Published in final edited form as:
Arch Dis Child Fetal Neonatal Ed. 2013 March ; 98(2): F127–F132. doi:10.1136/archdischild-2011-300659.

Spontaneous Intestinal Perforation in Extremely Low Birth Weight Infants: Association with Indometacin Therapy and Effects on Neurodevelopmental Outcomes at 18-22 months Corrected Age

Rajan Wadhawan, MD[1], **William Oh, MD**[2], **Betty R. Vohr, MD**[2], **Shampa Saha, PhD**[3], **Abhik Das, PhD**[4], **Edward F. Bell, MD**[5], **Abbot R. Laptook, MD**[2], **Seetha Shankaran, MD**[6], **Barbara J. Stoll, MD**[7], **Michele C. Walsh, MD MS**[8], **Rosemary D. Higgins, MD**[9], and **for NICHD Neonatal Research Network**

[1]Division of Neonatology, All Children's Hospital, St. Petersburg, FL, USA

[2]Department of Pediatrics, Women & Infants Hospital, Providence, RI, USA

[3]Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC, USA

[4]Statistics and Epidemiology Unit, RTI International, Rockville, MD, USA

[5]Department of Pediatrics, University of Iowa, Iowa City, IA, USA

[6]Department of Pediatrics, Wayne State University, Detroit, MI, USA

[7]Department of Pediatrics, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, USA

[8]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH, USA

[9]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA

Abstract

Background—Spontaneous intestinal perforation (SIP) is associated with the use of postnatal glucocorticoids and indometacin in extremely low birth weight (ELBW) infants. We hypothesized: 1) an association of SIP with the use of antenatal steroids (ANS) and indometacin either as prophylaxis for IVH (P Indo) or for treatment of PDA (Indo/PDA) and 2) an increased risk of death or abnormal neurodevelopmental outcomes in infants with SIP at 18-22 months corrected age.

Design/Methods—We retrospectively identified ELBW infants with SIP in the Neonatal Research Network's generic database. Unadjusted analysis identified the differences in maternal, neonatal and clinical variables between infants with and without SIP. Logistic regression analysis identified the adjusted odds ratio for SIP with reference to ANS, P Indo and Indo/PDA. Neurodevelopmental outcomes were assessed among survivors at 18 to 22 months corrected age.

Corresponding author: Rajan Wadhawan, MD, Contact information: All Children's Hospital, 601 Fifth Street South, Fifth Floor OCC, St. Petersburg, FL 33701, USA, rajan.wadhawan@allkids.org, Tel: 727 767 4313, Fax: 727 767 4391.

Conflict of interest: There is no relevant conflict of interest for any of the authors.

Contributorship statement: All authors listed in the authors' list contributed to: conception and design of the study, analysis and interpretation of the data and drafting the article and revising it critically for important intellectual content. All of them also participated in the final approval of the version to be published.

Results—Indo/PDA was associated with an increased risk of SIP (adjusted OR 1.61; 95% CI 1.25,2.08), while P Indo and ANS were not. SIP was independently associated with an increased risk of death or NDI (adjusted OR−1.85; 95% CI 1.32,2.60) and NDI among survivors (adjusted OR−1.75, 95% CI 1.20,2.55).

Conclusion—Indometacin used for IVH prophylaxis and ANS were not associated with the occurrence of SIP in ELBW infants. Indometacin used for treatment of symptomatic PDA was however associated with an increased risk of SIP. ELBW infants with SIP have an increased risk of poor neurodevelopmental outcomes.

Keywords

extremely low birth weight infant; intestinal perforation; indometacin; cerebral palsy

INTRODUCTION

Spontaneous intestinal perforation (SIP) is a serious morbidity affecting ELBW infants, with an incidence ranging from 3-8 % (*1, 2*). It has been recognized as an entity distinct from necrotizing enterocolitis (NEC) (*3-5*) and has been proposed to occur in infants of lower birth weight and at an earlier postnatal age (*1, 6*). Although its pathogensis is unclear, several risk factors are associated with this complication. Very low birth weight infants born to mothers who received indometacin tocolysis have a higher incidence of SIP (*7*). A Neonatal Research Network trial of early postnatal steroid usage for the prevention of bronchopulmonary dysplasia was halted because of an increase in SIP in the steroid treated arm (*8*). A combination of postnatal indometacin treatment and early postnatal steroids has been proposed to be associated with an increased risk of SIP in ELBW infants (*9*). ANS, on the other hand have not been shown to be associated with an increased risk (*10*). The association between postnatal indometacin therapy and SIP, however, remains unclear. Although there have been isolated reports of SIP with indometacin therapy(*11*), a large randomized controlled trial of early indometacin use for prophylaxis of intracranial hemorrhage did not demonstrate this effect (*12*).

