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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 NICHD Neonatal Research Network**

[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 & Children's Hospital, Case Western Reserve University, Cleveland, OH

[8]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

[9]Statistics and Epidemiology Unit, RTI International, Rockville, MD

Abstract

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

Study design—Infants 401–1500 grams at birth who survived >72 hours and received care at NICHD Neonatal Research Network centers were studied. Frequency of culture positive BSI and pathogens were compared for infants with medical NEC, NEC managed surgically without IF, and surgical IF. Among infants with IF, duration of parenteral nutrition (PN) and other outcomes were evaluated.

Results—932 infants were studied (IF, n=78; surgical NEC without IF, n=452; medical NEC, n=402). The proportion with BSI after NEC diagnosis was higher in infants with IF than with surgical NEC (p=0.007) or medical NEC (p<0.001). Gram positive pathogens were most frequent. Among infants with IF, increased number of infections was associated with longer hospitalization

Corresponding Author: Conrad R. Cole MD, MPH, MSc; Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. conrad.cole@cchmc.org, Phone: (513)636-6615, Fax: (513)636-4805.

*List of members of the NICHD Neonatal Research Network (NRN) is available at www.jpeds.com (Appendix).

and duration on PN (0, 1, ≥2 infections; median stay (days): 172, 188, 260, p=0.06; median days on PN: 90, 112, 115, p=0.003), and the proportion who achieved full feeds during hospitalization decreased (87%, 67%, 50%, p=0.03).

Conclusion—Recurrent BSIs are common in VLBW infants with IF. Gram positive bacteria were most commonly identified in these infants.

Keywords

Short bowel syndrome; Bloodstream infections; Late onset sepsis; Very low birth weight; Nutrition; Intestinal failure

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 ≤ 1500g) are at increased risk for surgical SBS and subsequent intestinal failure (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 (NICHD) Neonatal Research Network (NRN) registry was 0.7% (7/1,000) [2]. Sepsis and complications of NEC were 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 (LOS) 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 has also 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 remains unclear. This study was undertaken to examine the frequency of culture confirmed BSI and associated pathogens in infants with IF compared with children with surgical NEC (NEC managed surgically that did not result in IF) and medical NEC (NEC managed medically without surgery). We also evaluated associations between recurrent BSI and the duration of PN, time to achieve full feeds, and length of hospitalization among infants with IF.

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 weights 401–1000 grams were also eligible for a comprehensive follow-up assessment at 18–22 months corrected age. The institutional review board (IRB) at each of the centers 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 [2, 6]. Infants who are still in the hospital at 120 days are followed for final status (death, discharge, transfer) until one year of age.

For this analysis, IF was recorded if an infant with NEC had gastrointestinal surgery that resulted in PN dependence greater than 6 weeks duration [2, 7, 8]. Data regarding 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's stage IIA or greater [9]. Late-onset BSI were defined by a blood culture positive for bacteria or fungi from a sample

taken more than 72 hours after birth and treatment with antibiotics for ≥ 5 days. Blood samples were obtained from peripheral vessels or catheters inserted into peripheral or centrally located vessels. Infecting pathogen(s) and date of each positive culture treated for ≥ 5 days were recorded. Infants with positive cultures and intent to treat for 5 or more days who died before day 5 of therapy were also considered to have BSI.

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

Information collected at the 18–22 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 10^{th} percentile for sex and corrected age using standard Centers for Disease Control and Prevention growth charts [11].

Statistical analysis

Incidence of BSI and infecting pathogens were compared among infants with IF, surgical NEC, and medical NEC. Among infants with IF, clinical, nutritional (days on parenteral nutrition, age of initiating enteral feeds, age when full enteral feeds were achieved) and growth outcomes were compared between those with no infections after diagnosis, 1 infection and >1 infection. Additionally, these outcomes were compared by pathogen group for infants with IF who had at least one BSI after the diagnosis. Each infant was classified into one pathogen group only with the groups defined as: CoNS—single or multiple episodes involving CoNS only; other gram positive—one or more episodes involving non-CoNS gram positive organisms or one or more episodes involving both CoNS and non-CoNS gram positive organisms; gram negative—one or more episodes involving gram negative organisms only; fungal—one or more episodes involving fungal organisms only; combinations—more than one episode involving pathogens of different types (gram positive, gram negative, 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 by the Cochran-Mantel-Haenszel row mean score chi-square test for ordinal outcomes, by Fisher exact or chi-square tests for categorical variables and Kruskal-Wallis tests 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 (10 infants) and missing data (8 infants), 932 infants were included in the analysis: IF, n=78; surgical NEC without IF, n=452; medical NEC, n=402. NEC diagnosis date was used to determine timing of BSI for 922 (99%) infants and date of spontaneous intestinal perforation for 10. Among the subset of infants with IF, the NEC date was used as the diagnosis date for 75 infants (96%) and date of first spontaneous intestinal perforation for 3 (4%).

