NUTRITION AND NEURODEVELOPMENTAL OUTCOMES AMONG A COHORT OF NEONATES WITH INTESTINAL FAILURE AND/OR SURGICAL SHORT BOWEL SYNDROME

SPECIAL STUDIES PROJECT

Submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of requirements of the degree of Masters in Public Health in the Career Masters of Public Health Program

BY

Ira Adams-Chapman
BA, Emory University 1987
MD, Medical College of Georgia 1991

Emory University
Rollins School of Public Health
CMPH Candidate
May 2011

Special Studies Committee

Silke von Esenwein, PhD	**Committee Chair**
Walter Burnett, PhD	**Healthcare Outcomes Advisor**
Theresa Gauthier, MD,	**Field Advisor**
Deanne Swan PhD	**Committee Member**

NUTRITION AND NEURODEVELOPMENTAL OUTCOMES AMONG A COHORT OF NEONATES WITH INTESTINAL FAILURE AND/OR SURGICAL SHORT BOWEL SYNDROME

Approved

Silke von Esenwein, PhD Committee Chair	Date
Theresa Gauthier, MD Field Advisor	Date
DeAnne Swan, PhD Committee Member	Date
Melissa Alperin, MPH, CHES Director, Career MPH Program	Date

In presenting this report as a partial fulfillment of the requirements for an advanced degree from Emory University, I agree that the School of Public Health shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to copy from, or to publish, this report may be granted by the professor under whose direction is was written, or in his/her absence, by the Director of the Career MPH Program, when such copying or publication is solely for scholarly purposes and does not involve potential financial gain. It is understood that any copying from, or publication of, this report which involves potential financial gain will not be allowed without written permission.

_____

Signature of Student Date

(**DO NOT FORGET TO SIGN YOUR COMPLETE DOCUMENT**)

NOTICE TO BORROWERS

Unpublished papers deposited in the Rollins School of Public Health of Emory University must be used only in accordance with the stipulations prescribed by the author in the preceding statement.

The author of this SSP is:
NAME: Ira Adams-Chapman, MD
ADDRESS: 2818 Payton Road Atlanta, GA 30345

The SSP Chairperson of this report is:
NAME: Silke von Esenwein, PhD
ADDRESS: Rollins School of Public Health, Atlanta, GA 30303

Users of this report are required to attest acceptance of the preceding stipulations by signing below.

Name of User Address Date Type of Use
(Examination only or copying)

EMORY UNIVERSITY SCHOOL OF MEDICINE

CURRICULUM VITAE

Revised: August 1,2010

1. Name: Ira Adams-Chapman, MD

2. Office Address:

46 Jesse Hill Jr. Drive

Atlanta, GA 30303

Telephone: 404-778-1450

Fax: 404-778-1467

3. E-mail Address: iadamsc@emory.edu

4. Citizenship: US Citizen

5. Current Titles and Affiliations:

a. Academic appointments:

Primary appointment:
Assistant Professor of Pediatrics

Emory University School of Medicine

Department of Pediatrics/Division of Neonatology

b. Clinical appointments:
Medical Director, Developmental Progress Clinic

Emory University School of Medicine

Department of Pediatrics/Division of Neonatology

2002

6. Previous Academic and Professional Appointments:

7/91-7/94 Pediatrics Internship/Pediatric Residency
Children's Hospital Medical Center
Cincinnati, OH

7/94-7/95 Staff Physician
Children's Hospital Medical Center
Department of Pediatrics, Division of Neonatology
Cincinnati, OH

7/98-9/98 Staff Physician
Children's Hospital San Diego
Division of Neonatology/Children Associated Medical Group
San Diego, CA

7/95-7/98 Neonatology Fellowship
University of California San Diego
Department of Pediatrics, Division of Neonatology
San Diego, CA

11/98-present Assistant Professor of Pediatrics
Emory University School of Medicine
Department of Pediatrics, Division of Neonatology
Atlanta, GA

5/09-5/10 Consultant

Research Triangle Institute

Project: Consultant Needs for Division of Birth Defects and Developmental Disabilities in Response to H1N1 Activities

7. Licensures/Boards:

1993	State of Ohio Medical Board (inactive)	
1995	State of California Medical Board (inactive)	#G81564
1998	State of Georgia (active)	#406343
1992	National Board of Medical Examiners	#403332
1994	American Board of Pediatrics	#052543
1999	Sub-Board of Neonatal-Perinatal Medicine	

8. Specialty Boards:

1994	Diplomate of the American Board of Pediatrics
1992	Diplomate of the National Board of Medical Examiners
1999	Neonatal-Perinatal Medicine Certification
2002	Recertification in General Pediatrics
2006	Recertification in Neonatal-Perinatal Medicine
2008	Recertification in General Pediatrics