SIP adds a substantial burden to the morbidities of ELBW infants. Mortality and in-hospital morbidities of infants with SIP, while better than infants with surgical NEC (*13*), have been proposed to be worse than for infants without intestinal perforation (*2*). Outcomes of ELBW infants with SIP at 18-22 months corrected age and the effect of SIP on neurodevelopmental outcome, however, remain largely unknown.

The objectives of this study are twofold: 1) To assess the association of indometacin (prophylactic or treatment) and ANS exposure with the development of SIP in ELBW infants and 2) To assess the neurodevelopmental outcome of infants with SIP at 18-22 months corrected age.

METHODS

This is a retrospective cohort study of ELBW infants (birth weight between 401 g and 1000 g) admitted to one of 19 Neonatal Intensive Care Units in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) during calendar years 1998-2005. Infants who died at less than 12 hours of age were excluded.

Infants were categorized into two groups: infants with and without SIP. SIP was defined as occurrence of intestinal perforation during the first 14 days of life without evidence of NEC. Infants with intestinal perforation occurring after the first 14 days of life, who were recorded

as having SIP were excluded a priori, because these events may have been a complication of NEC that was not diagnosed. Infants with SIP were compared with those without SIP with respect to the use of prophylactic indometacin (P Indo-indometacin usage within the first 24 hours of life), indometacin for medical treatment of patent ductus arteriosus (Indo/PDA-indometacin usage after 24 hours of life with a concurrent diagnosis of PDA) or ANS exposure (one or more dose) using the chi-square test. Data on antenatal exposure to indometacin were not available.

Adjusted odds ratios were calculated using logistic regression analysis to evaluate the independent association of these therapeutic exposures and the occurrence of SIP, controlling for factors selected from unadjusted analysis. The factors included in the logistic regression were those that differed significantly between the groups based on unadjusted analysis and those that were thought to be involved in the causal pathway of SIP. Antenatal antibiotics were used as a surrogate for maternal chorioamnionitis, as data on chorioamnionitis were not available.

Prospectively collected data in the NRN generic database (GDB) included maternal and neonatal information, treatment and clinical outcomes. Trained research coordinators obtained the data based on the definitions listed in the Manual of Operations. All centers participating in the Neonatal Research Network received local IRB approval for data collection.

At 18-22 months corrected age, the survivors were seen in each center's follow up clinic. Evaluation on follow up visit consisted of the following: neurologic evaluation by a developmental pediatrician and hearing, vision and developmental testing by a certified examiner. The neurological examination was based on the Amiel-Tison assessment, including an evaluation of tone, strength, reflexes, angles and posture. Cerebral palsy was defined as a non-progressive CNS disorder with abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Hearing and visual status was obtained by parental history, deafness was confirmed by audiologic testing and a standard vision assessment was completed. Deafness was defined as hearing loss needing bilateral amplification. Blindness was defined as bilateral corrected vision of less than 20/200. The Bayley Scales of Infant Development–II [BSID-II] was administered and a Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were derived. A score < 70 indicated significant delay. Children who could not be assessed due to severe developmental delay were assigned MDI and PDI scores of 49.

Neurodevelopmental impairment (NDI) was defined as the presence of one or more of the following: cerebral palsy, bilateral blindness, bilateral deafness, Bayley MDI or Bayley PDI less than 70. Death occurring after 12 hours of age and before 18-22 months follow-up was included in our composite primary outcome measure of death or NDI.

The primary outcome of death or NDI at 18-22 months corrected age was compared among infants with SIP and those without SIP. Secondary outcome included NDI among survivors. Adjusted odds ratios were calculated to evaluate the independent association of the occurrence of SIP with death and adverse neurodevelopmental outcome at 18-22 months of corrected age. In addition to SIP, the variables included in the regression analyses for NDI/death and NDI were those that have previously been shown to affect neurodevelopmental outcomes(*14*), including male gender, birth weight, gestation, antenatal antibiotics, maternal hypertension, inborn status, APGAR score less than 3 at 5 minutes, severe IVH, surgery for PDA and center.

RESULTS

A total of 11,960 ELBW infants were admitted to the NICHD NRN neonatal units during the years 1998 to 2005 and survived beyond 12 hours of age. For evaluation of association between SIP and use of various perinatal interventions, the study subjects consisted of 280 infants with SIP and 11,680 without SIP. 3,066 of the11,960 infants died either before or after discharge. Of the remaining 8,894 infants, 9 were ineligible for follow-up and 7,579 of the remaining 8,885 (85%) were seen in the follow-up clinics.

The maternal demographic and clinical characteristics studied were similar between infants with and without SIP, with the exception of the incidence of maternal hypertension and diabetes and the likelihood of having received antenatal antibiotics among their mothers (Table 1). Clinical characteristics of infants in the two groups were significantly different (Table 2). On unadjusted analysis, ANS were associated with a lower incidence of SIP, whereas both P indo and Indo/PDA were associated with a higher incidence of SIP (Table 3). Logistic regression analysis showed a higher risk of SIP with indo/PDA (adjusted OR −1.61; 95% CI 1.25,2.08). ANS (adjusted OR 0.92; 95% CI 0.69,1.20) and P indo (adjusted OR 1.21; 95% CI 0.88,1.66) were not associated with an increased risk of SIP (Figure 1).