Number of Infections: Infants with IF and/or NEC

NEC was diagnosed within 7 days of birth for 128 (14%) of the 932 infants studied. Among the remaining 804 infants, the percent who had at least one BSI more than 7 days prior to NEC diagnosis was not significantly different in infants with IF compared with those with surgical NEC (p=0.5) or with medical NEC (p=0.6). In each group, most infants (~80%) had no culture proven infection prior to diagnosis and 20% had 1–3 infections. The percent of infants with an infection around the time of diagnosis (± 7 days) could be examined among all 932 infants. The proportion of these infants with one or more infections at the time of diagnosis was higher among infants with IF compared with surgical NEC (45% vs. 33%, p=0.04) and medical NEC (45% vs. 20%, p<0.001) (Table I).

The mortality rate varied across the groups (IF: 20%, surgical NEC: 53%, medical NEC: 19%) with death occurring earlier among infants with surgical NEC [2]. Accordingly, final study status was reached within 7 days of NEC diagnosis for 204 (22%) of the 932 infants, a majority of whom had surgical NEC (surgical NEC - 160 died within 7 days of diagnosis; medical NEC - 43 died, 1 was recorded as being discharged home). Among the 738 infants alive and in the hospital > 7 days after NEC diagnosis, the proportion with one or more BSI occurring 8 or more days after diagnosis was higher among infants with subsequent IF compared with infants with surgical NEC (60% vs. 42%, p=0.007) or medical NEC (60% vs. 20%, p<0.001) (Table I). Timing of infection varied between the groups. Among infants remaining in the hospital > 30 days the proportion with a BSI > 30 days after diagnosis was higher in those with IF (52%) compared with surgical NEC (32%, p=0.002) or medical NEC (10%, p<0.001). Due to concerns that some infants who died soon after diagnosis did not survive long enough to develop an infection, analyses were repeated among the subset who survived to discharge. Comparisons on number and timing of infections after diagnosis in this subgroup of survivors were similar to those in the larger cohort (data not shown).

Among the 619 infants with birth weight 401–1000 grams, BSI results were similar to those in the complete cohort. The percent of infants with an infection prior to NEC diagnosis was not significantly different in the three groups. A greater proportion of infants with IF had one or more BSI at the time of diagnosis compared with infants with surgical NEC (51% vs. 33%, p=0.01) and medical NEC (51% vs. 21%, p<0.001), as well as after diagnosis (IF 66% vs. surgical NEC 45%, p=0.01; vs. medical NEC 24%, p<0.001). Although trends were generally similar among the 313 infants with birth weight 1001–1500 grams, there were no statistically significant differences in the percent of infants with at least one BSI between those with IF and with surgical NEC (at the time of diagnosis: 32% vs. 35%, p=0.8; after diagnosis: 48% vs. 33%, p=0.2). However, the proportion of infants weighing 1001–1500 grams at birth who had an infection was higher in those with IF compared with medical NEC around the time of NEC diagnosis (32% vs. 18%, p=0.08) and after NEC diagnosis (48% vs. 16%, p<0.001).

Pathogens: Infants with IF and/or NEC

Gram positive pathogens were most frequently identified around the time of and after diagnosis in all three groups, with CoNS being the most frequently isolated pathogen (Table II). *Klebsiella* was the most common gram negative pathogen identified (10% of infections among infants with IF and surgical NEC, 3% of infections among infants with medical NEC). The proportion of infants who had at least one gram negative infection was similar among those with IF (39%) and surgical NEC (36%), but higher in these groups than among infants with medical NEC (23%), p=0.02. There was no difference in the proportion of infants with at least one fungal infection, primarily *candida*, among those with IF (13%), surgical NEC (18%), and medical NEC (12%), p=0.35. More than half of the mixed infections in each group involved *E. coli* and/or *Klebsiella*.