9. Education:

1983 – 1987	Bachelor of Arts in Biology and Political Science
	Emory University – Atlanta, GA
1987 – 1991	Doctor of Medicine
	Medical College of Georgia – Augusta, GA
20007- Present	Career Masters in Public Health (Emphasis in Health Outcomes)
	Rollins School of Public Health
	Emory University –Atlanta, GA (Projected completion December 2010)

10. Undergraduate Education:
Emory University

Atlanta, Georgia

1983-1987

Bachelor of Arts – Major in Biology and Political Science

11. Postgraduate Training:
Medical College of Georgia

Augusta, Georgia

1987-1991

Doctor of Medicine

Children's Hospital Medical Center

Cincinnati, Ohio

1991-1994

Internship and Residency – Pediatrics

Mike Farrell, Residency Program Director

University of California, San Diego

San Diego, California

1995-1998

Fellowship – Neonatology

Neil Finer, Division Director

Emory University

Rollins School of Public Health

Atlanta, Georgia

2007 – present

Career Masters of Public Health - Emphasis in Health Outcomes

12. Military or Government Service:

5/88-7/88 National Institute of Health/National Institute of Allergy and Immunology AIDS Program Extramural Activities.

Drs. Diggs and Froehlich, Mentors

Summer Externship

US Public Health Service Commissioned Officer Student Training Extern Program

5/89-5/90 Federal Drug Administration/CDRH/Division of Life Sciences

Dr. Hitchins, Mentor

US Public Health Service Commissioned Officer Student Training Extern Program

13. Committee Memberships:

a. National and International:
Centers for Disease Control and National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention – Extramural Programs

NIH Grant Review Committee Member

Long Term Outcome of Infants Identified with Congenital CMV

July 2009

b. Regional and State:

State of Georgia Regional Perinatal Centers Developmental Follow-up Program Director

c. Institutional

Search Committee for Division Director of Neonatology – 2006-2007

Clinical Care Committee, Department of Pediatrics 2007

Outstanding Clinician Award Committee, Department of Pediatrics 2008

14. Manuscript Reviewer

Pediatrics

Journal of Pediatrics

Journal of Perinatology

JAMA

15. Honors and Awards:

Outstanding Fellow Teaching Award – University of California San Diego	1998
Outstanding Resident Award – Division of Neonatology	1994
Cincinnati Children's Hospital Medical Center	
Harry B. O'Rear Award – Outstanding Medical Student in Pediatrics	1991

16. Society Memberships:
Southeast Neonatology Association
American Academy of Pediatrics

Society for Pediatric Research

17. Research focus:
Neurodevelopmental Outcome of Preterm Infants

Neonatal Infections

Prevention of Nosocomial Infection

Necrotizing Enterocolitis

18. Grant Support:
a. Active support:

I. Federally funded:
NICHD Multicenter Network of Neonatal Intensive Care Unit
National Institute of Child Health and Human Development
NICHD Neonatal Network Follow-up Program Principal Investigator – 5% Effort
2006-2011

II. Private foundation funded: None

b. Previous Support
Contracts:
LIONS Study: Longitudinal iNOmax Observational Neonate Study: A study of term and near term infants receiving iNOmax Therapy.

Sponsored by iNO Therapeutics

19. Clinical Service Contributions:

2000 - Organized and providing training to develop the Neonatal PICC team in the Emory University NICU's (Grady, CWL and CHOA-ECH)

2007 – Organized and led the committee to reevaluate clinical scheduling issues for the division

of Neonatology. We organized a committee and analyzed our clinical needs, investigated national standards and proposed several solution for clinical coverage.

2008 – Developing the data elements for the state wide follow-up variable for the Dept of Human Resources Perinatal Centers Follow-up Project. Initiated the background and training process and will develop training manuals and videos in 2009 for the 5 perinatal centers

20. Formal Teaching:

a. Medical Student Teaching – ongoing but intermittent contact with the MS3 students during the Pediatrics rotation

b. Graduate Program
Emory University School of Medicine School of Nursing

Pediatric Nurse Practitioner Program

Long term care of the NICU Graduate

Annual lecture since 2005-present

21. Supervisory Teaching:

a. Ph.D. students directly supervised:
N/A

b. Post-doctoral fellows directly supervised:
N/A

c. Residency Program
Training programs: I have assisted with the supervision of various Neonatal Nurse Practioners from the Emory University School of Nursing and Georgia State Nurse Practioner Program

Residency program: Actively involved in resident education during the NICU rotations at our various clinical sites. I have served as a Faculty Advisor since 2000.