The incidence of death or NDI at 18-22 months corrected age was higher in infants with SIP as compared to infants without SIP (Table 4). Similarly, the incidence of NDI and its components was higher among survivors with SIP. On logistic regression analysis, SIP was associated with an increased risk of death or NDI (adjusted OR −2.06; 95% CI 1.40,3.02) (Figure 2) and NDI among survivors (adjusted OR −2.06; 95% CI 1.39,3.06-figure not shown).

DISCUSSION

We examined the association of SIP with indometacin administered for two clinical indications: for IVH prophylaxis, administered within first 24 hours of birth and for PDA treatment. We showed that indometacin administered for PDA treatment was associated with an increased risk of SIP. A similar association has been reported previously (*11, 15*). Our results are in agreement with those studies. Administration of indometacin for IVH prophylaxis however, was not associated with increased SIP risk. The reason for this difference based on timing of indometacin administration is not clear. However, one can speculate that the potential increased risk of early indometacin usage may be blunted by the potential beneficial effect of ANS administration. On the other hand, administration of indometacin in the presence of a hemodynamically significant PDA may worsen the already compromised intestinal blood flow. Our findings regarding P indo and SIP however need to be interpreted with caution, since we found an association on univariate analysis but it was not borne out on logistic regression.

Attridge et al showed an independent association of early indometacin usage (within 3 days of birth) with SIP using a large national dataset (*16*). They did not differentiate between prophylactic indometacin usage and its therapeutic use for PDA closure. However, they reported an association of SIP with PDA and with usage of vasoactive agents during the first few days of life. This lends further support to the possibility of intestinal hypo-perfusion from a combination of different factors, including symptomatic PDA with left to right shunt and the use of indometacin for its closure. In addition, the dose of indometacin used for Indo/PDA is generally higher than the dose for P Indo (0.2 or 0.3 mg/kg/dose vs. 0.1 mg/kg/dose respectively) and may contribute to this observed difference. However, this association of dose and risk of intestinal perforation remains unclear (*17*). Sharma et al (*18*) evaluated infants who had been exposed to indometacin with respect to SIP and NEC. They showed an

increased risk of SIP with indometacin exposure at less than 12 hours of age and a decreased risk of NEC with later use of indometacin for PDA treatment. Their analysis was dissimilar to ours, as we evaluated infants with and without SIP with respect to indometacin exposure instead of evaluating all infants with indometacin exposure with respect to these outcomes.

Previous studies have reported an association of ANS administration and an increased risk of NEC (*19*). Systematic review of previous studies has however found a decreased risk of NEC with ANS (*20*). Others have failed to demonstrate a harmful association between ANS and SIP (*10*). In fact, one report suggested that ANS administration may be protective for SIP (*21*). We also evaluated the possible association of ANS administration with SIP and found that administration of ANS had a protective effect against SIP on unadjusted analysis but not after controlling for other factors on logistic regression analysis.

Since SIP is a localized disease, it is often assumed that SIP is less likely to be associated with a systemic inflammatory reaction than NEC, and hence less likely to result in adverse outcomes. Adesanya et al evaluated one year follow up data on VLBW infants with intestinal perforation and showed that VLBW infants with NEC had worse neurodevelopmental outcomes at 1 year as compared to infants with SIP (*22*). Blakely et al (*13*) evaluated the 18-22 months outcomes of ELBW infants undergoing laparotomy or peritoneal drainage for intestinal perforation secondary to SIP or NEC. They showed a poor prognosis in both subgroups. The primary focus of their study however was to compare outcomes of infants undergoing laparotomy versus peritoneal drainage, rather than outcomes of infants with SIP or NEC. There have been no reports of large studies evaluating follow-up outcomes of ELBW infants with SIP.

We found that SIP was independently associated with an increased risk of death or NDI at 18-22 month corrected age in ELBW infants. The risk of NDI and its components was also similarly higher among survivors in the SIP group.

Our study has several limitations. Since the diagnosis of SIP was based on clinical grounds, it is possible that some of these infants may have had intestinal perforation resulting from NEC. The timing of intestinal perforation, however, makes it less likely that this was the case. We only included infants with a diagnosis of intestinal perforation within the first 14 days of life in the SIP group, possibly excluding some ELBW infants who developed isolated intestinal perforation after the first 14 days of life. Unless all infants with SIP undergo laparotomy, the diagnosis of SIP cannot be confirmed and there is a possibility of misclassification of the primary disease process. We presumed all indometacin usage in the first 24 hours of life to be for prophylactic use. It is possible though unlikely that indometacin was given for PDA closure in the first 24 hours. The association of SIP with indometacin used for PDA treatment may have been secondary to the interaction of indometacin with other factors such as systemic hypotension at the time of indometacin administration. We, however, did not have data on hypotension or the use of vasopressors at the time of indometacin administration.