Outcomes by infection status and pathogen type after diagnosis: Infants with IF

Infants with IF who had an infection after diagnosis of NEC tended to have lower gestational age at birth than those with no infections (median weeks, ≥ 2 infections: 25.5; 1 infection: 26; 0 infections: 27; p=0.07). Those with 2 or more infections were also in the hospital longer than infants who had only 1 infection or were uninfected (median days: 260, 188, 172, respectively, p=0.06) (Table III). The duration of PN was also associated with the number of infections.

Infants with IF and no infections after NEC diagnosis received PN for a median 90 days, and those with 1 infection after diagnosis and with 2 or more infections received PN for 112 and 115 days, respectively (p=0.003). Enteral feeds were initiated somewhat later among infants with 2 or more infections (interquartile range: 3–22 days). The proportion of infants who achieved full feeds during the hospitalization was highest among infants with IF who had no infections after diagnosis (87%) compared with those with 1 (67%) and 2 or more infections (50%), p=0.03. Among the 63 infants with IF who survived to discharge, the percent who achieved full feeds was higher for those with no infection (84%) than with 1 (68%) or ≥ 2 infections (70%) but differences were no longer statistically significant, p=0.4.

Among the 53 infants with IF who weighed ≤1000 grams at birth, 12 (23%) died before discharge and 5 of the remaining 41 infants (12%) died after discharge. All 36 infants still alive at 18–22 months corrected age completed the follow-up visit. Among these survivors, the proportion of infants with weight <10th percentile at 18–22 months corrected age increased across infection groups (0 infections: 43%, 1 infection: 60%, 2+ infections: 71%) (Table III), although differences were not statistically significant (p=0.5).

The majority of children with IF who had at least one infection >7 days after NEC diagnosis (n=47) had CoNS (14 had 1 episode involving CoNS, 2 infants had 2 episodes, 1 infant had 3 episodes) or other gram positive pathogens (9 infants had 1 episode, 2 infants had 2 episodes, 1 had 3 episodes) identified. Among the 35 children who weighed ≤ 1000 grams at birth, 13 (37%) died before 18–22 months corrected age. No statistically significant differences on weight or other growth parameters at 18–22 months were detected by pathogen group among this small subset of 22 survivors.

Discussion

Intestinal failure and SBS are associated with significant morbidity and mortality in children [2, 12]. The cost of managing these children is very high, especially in the first year of life because of the length of hospitalization and multiple readmissions associated with complications [4]. Single center studies have reported BSI as a very common complication of SBS [1, 13]. Although infections are relatively common, the distribution of the pathogens identified on blood culture of VLBW infants with IF is not well described. Identification of

common pathogens is important because it will assist clinicians in providing appropriate empiric therapy to these patients while waiting for identification and antibiotic sensitivities. We examined relationships between recurrent late-onset BSI and duration of PN, time to achieve full feeds and length of hospitalization.

Understanding the epidemiology of BSI in this population of infants is important because recurrent BSI has been identified as a contributor to poor outcome [1]. In this study, we found that a larger proportion of VLBW infants who subsequently developed IF had at least one BSI around the time of NEC diagnosis (± 7 days) compared with VLBW infants with medical NEC. Neonates who are very ill with significant bowel necrosis and associated BSI may subsequently develop IF after surgical resection. BSI was also more common after diagnosis of NEC (> 7 days) in VLBW infants who develop IF (60%) compared with VLBW infants with surgical NEC without IF (42%) and medical NEC (20%). The incidence of new BSI was also significantly higher > 30 days after the diagnosis of NEC in infants with IF compared with infants in the other two groups. Increased rates of infection among infants with IF could be partially due to prolonged hospitalization and the continued presence of central lines needed for PN. This finding is similar to that previously reported for children in intensive care units in which the risk for developing a central line associated BSI increased with the duration of central line access and PN [14]. Increased intestinal permeability which develops in infants due to the lack of or inadequate enteral nutrition stimulation could also increase risk for BSI in these infants > 30 days after diagnosis [15].