22. Lectureships, Seminar Invitations, and Visiting Professorships:

Neonatology 2004

Emory University School of Medicine, Department of Pediatrics/Division of Neonatology, Atlanta, GA
Topic - Guidelines for Neurodevelopmental Follow-up

Georgia Association of Neonatal Nurses 2004

Atlanta, GA

Topic – Hypoxic Ischemic Encephalopathy

March of Dimes Conference 2006

Long Beach, California

Preventing Birth Defects and Infant Mortality: Threats, Opportunities and Challenges

Topic – Developmental Outcome After Brain Injury in the Preterm Infant

Neonatal/Perinatal Medicine Conference 2006

Henry Medical Center, Atlanta, GA

Topic - Neurodevelopmental Outcome of the Preterm Infant

Neonatology 2007

Atlanta, GA

Emory University School of Medicine, Department of Pediatrics/Division of Neonatology

Topic - Pathogenesis of Brain Injury After Intraventricular Hemorrhage in the Preterm Infant

School of Public Health Pediatric Nurse Practioner Program

Annual Presentation

Atlanta, GA

Topic – Long Term Care of Preterm Infants

APNEC Lecture Series

Emory University School of Medicine, Division of Neonatology Outreach Program

Various lectures including Fluids and Electrolytes, Neurodevelopmental Outcome and Necrotizing Enterocolitis 2001- present

Georgia Pediatric Nurses Association/Georgia Academy of Pediatrics

Long Term Care of the Premature NICU Graduate

Cobb Galleria

September 27, 2007

American Public Health Association (APHA) Annual Meeting and Expo: Public Health Without Borders

Platform Presentation: Celebration 100th Anniversary of Universal Declaration of Human Rights

Fundamental Right to Health Care

San Digeo, CA

October 25, 2008

American Academy of Women in Medicine (AAMC) Early Career Women's Conference

Invited attended

Washington, DC

July 2009

Georgia American Academy of Pediatrics Meeting

Atlanta, GA

October 2010

Invited speaker – What the General Pediatrician Should Know About Long Term Care of the Extremely Premature Infant

23. Invitations to National or International Conferences: (Some in 22 need to move)

18th Annual ASHA-NIH Research Symposium

Insults to the Developing Brain and their Effect on Neurodevelopmental Outcomes

Chicago, Illinois

November 21, 2008

x. Bibliography:

a. Manuscripts:

Adams-Chapman I, Vaucher YE, Bejar RF, Benirschke K, Baergen RN, Moore TR. Maternal floor infarction of the placenta: Association with central nervous system injury and adverse neurodevelopmental outcome. Journal of Perinatology, 2002;22:236-241.

Stoll BJ, Hansen N, **Adams-Chapman I**, Fanaroff AA, Hintz SR, Vohr BR, Higgins RD. Neurodevelopmental and growth impairment among extremely low birth-weight infants with neonatal infection. JAMA, 292:2357-2365, 2004.

Hintz SR, Van Meurs KP, Perritt R, Poole WK, Das A, Stevenson DK, Ehrenkranz RA, Lemons JA, Vohr BR, Heyne R, Childres DO, Peralta-Carcelen M, Dusick A, Johnson YR, Morris B, Dillard R, Vaucher Y, Steichen J, **Adams-Chapman I,** Konduri G, Myers GJ, deUngria M, Tyson JE, Higgins RD for the NICHD Neonatal Research Network. Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a randomized controlled trial of inhaled nitric oxide. J Pediatr 2007;151:16-22

Deulofout R, Critz A, **Adams-Chapman I**, Sola A. Avoiding hyperoxia in infants < or = 1250 g is associated with improved short- and long-term outcomes. J Perinatol. 2006 Nov;26(11):700-5.

Adams-Chapman I, Hansen N, Stoll BJ, et al: Neurodevelopmental outcome of the extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics. 2008 May;121(5):e1167-77. Epub 2008 Apr 7.

Adams-Chapman, I. Insults to the developing brain and impact on neurodevelopmental outcome. J Commun Disord. 2009 Jul-Aug;42(4):256-62. Epub 2009 Apr 17.

Peralta-Carcelen M; Moses M; **Adams-Chapman I**; Gantz M; Vohr BR. Stability of neuromotor findings in extremely low birth weight children at 18 and at 30 months of age. Pediatrics. 2009 May;123(5):e887-95.

Adams-Chapman I, Carter S, Bann C and Stoll BJ for the NICHD Neonatal Research Network: Speech and Language Outcomes Among Cohort of ELBW Infant. Submitted to publication.

Adams-Chapman I, Bann CM, Vaucher YE, Stoll BJ for the NICHD Neonatal Research Network: Relationship Between Feeding and Language Development in Preterm Infants Using Bayley III in Early Childhood (Submitted for publication)

Adams-Chapman I, Bann CM, Goldberg R, Benjamin D, et al for the Candida Subcommittee of the NICHD Neonatal Research Network: Neurodevelopmental Outcome of ELBW Infants with Systemic Candidasis. (Submitted for publication)

b. Review articles:

Adams-Chapman I, Stoll BJ. Prevention of nosocomial infections in the neonatal intensive care unit. Current Opinion in Pediatrics 2002;14:157-164.