Previous studies have shown an association of neonatal cortisol levels with outcome in ELBW infants (*23*). We, however, did not have data on the timing of administration of ANS or neonatal cortisol levels available in this database. Infants with SIP had a higher rate of postnatal steroid use. However, the mean age at the time of receiving the first dose of steroids was substantially higher than the age at which SIP is most likely to occur (Table 2). Only a small percentage of infants (8.9% in the SIP group and 6.9% in the no SIP group) received the first dose of postnatal steroids during the first 14 days of life. We did not have data on the type of postnatal steroid used, i.e. dexamethasone or hydrocortisone. These

limitations in the database do not allow us to explore the association of combined exposure to indometacin and postnatal steroids with SIP that has been reported by others (*9, 24*).

There were significant differences in the clinical characteristics of infants in the two groups, which raises the possibility that the differences in death or NDI may simply be a reflection of increased illness severity. This increased risk, however, persisted after logistic regression analysis controlling for these characteristics, thus making that unlikely to be the case.

Our overall follow up rate was 85% of eligible infants. The follow-up rates were similar in the group of infants with and without SIP. Although the infants seen in follow-up were similar to ones who were lost to follow-up, there were minor differences in some of the clinical characteristics (higher rate of inborn status and surgery for PDA among those lost to follow-up). It is possible but unlikely that these differences influenced our results.

Despite these limitations, this study adds valuable information to the literature by utilizing a large dataset of ELBW infants to show that indometacin used for PDA treatment is associated with an increased risk of SIP, where as prophylactic indometacin and ANS are not associated with SIP. We also show that SIP is independently associated with an increased risk of adverse neurodevelopmental outcomes at 18-22 months corrected age in ELBW infants.

Acknowledgments

The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Shampa Saha (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. 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 (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Brigham and Women's Hospital, Children's Hospital Boston, and Beth Israel Deaconess Medical Center (GCRC M01 RR2172, GCRC M01 RR2635, U10 HD34167) – Ann R. Stark, MD; Stacy Dow, RN; Colleen Driscoll; Kerri Fournier, RN; Kimberly Gronsman Lee, MD.

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

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

Duke University School of Medicine University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (GCRC M01 RR30, U10 HD40492) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Ricki F. Goldstein, MD; Kathy J. Auten, MSHS; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN.

Emory University Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (GCRC M01 RR39, U10 HD27851) – Ira Adams-Chapman, MD; Linda Black; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Ellen C. Hale, RN BS CCRC; Judson Miller, MD; Maureen Mulligan LaRossa, RN; Irma Seabrook, RRT; Gloria V. Smikle, PNP MSN.

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

Indiana University Indiana University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (GCRC M01 RR750, U10 HD27856) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Anna M. Dusick, MD FAAP; Diana D. Appel, RN BSN; Lon G. Bohnke; MS; Marilyn Bull; MD; Ann B. Cook, MS; Greg Eaken, PhD; Dianne E. Herron, RN; Darlene Kardatzke, MD; Carolyn Lytle, MD MPH; Lucy C. Miller, RN BSN CCRC; Heike M. Minnich, PsyD HSPP; Leslie Richard, RN; Leslie Dawn Wilson, BSN CCRC.

RTI International (U01 HD36790) – W. Kenneth Poole, PhD; Betty K. Hastings; Elizabeth M. McClure, MEd; Jamie E. Newman, PhD MPH; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; Scott E. Schaefer, MS; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University California Pacific Medical Center, El Camino Hospital, and Lucile Packard Children's Hospital (GCRC M01 RR70, U10 HD27880) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; Marian M. Adams, MD; Charles E. Ahlfors, MD; Monica Hajdena-Dawson, MD; Susan R. Hintz, MD MS; M. Bethany Ball, BS CCRC; Robert D. Stebbins, MD; Joan M. Baran, PhD; Lori E. Bond, PhD; Ginger K. Brudos, PhD; Anne M. DeBattista, RN PNP; Jean G. Kohn, MD MPH; Carol G. Kuelper, PhD; Julie C. Lee-Ancajas, PhD; Renee P. Pyle, PhD; Dharshi Sivakumar, MD MRCP; Nicholas H. St. John, PhD.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (GCRC M01 RR32, U10 HD34216) – Waldemar A. Carlo, MD; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Monica V. Collins, RN BSN MaEd; Stephanie A. Chopko, PhD; Shirley S. Cosby, RN BSN; Mary Beth Moses, PT MS PCS; Kathleen G. Nelson, MD; Myriam Peralta-Carcelen, MD MPH; Vivien A. Phillips, RN BSN; Julie Preskitt, MSOT MPH; Richard V. Rector, PhD; Sally Whitley, MA OTR-L FAOTA.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD; Paul R. Wozniak, MD; Maynard R. Rasmussen, MD; Yvonne E. Vaucher, MD MPH; Martha G. Fuller, RN MSN; Kathy Arnell, RNC; Rene Barbieri-Welge; Ayala Ben-Tall; Renee Bridge, RN; Clarence Demetrio, RN; Chris Henderson, RCP CRTT; Elaine Ito; Meghan Lukasik; Deborah Pontillo; Donna Posin, OTR/L MPA; Wade Rich, BSHS RRT; Cheryl Runyan; James Wilkes.