The pathogen distribution among infected infants in this study is similar to that previously reported in other studies among neonatal intensive care patients [16–18]. Gram positive organisms were most frequently identified in all 3 groups with CoNS the single most frequently isolated pathogen [16–18]. The predominance of CoNS in these patients may be due to either skin colonization/contamination or intestinal permeability associated with prolonged use of intravascular devices and PN (13, 19). Although not considered an enteric bacteria, CoNS has been shown to colonize the gastrointestinal tract of neonates in western countries during the first month of life and as early as the 3rd day of life [19, 20]. In these studies, it is the predominant intestinal bacteria identified initially in fecal samples from preterm infants and decreases as the intestinal microbiome diversifies [19, 20]. Understanding changes in intestinal microbiota of children with IF and the potential role of these changes in development of BSI is extremely important and will have a significant role in examining the origin of bacteria cultured from the blood stream of these patients. *Klebsiella* was the most frequently isolated Gram negative pathogen among infants with IF and surgical NEC without IF, and *E. coli* was the most frequent Gram negative bacteria isolated among patients with medical NEC. Infection with these gram negative enteric pathogens is also considered to be due to increased intestinal permeability [12, 13].

Infants with IF who had 2 or more BSI had a longer duration of PN, and later initiation of enteral feeds compared with those who remained uninfected or had only 1 infection reported. This could be due to the extent of the initial injury experienced by these infants as the sicker children had need for prolonged PN/prolonged catheter days. The dependence on PN for survival puts these infants at greater risk for recurrent BSI and prolonged hospitalization. Meticulous central line care during hospitalization, including compliance with infection control guidelines, would reduce BSI in these children [21, 22]. The high mortality rate among infants with surgical NEC in the NRN has been previously evaluated and is likely due to the inclusion of neonates with NEC Totalis and abdominal drains in that group [2].

High quality research on the preferred type of enteral nutrition for children post resection for NEC is limited [23]. However, early initiation of feeds has been identified as a significant

factor for reducing PN duration [23, 24]. Although the data is limited, breast milk as the initial enteral feed should be considered in these children as its use is associated with shorter duration of PN dependence in neonates with SBS [23–25]. Unfortunately, the potential effect of breast milk on decreasing the duration of PN could not be evaluated in this study as the NRN registry did not include information on breast feeding.

Other limitations of this study are that this is a secondary analysis of prospectively collected data from the NRN registry. As a result variables such as site of infected line, type of line (central vs. peripheral) and the presence of ostomies, that are of interest for evaluating the impact of BSI in infants with IF were not included in the data collected during the duration of the study. The absence of statistically significant differences in growth outcomes (weight, length and head circumference) when examined by number of BSI is likely due to the small numbers of children in this cohort. In spite of these limitations, this study has significant strengths.

Recurrent BSIs were common in hospitalized infants with IF, and gram positive organisms, especially CoNS, were the most common infecting pathogens. The strengths of this study include the large sample size, the participation of multiple geographically and ethnically diverse clinical centers, and the ability to compare infants with IF with other infants of similar GA and BW who were diagnosed with NEC treated medically or surgically without the development of IF. However, the number of infants in each pathogen group was too small to allow us to evaluate the association of pathogen type with outcome. Interventional trials are needed to evaluate the effect of specific therapeutic interventions aimed at reducing BSI in infants with IF. Interventions (including evaluating the effect of specific types of enteral nutrition and trophic agents) are also needed to reduce time needed to achieve full enteral feeds and thus decrease duration of PN, with the ultimate aim of optimizing anthropometric growth and cognitive development.

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Abbreviations

NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
IF	Intestinal failure
SBS	Short bowel syndrome
VLBW	Very low birth weight
ELBW	Extremely low birth weight
NEC	Necrotizing enterocolitis
LOS	Late onset sepsis
GA	Gestational age

PDA	Patent ductus arteriosus
IVH	Intraventricular hemorrhage

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Appendix

The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2002–2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Abbot R. Laptook, MD; Betty R. Vohr, MD; Bonnie E. Stephens, MD; Angelita M. Hensman, RN BSN; Victoria Watson, BA, MS, CAS; Theresa M. Leach, MEd CAES; Suzy Ventura.

Case Western Reserve University Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Michele C. Walsh, MD MS; Deanne Wilson-Costello, MD; Nancy S. Newman, BA RN; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center University Hospital and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Kurt Schibler, MD; Edward F. Donovan, MD; Jean Steichen, MD; Kimberly Yolton, PhD; Kathleen Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Mersmann, RN; Holly L. Mincey, RN BSN; Jody Shively, RN; Teresa L. Gratton, PA.