Adams-Chapman I, Stoll BJ. Systemic inflammatory response syndrome. Seminars in Pediatric Infectious Diseases, 2001;12:5-16.

Stoll BJ, Hansen N, ***Adams-Chapman I***, Fanaroff AA, Hintz SR, Vohr BR, Higgins RD. Neurodevelopmental and growth impairment among extremely low birth-weight infants with neonatal infection. JAMA, 292:2357-2365, 2004.

***Adams*-Chapman I,** Stoll BJ: Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. Current Opinion in Infectious Diseases 2006;19:290-297.

Adams-Chapman I: Neurodevelopmental Outcome of the Late Preterm Infant. Clinics in Perinatology 2006;33:947-964.

Adams-Chapman I: Long-term neurologic outcome of infants born by cesarean section.

Clinics in Perinatol. 2008 Jun;35(2):437-54, viii.

c. Symposium contributions:
CMV Research Conference
Presentation 2007 and scheduled to present 2008

e. Book chapters:

Adams-Chapman I, Stoll BJ: The fetus and the neonatal infant, Part XI, Section I, Noninfectious disorders, In Behrman RE, Kliegman RM, Jenson HB (eds): Nelson's Textbook of Pediatrics (18^{th} ed). Philadelphia: W.B. Saunders (in press)
Chapter 99: Nervous system disorders

Stoll BJ, **Adams-Chapman I**: The fetus and the neonatal infant, Part XI, Section I, Noninfectious disorders, In Behrman RE, Kliegman RM, Jenson HB (eds): Nelson's Textbook of Pediatrics (18th ed). Philadelphia: W.B. Saunders
Chapter 94: The Newborn Infant
Chapter 95: High-Risk Pregnancies
Chapter 96: The Fetus
Chapter 97: The High-Risk Infant
Chapter 100: Delivery Room Emergencies

Adams-Chapman I and Stoll BJ: Neonatal Infectious Diseases. (William Oh, Editor) Handbook of Neonatology. (In press)

ACKNOWLEDGEMENTS

I do not have any conflicts of interests to report.

Grant funding was obtained from Children's Healthcare of Atlanta to support development of the database and data collection for phase one of this study.

I would like to thank my committee members for sharing their time, expertise and insight to help guide the development and implementation of this project. My fellow colleagues in the Health Outcomes track have provided valuable feedback during our tenure in the program. The skills that I have learned from my professors and instructors at the Rollins School of Public Health have built the framework and fundamental skills necessary for project development, data preparation, analysis and interpretation.

I gratefully acknowledge my collaborators in this project, particularly, Conrad Cole, MD, Meghan Durham, MD, Lynn Wineski, NNP, Wendy Coto-Puckett, MD and DeAnne Swan, PhD.

I would like to acknowledge the many physicians, nurses and staff members who have cared for the infants referenced in this study. My colleagues have been fully supportive of this project as a part of our ongoing efforts to improve healthcare outcomes for the neonates under our care in the Neonatal Intensive Care Unit at Children's Healthcare of Atlanta-Egleston.

I would like to thanks Mrs. Jacqueline Walton for her ever present assistance and also my staff in the Emory University Developmental Progress Clinic for your support and the care that you provide to the infants involved in this study and their families.

Finally, I would like to thank my husband, Thaddeus Chapman, and my two children, Jordan and Julian Chapman, for their support, encouragement and patience during my enrollment in the MPH program.

Abstract

Title: Factors associated with achieving enteral autonomy in a cohort of neonates at risk for intestinal failure

Background: Currently, there are limited data evaluating the relationship between prolonged parenteral nutrition in neonates with gastrointestinal complications and predictors of death or long term nutritional outcome.

Objective: To identify factors associated with failure to achieve enteral autonomy in a cohort of neonates from a single center at risk for intestinal failure

Methods: A retrospective chart review was performed of patients with intestinal failure (defined as parenteral nutrition > 60 days) born between April 1, 2004 and July 30, 2009 from a single center Level III NICU. Primary endpoints were death or enteral autonomy (EA) is defined as reaching full feeds ≤365 days. Analyses were performed to evaluate differences in demographic, clinical, laboratory and nutritional outcome data and outcome status using SPSS statistical software.

Results: Eighty patients met criteria for IF during the study period, of whom 60% were male and the mean birth weight and gestation age was 1.48±.88 kg and 30.2 ±4.6 weeks, respectively. Sixty three (78.8%) infants survived and 4 (5%) received a small bowel/liver transplant. Patient diagnoses included Necrotizing enterocolitis (64%), abdominal wall defects (10.1%) and small bowel atresia (10%).