University of Miami Holtz Children's Hospital (GCRC M01 RR16587, U10 HD21397) – Charles R. Bauer, MD; Shahnaz Duara, MD; Maria Calejo, RN; Alexis N. Diaz, BA; Ruth Everett-Thomas, RN MSN; Silvia M. Frade Eguaras, MA; Yamiley C. Gideon, BA; Sylvia Hiriart-Fajardo, MD; Amy Mur Worth, RN MS; Alexandra Stroerger.

University of New Mexico Health Sciences Center (GCRC M01 RR997, U10 HD53089) – Lu-Ann Papile, MD; Conra Backstrom Lacy, RN; Ginny Laadt, PhD OTR; Debra V. Long, BSN; Jean Lowe, PhD; Rebecca Montman, RN.

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

University of Tennessee (U10 HD21415) – Sheldon B. Korones, MD; Henrietta S. Bada, MD; Tina Hudson, RN BSN; Marilyn Williams, LCSW; Kimberly Yolton, PhD.

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

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) -Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Pamela J. Bradt, MD MPH; Patricia W. Evans, MD; Beverly Foley Harris, RN BSN; Terri Major-Kincade, MD MPH; Brenda H. Morris, MD; Laura L. Whitely, MD; Esther G. Akpa, RN BSN; Nora I. Alaniz, BS; Magda Cedillo; Patty A. Cluff, RN; Susan Dieterich, PhD; Claudia I. Franco, RNC MSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Maegan C. Simmons, RN; Patti Pierce Tate, RCP; Stacey Reddoch, BA; Sharon L. Wright, MT.

Wake Forest University Baptist Medical Center, Forsyth Medical Center, and Brenner Children's Hospital (GCRC M01 RR7122, U10 HD40498) – 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) – Virginia Delaney-Black, MD MPH; Athina Pappas, MD; Rebecca Bara, RN BSN; Debra Driscoll, RN BSN; Laura Goldston, MA; Yvette R. Johnson, MD MPH; Deborah Kennedy, RN BSN; Geraldine Muran, RN BSN.

Women & Infants' Hospital of Rhode Island (U10 HD27904) – Regina A. Gargus, MD FAAP; James R. Moore, MD; Bonnie E. Stephens, MD; Rachel V. Walden, MD; Barbara Alksninis, PNP; Angelita M. Hensman, RN BSN; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Lucy Noel; Victoria E. Watson, MS CAS.

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

References

1. Meyer CL, Payne NR, Roback SA. Spontaneous, isolated intestinal perforations in neonates with birth weight less than 1,000 g not associated with necrotizing enterocolitis. J Pediatr Surg. 1991; 26:714–717. [PubMed: 1941464]
2. Attridge JT, Herman AC, Gurka MJ, et al. Discharge outcomes of extremely low birth weight infants with spontaneous intestinal perforations. J Perinatol. 2006; 26:49–54. [PubMed: 16319939]
3. Aschner JL, Deluga KS, Metlay LA, et al. Spontaneous focal gastrointestinal perforation in very low birth weight infants. J Pediatr. 1988; 113:364–367. [PubMed: 3397802]
4. Adderson EE, Pappin A, Pavia AT. Spontaneous intestinal perforation in premature infants: a distinct clinical entity associated with systemic candidiasis. J Pediatr Surg. 1998; 33:1463–1467. [PubMed: 9802791]
5. Alpan G, Eyal F, Vinograd I, et al. Localized intestinal perforations after enteral administration of indomethacin in premature infants. J Pediatr. 1985; 106:277–281. [PubMed: 3968618]
6. Okuyama H, Kubota A, Oue T, et al. A comparison of the clinical presentation and outcome of focal intestinal perforation and necrotizing enterocolitis in very-low-birth-weight neonates. Pediatr Surg Int. 2002; 18:704–706. [PubMed: 12598969]
7. Gordon PV, Swanson JR, Clark R. Antenatal indomethacin is more likely associated with spontaneous intestinal perforation rather than NEC. Am J Obstet Gynecol. 2008; 198:725–726. [PubMed: 18538165]
8. Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med. 2001; 344:95–101. [PubMed: 11150359]
9. Paquette L, Friedlich P, Ramanathan R, et al. Concurrent use of indomethacin and dexamethasone increases the risk of spontaneous intestinal perforation in very low birth weight neonates. J Perinatol. 2006; 26:486–492. [PubMed: 16791261]
10. Attridge JT, Clark R, Gordon PV. New insights into spontaneous intestinal perforation using a national data set (3): antenatal steroids have no adverse association with spontaneous intestinal perforation. J Perinatol. 2006; 26:667–670. [PubMed: 17024144]
11. Scholz TD, McGuinness GA. Localized intestinal perforation following intravenous indomethacin for patent ductus arteriosus. J Pediatr Gastroenterol Nutr. 1988; 7:773–775. [PubMed: 3183883]
12. Schmidt B, Davis P, Moddemann D, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001; 344:1966–1972. [PubMed: 11430325]
13. Blakely ML, Tyson JE, Lally KP, et al. Laparotomy versus peritoneal drainage for necrotizing enterocolitis or isolated intestinal perforation in extremely low birth weight infants: outcomes through 18 months adjusted age. Pediatrics. 2006; 117:e680–687. [PubMed: 16549503]
14. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics. 2000; 105:1216–1226. [PubMed: 10835060]