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki Goldstein, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Melody B. Lohmeyer, RN MSN.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown (U10 HD27851, UL1 RR25008, M01 RR39) – Barbara J. Stoll, MD; David P. Carlton, MD; Ira Adams-Chapman, MD; Ellen C. Hale, RN BS CCRC.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Linda L. Wright, MD; Elizabeth M. McClure, MEd; Stephanie Wilson Archer, MA.

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Anna M. Dusick, MD FAAP; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC.

RTI International (U10 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Jeanette O'Donnell Auman, BS; Margaret Cunningham, BS; Betty K. Hastings; Elizabeth M. McClure, MEd; Carolyn M. Petrie Huitema, MS; James W. Pickett II, BS; Scott E. Schaefer, MS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University Lucile Packard Children's Hospital (U10 HD27880, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Susan R. Hintz, MD MS; M. Bethany Ball, BS CCRC; Barry E. Fleisher, MD; Anne M. DeBattista, MS PNP; Joan M. Baran, PhD; Lori E. Bond, PhD; Barbara Bentley, PhD; Ginger K. Brudos, PhD; Renee P. Pyle, PhD; Nicholas H. St. John, PhD.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Reed Dimmitt, MD; Myriam Peralta-Carcelen, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN; Vivien Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD; David Kaegi, MD; Maynard R. Rasmussen MD; Yvonne E. Vaucher, MD MPH; Paul R. Wozniak, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Chris Henderson, RCP CRTT; Wade Rich, BSHS RRT.

University of Miami Holtz Children's Hospital (U10 HD21397) – Charles R. Bauer, MD; Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Kasey Hamlin-Smith, PhD; Silvia Hiriart-Fajardo, MD; Silvia M. Frade Eguaras, BA; Yamiley C. Gideon, BA; Elaine O.Mathews, RN; Alexis N. Diaz, BA; Andrea Garcia, MA.

University of Rochester Medical Center Golisano Children's Hospital (U10 HD40521, M01 RR44) – Dale L. Phelps, MD; Gary Myers, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN; Diane Hust, RN PNP; Rosemary Jensen; Mary Rowan, RN; Kelley Yost, PhD; Lauren Zwetsch, RN MS PNP; Joan Merzbach, LMSW; Emily Kushner, MA.

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Abbot R. Laptook, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; R. Sue Broyles, MD; Roy J. Heyne, MD; Gaynelle Hensley, RN; Jackie F. Hickman, RN; Susie Madison, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Alicia Guzman; Elizabeth Heyne, PA-C; Linda A. Madden, BSN RN CPNP; Sally Adams, MS, RN, CPNP; Cristin Dooley, Ph.D., LSSP; Cathy Boatman, MS, CIMI.

University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (U10 HD21373) – Jon E. Tyson, MD MPH; Kathleen A. Kennedy, MD MPH; Pamela J. Bradt, MD MPH; Patricia Evans, MD; Terri Major-Kincade, MD MPH; Brenda H. Morris, MD; Laura L. Whitely, MD; Nora I. Alaniz, BS; Esther G. Akpa, RN BSN; Magda Cedillo; Patty A. Cluff, RN; Susan Dieterich, PhD; Claudia I. Franco, RNC MSN; Charles Green, PhD; Anna E. Lis, RN BSN; Georgia E. McDavid, RN; Stacey Reddoch, BA; Maegan C. Simmons, RN; Patti L. Pierce Tate, RCP; Sharon L. Wright, MT (ASCP).

Wake Forest University Baptist Medical Center, Forsyth Medical Center, and Brenner Children's Hospital (U10 HD40498, M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Cherrie D. Welch, MD MPH; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Barbara G. Jackson, RN BSN; Nancy J. Peters, RN CCRP; Carroll Peterson, MA; Ellen L. Waldrep, MS; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University Hutzel Women's Hospital and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Yvette R. Johnson, MD; Athina Pappas, MD; Rebecca Bara, RN BSN; Geraldine Muran, RN BSN; Deborah Kennedy, RN BSN; Laura A. Goldston, MA.

Yale University Yale-New Haven Children's Hospital and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125, M01 RR6022) – Richard A. Ehrenkranz, MD; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Elaine Romano, MSN; Janet Taft, RN BSN; Joanne Williams, RN BSN.