Overall, 60% of infants reached EA by 365 days; however, only 41% had reached full enteral feeds by 6 months of age. Peak serum AST levels (508 v. 324, $p<.004$) and days of parental nutrition and intralipid days (620 days v. 154 days, $p< .000$) were significantly higher among those who did not reach EA. Patients in both groups had similar peak serum levels of direct bilirubin and ALT. Patients who failed to reach EA were more likely to die. The percentage of eligible infants with IF who achieved EA increased with increasing birth year cohort.

Conclusion: The primary endpoints of death or EA were both associated with days of exposure to parenteral nutrition. Peak liver function studies were not consistently associated with delay in achieving EA or prolonged exposure to parenteral nutrition.

Table of Contents

Chapter V: Conclusions

LISTS OF TABLES

LISTS OF FIGURES

Chapter I

Introduction

Statement of the Problem

As a neonatologist working in the neonatal intensive care unit (NICU) at Children's Healthcare of Atlanta-Egleston where we care for a large number of newborns who require surgery, I developed a keen interest in infants with a condition known as Necrotizing Enterocolitis (NEC). This condition primarily affects prematurely born infants and is associated with both short and long term morbidity and an increased mortality risk. Researchers have unraveled the mystery surrounding many complications associated with prematurity; however, the underlying etiology for NEC remains poorly understood. As such, the incidence of this disorder has remained relatively static over the past decade. Although certain risk factors are common among affected neonates, the variability in presentation and severity makes one suspect that some risk factors for this disease process may be modifiable. Furthermore, the variability in incidence rate suggests that there may be underlying epidemiologic contributors affecting the risk for this disease process.

As an academic neonatologist at Emory University School of Medicine, my clinical research activity has focused on causes of adverse neurodevelopmental (ND) outcome in preterm infants. NEC has been shown to be associated with an increased risk for brain injury and abnormal ND outcome in early childhood. I continue to be intrigued by both the immediate pathophysiology and the long term consequences associated with this disease.

Improved understanding of our site specific outcomes for patients cared for in our clinical center is critically important to improve overall health outcomes for this subpopulation. Although this disorder affects a small percentage of the prematurely born infants each year, the consequences for affected infants are often devastating and lifelong. The public health impact of providing medical, emotional and educational support for affected children over a lifetime is substantial. Any marginal improvement in care which modifies this neonatal morbidity is important and can be translated to similar populations across the globe.

This special studies project focuses on evaluation of nutrition and neurodevelopmental outcomes of prematurely born infants at risk for intestinal failure with NEC or other diagnoses resulting in surgical short bowel syndrome cared for at Children's Healthcare of Atlanta-Egleston.

Chapter II

Review of the Literature

Advances in neonatology over the past 30 years have led to a remarkable increase in the survival of low birth weight infants; however, these infants remain at risk for adverse long term neurodevelopmental outcomes and chronic medical illnesses.[1-4] The risk for poor long term outcome is inversely related to gestational age and birth weight and is further modified by the presence of specific neonatal morbidities, including necrotizing enterocolitis (NEC).[5-7] NEC is a potentially life threatening condition that affects approximately 11% of extremely low birth weight infants (ELBW) secondary to inflammation and necrosis in the neonatal intestine.[8-11]. The associated proinflammatory state frequently associated with this disorder likely contributes to the adverse outcome seen in affected infants. NEC is the most common cause for short bowel syndrome (SBS) and intestinal failure (IF) during the neonatal period. [10] The toxicity associated with prolonged parenteral is unclear; however, progressive liver failure resulting in death is not uncommon in the most severely affected infants.

The objective of this project is to evaluate the site specific nutritional and neurodevelopmental outcomes of a contemporary cohort of newborns at risk for intestinal failure cared for at Children's Healthcare of Atlanta at Egleston, the majority of whom had NEC as the underlying diagnosis. Improved understanding of the relationship between infection, inflammation, suboptimal nutrition during a period of critical brain development is needed to improve the outcome of neonates with NEC and SBS.

The specific etiology of NEC continues to elude investigators but is most likely secondary to multiple factors including structural immaturity of the premature gastrointestinal tract, barrier function, abnormal bowel colonization patterns and hypoxic ischemic injury. [12, 13] The lack of understanding of the underlying pathology makes it difficult to develop prevention strategies.

The typical clinical presentation includes feeding intolerance, abdominal distension and bowel wall erythema. With increased severity of illness, the infant develops systemic signs of illness including respiratory distress, apnea and hypotension. Metabolic derangement including metabolic acidosis, coagulopathy and renal failure are common. The pathologic findings include focal or diffuse bowel wall ischemia, necrosis, and gangrene. As shown in **Figure 1,** affected areas of bowel become distended and have focal areas of ischemia and necrosis.[14] The integrity of the bowel wall becomes compromised and can be so weak that the intestinal wall ruptures resulting in a pneumoperitoneum (free air in the abdomen).