15. Nagaraj HS, Sandhu AS, Cook LN, et al. Gastrointestinal perforation following indomethacin therapy in very low birth weight infants. J Pediatr Surg. 1981; 16:1003–1007. [PubMed: 7338750]
16. Attridge JT, Clark R, Walker MW, et al. New insights into spontaneous intestinal perforation using a national data set: (1) SIP is associated with early indomethacin exposure. J Perinatol. 2006; 26:93–99. [PubMed: 16319937]
17. Lee J, Rajadurai VS, Tan KW, et al. Randomized trial of prolonged low-dose versus conventional-dose indomethacin for treating patent ductus arteriosus in very low birth weight infants. Pediatrics. 2003; 112:345–350. [PubMed: 12897285]
18. Sharma R, Hudak ML, Tepas JJ 3rd, et al. Prenatal or postnatal indomethacin exposure and neonatal gut injury associated with isolated intestinal perforation and necrotizing enterocolitis. J Perinatol. 2010; 30:786–793. [PubMed: 20410905]
19. Guthrie SO, Gordon PV, Thomas V, et al. Necrotizing enterocolitis among neonates in the United States. J Perinatol. 2003; 23:278–285. [PubMed: 12774133]
20. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006; 3:CD004454. [PubMed: 16856047]
21. Watterberg KL. Letter to editor. Pediatrics. 2005; 115:1446–1447. [PubMed: 15867074]
22. Adesanya OA, O'Shea TM, Turner CS, et al. Intestinal perforation in very low birth weight infants: growth and neurodevelopment at 1 year of age. J Perinatol. 2005; 25:583–589. [PubMed: 16034475]
23. Aucott SW, Watterberg KL, Shaffer ML, et al. Early cortisol values and long-term outcomes in extremely low birth weight infants. J Perinatol. 2010; 30:484–488. [PubMed: 20010616]
24. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics. 2004; 114:1649–1657. [PubMed: 15574629]

What is already known on this topic:

Combination of postnatal steroids and indometacin therapy are associated with an increased risk of intestinal perforation in ELBW infants.

Infants born with ELBW are at increased risk of death or neurodevelopmental disability.

What this study adds:

This study adds to the literature by showing an increased risk of intestinal perforation in ELBW infants in association with indometacin usage for symptomatic PDA.

This study also shows an independently increased risk of death or neurodevelopmental impairment in ELBW infants with intestinal perforation.

