizing enterocolitis (NEC) and other predisposing surgical conditions.[2,3] The incidence of surgical SBS among VLBW infants enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's Neonatal Research Network (NRN) registry is 0.7%.[2] Sepsis and complications of NEC are the most commonly reported causes of death among these infants. Recurrent hospitalizations (the majority of which are associated with infections) are a significant contributor to the high direct cost associated with the management of children with SBS and IF.[2,4] Late-onset sepsis and NEC are both associated with an increased risk of adverse neurodevelopmental outcomes.[5] Furthermore, infants with SBS and associated IF are more likely to have growth failure, which also has been associated with poor neurodevelopmental outcomes.

Data on the organisms responsible for BSI in infants with IF are limited. The relationship between recurrent BSI in these infants and duration of parenteral nutrition (PN) and length of hospitalization also remains unclear. The present study was undertaken to examine the frequency of culture confirmed BSI and associated pathogens in infants with IF compared with children with surgical NEC (ie, NEC managed surgically that did not result in IF) and medical NEC (ie, NEC managed medically without surgery). Associations between recurrent

BSI	Bloodstream infection
CoNS	Coagulase-negative *Staphylococcus*
IF	Intestinal failure
NEC	Necrotizing enterocolitis
NRN	Neonatal Research Network
PN	Parenteral nutrition
SBS	Short bowel syndrome
VLBW	Very low birth weight

From the [1]Intestinal Rehabilitation Program, Division of Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [3]*Eunice Kennedy Shiver* National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, MD; [4]Department of Pediatrics, University of Iowa, Iowa City, IA; [5]Department of Pediatrics, Wayne State, Detroit, MI; [6]Department of Pediatrics, Brown University, Providence, RI; [7]Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, OH; [8]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA; and [9]Statistics and Epidemiology Unit, RTI International, Rockville, MD

*A list of members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Neonatal Research Network is available at www.jpeds.com (Appendix).

The Neonatal Research Network's Generic Database (2002-2005) and Follow-up Studies (2003-2007) were supported by grants from the National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Data collected at participating sites were transmitted to RTI International, the data-coordinating center for the network, which stored, managed, and analyzed the data for this study. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2011.06.034

BSI and the duration of PN, time to achieve full feeds, and length of hospitalization among infants with IF were evaluated as well.

Methods

The NRN, a consortium of academic neonatal centers within the United States, maintains a data registry of VLBW infants.[2] Infants born between January 1, 2002, and June 30, 2005, who were enrolled in the registry and had a diagnosis of NEC were the focus of this analysis. Surviving infants with birth weight 401-1000 g were also eligible for a comprehensive follow-up assessment at 18-22 months corrected age. The Institutional Review Board at each NRN center approved participation in the registry and follow-up studies. Written informed consent was obtained from parents/legal guardians for follow-up at all centers. The registry includes maternal and delivery information collected soon after birth and infant data collected prospectively from birth until death, hospital discharge, or up to 120 days after birth.[2,6] Infants who are still in the hospital at 120 days are followed for final status (death, discharge, or transfer) up until 1 year of age.

For this analysis, IF was recorded if an infant with NEC had gastrointestinal surgery that resulted in PN dependence for >6 weeks.[2,7,8] Data on the length of bowel resected, length of remaining bowel, or percentage of bowel resected were not documented in the registry. NEC was defined as modified Bell stage IIA or greater.[9] Late-onset BSI was defined as a blood culture positive for bacteria or fungi from a sample obtained >72 hours after birth and treatment with antibiotics for ≥5 days. Blood samples were obtained from peripheral vessels or catheters inserted into peripheral or central vessels. Data on infective pathogen(s) and the date of each positive culture treated for ≥5 days were recorded. Infants with positive cultures and an intent to treat for ≥5 days who died before day 5 of therapy were also considered to have BSI.

Ten infants with IF without a diagnosis of NEC (6 with spontaneous intestinal perforation, 2 who underwent surgery for a birth defect, and 2 with volvulus) were excluded from the analysis. The NRN did not record surgery dates; thus, the date of NEC diagnosis was used as the diagnosis/onset date for most of the infants with IF, surgical NEC without IF, and medical NEC. In a few cases, the date of first spontaneous intestinal perforation was used if it was earlier than the NEC diagnosis date or if the NEC date was unavailable. BSIs were classified as occurring before diagnosis (≥8 days before the diagnosis date), at the time of diagnosis (±7 days around the diagnosis date), or after diagnosis (≥8 days after the diagnosis date). Positive blood cultures obtained 0-4 days apart were considered part of the same episode, either 1 episode with multiple pathogens (if more than 1 organism was found on a single blood culture or if different organisms were found on repeat cultures) or 1 episode with a single pathogen (1 culture with a single pathogen or repeat cultures 0-4 days apart with the same pathogen). In cases where a repeat culture positive for coagulase-negative *Staphylococcus* (CoNS) was obtained 0-4 days after a culture positive for a non-CoNS organism, CoNS was considered to be a contaminant, and the infection was considered 1 episode with the single non-CoNS pathogen. Positive blood cultures obtained ≥5 days apart were considered indicative of different episodes.[10]

Information collected at the 18- to 22-month follow-up assessment included the child's medical history, weight, length, and head circumference. These growth parameters were each classified as below or above the 10th percentile for sex and corrected age using standard Centers for Disease Control and Prevention growth charts.[11]

Statistical Analysis

The incidences of BSI and infecting pathogens were compared among infants with IF, surgical NEC, and medical NEC. In the infants with IF, clinical outcomes, nutritional outcomes (ie, days on PN, age at initiation of enteral feeds, age at achievement of full enteral feeds), and growth outcomes were compared among those with no infections after diagnosis, those with 1 infection, and those with >1 infection. In addition, these outcomes were compared by pathogen group in infants with IF who had at least 1 BSI after the diagnosis. Each infant was classified into only a single pathogen group, with the groups defined as follows: CoNS, single or multiple episodes involving CoNS only; other gram-positive, ≥1 episode(s) involving non-CoNS gram-positive organisms or ≥1 episode(s) involving both CoNS and non-CoNS gram-positive organisms; gram-negative, ≥1 episode(s) involving gram-negative organisms only; fungal, ≥1 episode(s) involving fungal organisms only; combinations, >1 episode(s) involving pathogens of different types (gram-positive, gram-negative, or fungal) or polymicrobial infections involving pathogens of different types (1 blood culture with at least 2 organisms of different types).

Statistical significance for unadjusted comparisons between groups was determined using the Cochran-Mantel-Haenszel row mean score χ^2 test for ordinal outcomes, the Fisher exact or χ^2 test for categorical variables, and the Kruskal-Wallis test for continuous variables. Median length of hospital stay was estimated using Kaplan-Meier curves for time from birth to discharge, with deaths treated as censored observations and significance between groups determined by the log-rank test.

Results

After excluding infants without a diagnosis of NEC (n = 10) and missing data (n = 8), a total of 932 infants were included in the analysis (IF, n = 78; surgical NEC without IF, n = 452; medical NEC, n = 402). The date of NEC diagnosis was used to determine the timing of BSI for 922 infants (99%), and date of spontaneous intestinal perforation was used for 10 infants (1%). Among the subset of infants with IF, the date of NEC diagnosis was used as the diagnosis date for 75 infants (96%) and the date of first spontaneous intestinal perforation was used for 3 infants (4%).