Table 1

Blood culture confirmed infections in VLBW infants with intestinal failure (IF) and/or NEC

	IF	Surgical NEC without IF	Medical NEC
At the time of diagnosis [a]			
Number of infants	78	452	402
Number of infections, n (%)			
0	43 (55)	301 (67) *	322 (80) ***
≥ 1	35 (45)	151 (33)	80 (20)
After diagnosis [b]			
Number of infants [c]	78	292	358
Number of infections, n (%)			
0	31 (40)	170 (58) **	285 (80) ***
1	33 (42)	81 (28)	55 (15)
≥ 2	14 (18)	41 (14)	18 (5)
Any infection 8–30 days after diagnosis	14 (18)	66 (23)	53 (15)
Number of infants in the hospital > 30 days [d]	75	250	302
Any infection >30 days after diagnosis	39 (52)	81 (32) **	29 (10) ***

[a] "At the time of diagnosis" is defined as ± 7 days around the diagnosis date

[b] "After the diagnosis" is defined as >7 days after the diagnosis

[c] 204 infants reached final status within 7 days of diagnosis and were not included in the "after" period (surgical NEC: 160 died; medical NEC: 43 died, 1 was discharged to home).

[d] 101 infants reached final status within 30 days of diagnosis (IF: 2 infants died, 1 was discharged to home; surgical NEC: 36 infants died, 5 were discharged to home, 1 was transferred to another hospital; medical NEC: 14 died, 42 were discharged to home).

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$ versus IF by the chi-square test

Table 2

Distribution of pathogens among VLBW infants with IF and/or NEC who had bloodstream infections at the time of and after diagnosis of NEC

Pathogen, n (% of infections) [1/]	IF	Surgical NEC without IF	Medical NEC
Gram negative	**29 (27.9)**	**94 (28.4)**	**32 (18.4)**
E. coli	7 (6.7)	25 (7.6)	9 (5.2)
Klebsiella	11 (10.6)	33 (10.0)	5 (2.9)
Citrobacter	1 (1.0)	4 (1.2)	2 (1.1)
Enterobacter	6 (5.8)	18 (5.4)	7 (4.0)
Pseudomonas aeruginosa	1 (1.0)	10 (3.0)	5 (2.9)
Other [2/]	3 (2.9)	4 (1.2)	4 (2.3)
Gram positive	**57 (54.8)**	**156 (47.1)**	**108 (62.1)**
Group B streptococcus	0	3 (0.9)	3 (1.7)
Viridans streptococcus	0	2 (0.6)	1 (0.6)
Other streptococci	11 (10.6)	30 (9.1)	9 (5.2)
CONS	37 (35.6)	100 (30.2)	74 (42.5)
S. aureus	3 (2.9)	15 (4.5)	14 (8.0)
Other [3/]	6 (5.8)	6 (1.8)	7 (4.0)
Fungi	**8 (7.7)**	**45 (13.6)**	**19 (10.9)**
Candida albicans	6 (5.8)	20 (6.0)	10 (5.7)
Candida parapsilosis	1 (1.0)	14 (4.2)	4 (2.3)
Candida sp.	1 (1.0)	7 (2.1)	2 (1.1) [6/]
Other [4/]	0	4 (1.2)	3 (1.7)
Mixed infections (>1 pathogen) [5/]	**7 (6.7)**	**24 (7.3)**	**8 (4.6)**
Unspecified pathogen	**3 (2.9)**	**12 (3.6)**	**7 (4.0)**
Number of infections	104 (100%)	331 (100%)	174 (100%)
Number of infants with infections	62	233	139

[1/] Infection episodes involving CONS and one other organism on the same culture were classified under the other organism. All other infections involving > 1 organism (including infections with CONS and 2 other organisms) were classified as mixed infections.

[2/] **IF**: *serratia marcescens* (2 infections) and *acinetobacter* (1 infection); **surgical NEC**: *serratia marcescens* (3 infections), *acinetobacter* (1); **medical NEC**: *serratia marcescens* (3), *acinetobacter* (1).

[3/] **IF**: *Staphylococcus species* not further identified (6 infections); **surgical NEC**: *Staphylococcus species* not further identified (5), *clostridia* (1); **medical NEC**: *Staphylococcus species* not further identified (4), *bacillus* (2), *clostridia* (1).