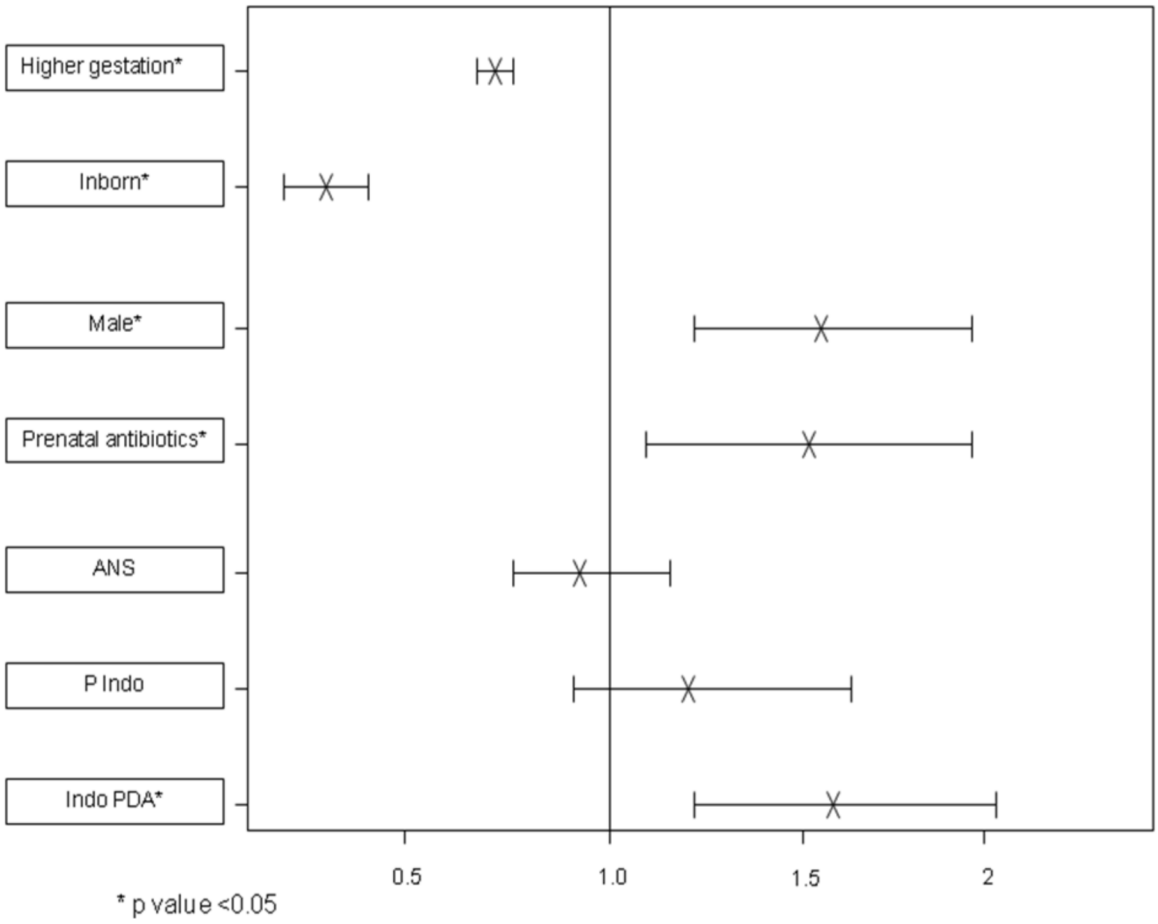
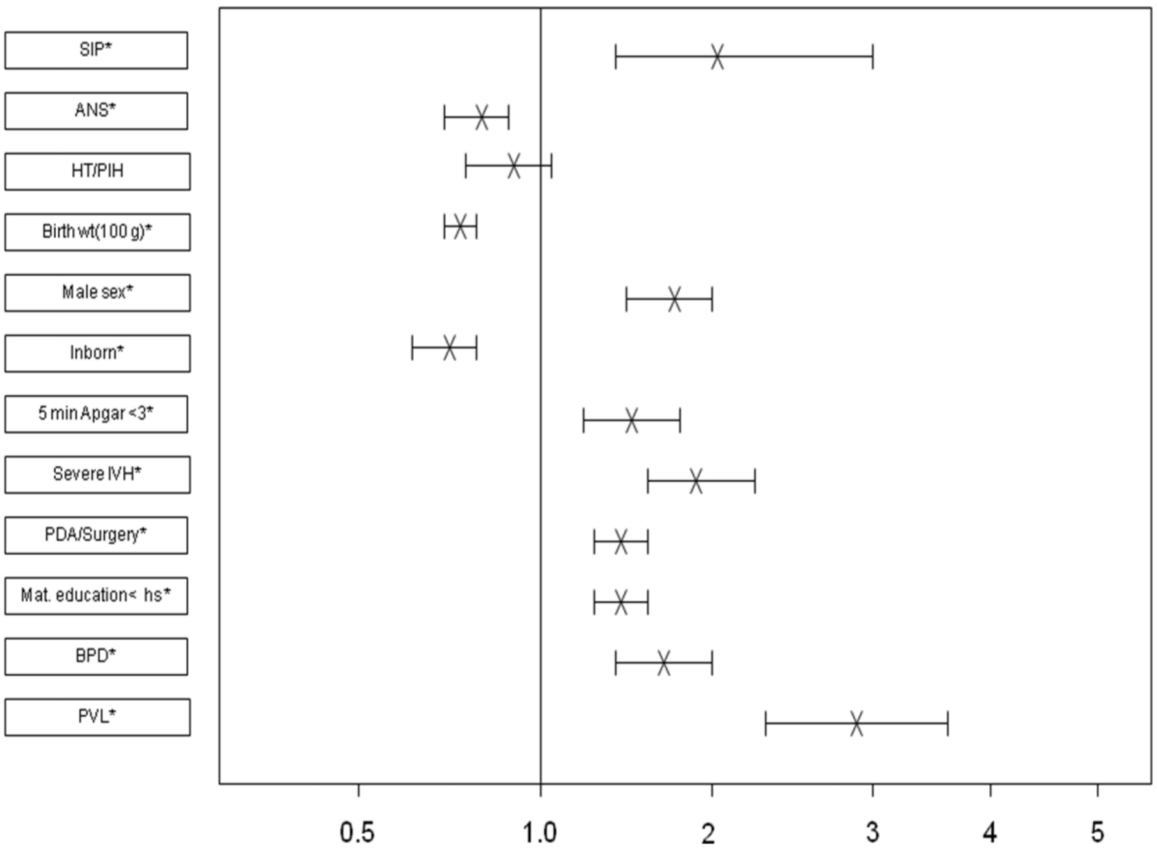


Figure 1.
Logistic regression analysis: Adjusted odds ratio for SIP versus no SIP Early onset sepsis ($p<0.05$), postnatal steroids ($p<0.05$) and center were also included in the logistic regression model.