The diagnosis is based on a combination of clinical judgment, x-ray findings and laboratory studies. The pathognomonic radiographic finding is pneumatosis, defined as air in the abdominal wall lining. Bell's staging criteria define the clinical stages of disease severity and management. [15] Surgery is considered for infants with known or suspected perforation and those unresponsive to medical therapy. [12] Among those infants requiring surgical intervention, the remaining bowel length and the ability to preserve the ileo-cecal valve have both been correlated with improved nutritional outcome and decreased mortality.[10, 16, 17]

Short Bowel Syndrome and NEC

Surgical resection of damaged intestines is the mainstay of therapy for NEC with the goal of preserving as much viable bowel as possible. Short bowel syndrome (SBS) is the devastating consequence of an extensive resection of bowel resulting in insufficient bowel length for adequate absorption of nutrients to support growth. This syndrome is potentially lethal and is associated with long term complications including growth impairment and long term neurodevelopmental delay.[10, 11, 18, 19] These infants are also more likely to be readmitted to the hospital and be discharged home on tube feeds. In a review by Cole, et al evaluating the incidence, morbidity, mortality and growth outcomes in a cohort of 12, 316 very low birth weight infants < 1500 grams birth weight, the overall incidence of SBS was 0.7% with the greatest risk being among those < 1000 grams.[10] Infants with SBS had an increased mortality rate and survivors were more likely to have had episodes of sepsis, smaller head circumferences and hospital readmissions at 18 months adjusted age compared to peers without SBS. **Figure 2**

Nutrition and NEC

Intestinal failure (IF) is defined as the need for parenteral nutrition for ≥ 60 days due to inability to absorption adequate nutrition from enteral feedings. The most common reason for IF in the neonatal period is surgical NEC. The decreased absorptive capacity and rapid transit time results in significant feeding difficulties during the perioperative period. Most infants are able to tolerate small amounts of enteral feeds but the majority of the nutrition is given intravenously.

Parenteral nutrition is life saving for these critically ill neonates; however, prolonged exposure to hyperalimentation can result in hepatic injury and possibly liver failure. Worsening liver dysfunction is an indication for referral for combined liver and small bowel transplantation; however, some infants will die prior to transplant. The associated mortality rate for liver/small bowel transplants in early childhood remains quite high, even though it has improved over the past 5 years.[20]

Enteral autonomy (EA), defined as the ability to achieve full enteral feeds < 12 months of age, has been associated with improved growth outcomes. Even among those wow achieve enteral autonomy, feeding dysfunction and dysphagia are common thus many children have surgical or temporary feeding tubes. Cole, et al reported that infants with surgical short bowel syndrome were more likely to require a feeding tube at hospital discharge and at the 18 month follow-up visit compared to infants with non-surgical NEC and those who were unaffected.[10] Slow continuous feedings are generally better tolerated than bolus feeding because they allow for a longer period of time to absorb the nutrition. Partially related to not being allowed to feed by mouth, many affected infants develop dysfunctional feeding pattern that extend well beyond the initial hospitalization. The most severely affected infants are discharged home on both parenteral nutrition and tube feedings. The intensity of long term care increases associated healthcare costs.

The goal for successful management of intestinal failure is to optimize medical and surgical management to support intestinal adaptation without increasing the risk of liver disease. Currently the fat emulsion used with parenteral nutrition in the United States is a soy based product. Researchers are trying to determine if modifications of the base for the fat emulsion can decrease the risk of liver failure. Current data is insufficient to endorse a broad scale change in clinical practice; however, multiple research groups have reported anecdotal improvement in single or small numbers of patients after changing the fat emulsion to an omega 3 fatty acid solution. [21-23]. Lipid minimization practices are already migrating into clinical practice among providers caring for infants at risk for intestinal failure based on these preliminary data, including neonatologist at Children's Healthcare of Atlanta-Egleston. Quantification of all components of the parenteral nutrition solution over time is needed to accurately determine the effect of long term outcome.

Neurodevelopmental Outcome and NEC

Necrotizing enterocolitis continues to be a potentially devastating complication of premature birth that is associated with an increased risk of death and significant long term morbidity, including adverse neurodevelopmental outcome.[18, 19] The contribution of nutritional deprivation on the developing preterm brain during critical phases of development is an important contributor to the neurocognitive impairment seen in this population. [24, 25] The prolonged need to maintain central venous catheters in situ has been associated with an increased risk of catheter related blood stream infections [10] in addition to the risk of bacterial

translocation in those with intestinal failure. [26, 27] Repeated late onset infections have been associated with adverse neurodevelopmental outcome in preterm infants. [19]