[4/] **Surgical NEC**: *Torulopsis glabrata* (2), *saccharomyces* (1), other fungi not further identified (1); **medical NEC**: *malassezia fur fur* (1), *saccharomyces* (1), *aureobasidium* (1).

[5/] **IF**: *E. coli* + *S. aureus* (1), *Klebsiella* + unspecified bacteria (1), *Klebsiella* + *proteus* + unspecified bacteria (1), *Enterobacter* + Group D strep (1), Enterobacter + Candida albicans (1), serratia marcescens + Group D faecalis streptococcus (1), Candida albicans + unspecified bacteria (1); **surgical NEC**: E. coli + S. aureus (1), E. coli + Group D faecalis strep + CONS (1), E. coli + Group D faecalis strep (2), E. coli + Klebsiella (1), E. coli + enterobacter (2), E. coli + candida albicans (1), Klebsiella + strep pneumoniae (1), Klebsiella + citrobacter (1), Klebsiella + enterobacter (1), Klebsiella + proteus (1), Klebsiella + pseudomonas (2), Klebsiella + bacteroides (1), Klebsiella + enterobacter cloacae + strep (1), enterobacter + torulopsis glabrata (1), pseudomonas aeruginosa + enterobacter cloacae (1), serratia marcescens + strep viridans + CONS (1), serratia marcescens +

Group D strep + unspecified bacteria (1), serratia marcescens + candida albicans (1), neisseria + strep viridans + bacillus (1), Group D strep + candida parapsilosis (1), strep + bacillus (1); **medical NEC**: E. coli + Klebsiella (1), E. coli + pseudomonas (1), E. coli + candida albicans + CONS (1), Klebsiella + strep (1), Klebsiella + strep + CONS (1), Klebsiella + malassezia fur fur (1), Enterobacter + strep (1), Group A strep + candida albicans (1).

[6/] Includes one infection involving both *candida albicans* and *parapsilosis*

Table 3

Clinical, nutritional, and growth outcomes for VLBW infants with intestinal failure by infection status after diagnosis of NEC [1/]

	No blood culture positive infections after diagnosis	1 infection	≥ 2 infections
Initial hospitalization	**N=31**	**N=33**	**N=14**
Hospital course			
Days of hospitalization [2/]			
Median (25th–75th percentile)	172 (135–182)	188 (157–216)	260 (162–365)
Died before discharge, n (%)	6 (19)	5 (15)	4 (29)
Clinical, n (%)			
PDA	20 (65)	15 (45)	11 (79)
RDS	13/30 (43)	19/32 (59)	9/14 (64)
BPD [3/]	21/29 (72)	22/33 (67)	10/13 (77)
ROP exam done	27 (87)	31 (94)	14 (100)
ROP	19/27 (70)	21/31 (68)	13/14 (93)
Nutritional			
Days of parenteral nutrition**			
Median (25th–75th percentile)	90 (47–108)	112 (91–116)	115 (108–117)
Enteral feeds started, n (%)	31 (100)	33 (100)	13 (93)
Age at first enteral feed (days) *			
Median (25th–75th percentile)	6 (3–12)	4 (2–5.5)	6 (3–22)
Full enteral feeds achieved, n (%) *	27 (87)	22 (67)	7 (50)
Age when full feeds achieved (days)			
Median (25th–75th percentile)	25 (16–43)	18 (13–36)	14 (13–20)
Follow-up at 18–22 months (surviving infants with birth weight 401–1000 g)	**N=14**	**N=15**	**N=7**
Growth			
Weight <10th percentile	6 (43)	9 (60)	5 (71)
Length <10th percentile	7 (50)	8 (53)	6 (86)
Head circumference <10th percentile	8 (57)	8 (53)	3 (43)

PDA=patent ductus arteriosus; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; ROP=retinopathy of prematurity.

[1/] Diagnosis date for most infants was the date of NEC diagnosis (see Methods for details). The “after diagnosis” period was defined as >7 days after the diagnosis date.

[2/] p=0.06 for a difference between the groups by the log rank test.

[3/] Three infants who died before 36 weeks post-menstrual age could not be evaluated for BPD.

* $p \leq 0.05$,

** $p \leq 0.01$ for a difference between the groups by the Kruskal-Wallis test (continuous variables) or Fisher’s exact test (categorical variables).