*p < 0.05 Mat. Education < hs- maternal education less than high school diploma

Figure 2.
Logistic regression analysis: Adjusted odds ratio for NDI/death Postnatal steroids (p< 0.05), NEC (p< 0.05) and center were also included in the logistic regression model.

Table 1

Maternal demographic and clinical characteristics

Variable	SIP n= 280 Number (%)	No SIP n= 11,680 Number (%)
Maternal age *	26.3 ± 6.4	26.9 ± 6.7
Race		
White	112 (40.0)	4461/11661 (38.3)
Black	119 (42.5)	4874/11661 (41.8)
Hispanic	36 (12.9)	1895/11661 (16.2)
Asian	5 (1.8)	276/11661 (2.4)
Other	8 (2.9)	155/11661 (1.3)
Marital status		
Married	138 (49.3)	5370/11667 (46.0)
Single	139 (49.6)	6203/11667 (53.2)
Unknown	3 (1.1)	95/11667 (0.8)
At least one prenatal visit	263/279 (94.3)	10926/11672 (93.6)
Hypertension	42 (15.0)	3045 (26.1) †
Diabetes (insulin dependent)	10 (3.6)	396/11676 (3.4)
Antibiotics	211 (75.4)	7637 (65.4) †

* mean ± SD

† p value < 0.05

Table 2

Infant demographic and clinical variables

Variable	SIP n= 280 Number (%)	No SIP n= 11,680 Number (%)
Male gender	176 (62.9)	5750 (49.2) †
Birth weight (g) *	710.4 ± 138.3	763.1 ± 147.1 †
Gestational Age (weeks) *	24.8 ± 1.5	25.9 ± 2.1 †
Inborn	206 (73.6)	10387 (88.9) †
1 min APGAR ≤ 3	136 (48.6)	4539 (38.9) †
5 min APGAR ≤ 3	44 (15.7)	1129 (9.67) †
Respiratory support **	279 (99.6)	10778/11678 (92.3) †
Duration of respiratory support (days) *	39.6 ± 31.0	23.9 ± 26.0 †
Surgery for PDA	69/280 (24.6)	1476/11679 (12.6) †
Postnatal steroids	87/280 (31)	2776/11656 (23.8) †
Age at first postnatal steroids (days) *	32.6 ± 28.4	28.5 ± 21.2
Parenteral alimentation	280/280 (100)	11187/11678 (95.8) †
Duration of parenteral alimentation (days) *	48.1 ± 33.55	29.6 ± 22.97 †
Age at initiation of enteral feeds (days) *	14.7 ± 15.1	7.4 ± 6.8 †
Severe IVH (grade 3 or 4)	95/277 (34.3)	1942/11233 (17.3) †

* Mean ± SD

** Respiratory support defined as infant being on conventional or high frequency ventilation

† p value < 0.05

Table 3

Association between SIP and treatment (unadjusted analysis)

Treatment	SIP n=280 Number (%)	No SIP 11680 Number (%)	p value
ANS ≥ 1 dose *	**125 (44.6)**	6376 (54.6)	0.0010
P Indo **	133 (47.5)	4239 (36.3)	0.0001
Indo/PDA ***	137 (48.9)	4205 (36.0)	<.0001

* ANS ≥ 1 dose- Antenatal steroids at least one dose

** P Indo- Prophylactic indometacin (administered within the first 24 hours of life)

*** Indo/PDA- Indometacin for PDA (administered after 24 hours of life)

Table 4

Comparison of neurodevelopmental impairment and its components in infants with and without SIP

Variable	SIP Number (%)	No SIP Number (%)	p value
NDI/Death	198/249 (79.5)	5568/9987 (55.8)	<.0001
NDI among survivors	86/137 (62.8)	2614/7033 (37.2)	<.0001
MDI<70	72/134 (53.7)	2177/6953 (31.3)	<.0001
PDI<70	65/133 (48.9)	1476/6892 (21.4)	<.0001
Cerebral Palsy	24/140 (17.1)	486/7418 (6.6)	<.0001
Blind *	5/140 (3.6)	59/7419 (0.8)	<.01
Deaf **	8/140 (5.7)	131/7385 (1.8)	<.01

Data presented for infants with information as n/N (%)

* Bilateral corrected vision of less than 20/200

** Bilateral hearing loss needing amplification