Multiple researchers have documented the increased risk for CNS abnormalities on cranial ultrasound and adverse neurodevelopmental outcomes in patients with NEC.[28-30]. Though portable and convenient, recent data suggest that cranial ultrasounds underestimate the severity of white matter injury in preterm infants.[29, 31-33] Magnetic resonance imaging (MRI) is a more specific screening technique but not performed routinely in preterm population, therefore data are limited. Improved understanding of the timing and sequence of development of critical neuronal tissues has allowed researchers to define the pathophysiologic link between inflammation and brain injury. The pre-oligodendroglia are the predominant cell lineage in the cerebral white matter between 28 and 41 weeks gestation.[29, 34, 35] These cells are extremely vulnerable to cytotoxic injury from circulating cytokines. We now understand that the cerebral white matter is also important in neuronal networking, migration, synaptogenesis and elongation. Disruption of these cells at any point along the path can result in disruption in the development of distal structures. The intense inflammatory response noted in neonates with NEC can be overwhelming and result in significant multi-organ system dysfunction and/or death. Inflammatory mediators are known to cross the blood brain barrier, particularly in the immature brain which has poorly developed tight junctions. Theoretically, patients with a history of NEC are should be at increased risk for WMI due to the intense inflammatory state associated with this disorder. In previous reports, infants with NEC were noted to have an increased incidence of

PVL on cranial ultrasonography, microcephaly and developmental delay.[9, 36] At present, there are limited clinical data systematically evaluating MRI neuroimaging in this population.

Dysynchrony between cranial ultrasound findings and neurodevelopmental outcome, highlight the importance of systematically evaluating the neurodevelopmental outcome of at risk populations. NEC in preterm infants has been associated with adverse neurodevelopmental outcome in early childhood.[5, 9, 19] Hintz, et al, compared growth and neurodevelopmental outcomes of infants < 1000 grams with surgical NEC to infants with medically managed NEC and those who were unaffected.[9] Infants with a history of surgical NEC were more likely to have growth impairment at 18 months adjusted age in all three parameters measured –weight, height and head circumference. Furthermore, these infants were more likely to have lower cognitive and motor performance scores on the Bayley Scales of Infant Development-IIR and overall neurodevelopmental impairment compared to infants medically managed NEC and unaffected infants. **Figure 3.**

Short bowel syndrome is the most extreme manifestation of NEC. One would speculate that affected infants would have the highest risk of poor nutritional and neurodevelopmental outcome within this subgroup of patient. At present, there are limited data regarding the nutritional or neurodevelopmental outcome of preterm neonates with short bowel syndrome or those with prolonged exposure to parenteral nutrition.

Project Justification

There is significant variability in prevalence rates of NEC and SBS among clinical centers. Rates of SBS range from 0.1% to 1.6% across study centers.[10] This represents the wide variability in incidence, morbidity and mortality in different clinical centers. This highlights the importance of establishing a baseline for growth and neurodevelopmental outcomes at our clinical site at Children's Healthcare of Atlanta where a large number of infants with surgical gastrointestinal complications are referred for surgical evaluation and management. Furthermore, clinical practice nationally has shifted towards supporting infants with decreasing lengths of viable bowel, it is critically important to systematically collect growth and neurodevelopmental outcome data on affected infants.

This project is designed to occur in multiple phases which have some periods of overlap. Phase one focuses on outcomes from hospital admission until death or hospital discharge. Clinical, laboratory and patient data were collected to create a database to better understand the relationship between nutritional parameters, surgical history, laboratory data and the ability to achieve enteral autonomy (full enteral feeds < 12 months of age). Phase two of this project will focus on the post discharge period and evaluation of nutritional and neurodevelopmental outcome of survivors.

Public Health Implications

In a review by Neu and colleagues, the estimated annual cost of caring for affected infants in the Unites States in between $500 million to $1 billion.[14] NEC has been associated with increased length of stay, particularly among those requiring surgery.[10] The highest risk subgroup are those who require extensive bowel resection resulting in SBS who have an estimated 5 year cost estimated at $1.5 million per affected child.[14]

Two important changes in clinical practice will likely affect the total number of affected children over the next 5-10 years. The lower range of viability for prematurely born infants continues to decrease across the United States in addition to the fact that survival has also increased in the lower birth weight ranges. The improved 5 year survival after small bowel transplantation in young children has led to an increased tendency to attempt to save even those infants with extremely short lengths of remaining bowel (i.e. 25 cm of remaining bowel) who may have previously been considered unsalvageable. [20, 24, 37] One would speculate that the absolute number of affected infants with the most severe forms of this disease will likely increase over time. Furthermore, the inability to develop effective prevention strategies results in a stable baseline prevalence of disease over time in this population.

Patients unable to achieve full enteral autonomy are routinely discharged home with feeding tubes and central lines. Parenteral nutrition, which consists of intravenously administered protein, carbohydrates and fat, are administered at home by a skilled care provider or parent.

Affected families undergo chronic psychosocial stress and disruption to normal daily activity. It is often difficult for parents to maintain employment outside the home due to the need for skilled nursing care, frequent hospitalizations and the generally fragile nature of these infants. In the most extreme cases, those infants referred for evaluation for liver and small bowel transplantation must relocated to another state for the evaluation, surgery and prolonged post-transplant recovery period. This results in separation of family members, including spouses, other unaffected children and the extended family support system.

Chapter III
Methods

Hypotheses

Phase One

Primary Hypothesis:

Among a cohort of infants at risk for intestinal failure, failure to achieve enteral autonomy by 365 days will be directly related to specific risk factors including lower birth weight, diagnosis, amount of remaining bowel after resection and delayed timing of surgical reanastomosis.

Secondary Hypotheses:

Inability to achieve EA and/or death will be directly related to the number of days of exposure to hyperalimentation and intralipid.

Phase Two

Primary Hypothesis:

Among a cohort of infants at risk for intestinal failure, those infants who fail to reach enteral autonomy by 365 days of age will have worse neurodevelopmental outcome compared to those who achieve enteral autonomy by 365 days of age.

Phase Two

Secondary Hypothesis:

Infants at risk for intestinal failure will have impaired growth at hospital discharge and at 18 month follow-up compared to published normative populations and age matched preterm peers.

Study Objectives/Aims

Specific Aim #1: is to perform a retrospective review of a contemporary cohort of infants and children at risk for intestinal failure who were cared for at Children's Healthcare of Atlanta-Egleston to identify demographic, clinical, and nutritional risk factors that will predict the following critical outcomes: (1) need for parenteral nutrition > 60 days defined which is defined as intestinal failure (2) need for long-term PN (> 365 days), (3) discontinuation of PN, (4)

development of liver disease and cholestasis, (5) achieving enteral autonomy, (6) need for intestinal transplant, and (7) death.

Specific Aim #2: is to perform a retrospective review of a contemporary cohort of infants identified to be at risk for intestinal failure who were cared for at Children's Healthcare of Atlanta-Egleston to evaluate neurodevelopmental outcome including an assessment of cognitive, language and motor performance at various time points between 4 months and 4 years of age. These outcomes will be compared to standardized normative data and internal controls of other age matched peers without a history of intestinal failure or NEC. Primary developmental outcomes will be: (1) Cerebral Palsy, (2) Cognitive Impairment (Bayley Cognitive or MDI Score <70), (3) Motor Impairment (Bayley Motor or PDI Score < 70), (4) Bilateral blindness, (5) Hearing Impairment requiring amplification.

Specific Aim #3: Identify predictors of neurodevelopmental outcome among this cohort of infants at risk for intestinal failure including surgical history, nutritional parameters, laboratory data and neonatal co-morbidities that could impact neurologic outcome (intraventricular hemorrhage, periventricular leukomalacia and chronic lung disease).

Study Design

This study is a retrospective chart review.

Study Population

The study population is drawn from a convenience sample of all infants born between April 1, 2004 and July 31, 2009 who were treated at Children's Healthcare of Atlanta at Egleston with a diagnosis of either short bowel syndrome and/or surgically treated necrotizing enterocolitis who required parenteral nutrition > 60 days. Patients from this cohort who were evaluated in the Emory Developmental Progress Clinic after initial hospital discharge will be eligible for inclusion in the second phase of this study to evaluate neurodevelopmental outcomes. Patients who received parenteral nutrition ≤ 60 days and those for whom the primary endpoints cannot be ascertained from the medical record will be excluded from this analysis. Patients are referred to Children's Healthcare of Atlanta at Egleston, a Level IV NICU, from various hospitals within a 300 mile radius of the hospital based on the discretion of the attending neonatologist at the referring center.

Data Collection

Based on the specific aims outlined above specific laboratory, nutritional and patient data was collected at various time points. Information was extracted from the hospital electronic medical record which is formatted by Epic®.

<u>Laboratory data:</u>

Weekly laboratory samples to assess liver function are routinely obtained on neonates in the NICU who are receiving parenteral nutrition until they achieve full enteral feedings. Additional levels are obtained after this time if the most recent value at the time of achieving full feeds is outside of established laboratory ranges. Periodic data collection of lab values began when the patient had been on parenteral nutrition for at least 30 days and then at 1 (+ 1 week), 3 (+ 1

week), 6 (+ 2 weeks), 9 (+ 1 weeks) and 12 (+ 1 month) months following. Peak values at any time point during the hospitalization were recorded. The following laboratory values were extracted: SGOT, SGPT, Total Bilirubin, Direct Bilirubin, and GGT.

Nutritional Data:

Data to be collected and reviewed including growth parameters, nutritional data related to mode of nutrition, time to enteral feeds, length of parenteral nutrition, type of formula, complications related to parenteral nutrition, type of surgical procedures, length of bowel remaining after surgery. (**Appendix A)** Detailed information regarding the use of parenteral nutrition at each periodic assessment point includes current length, weight, macro- and micro-nutrient levels, enteral nutrition, total calories, carbohydrate infusion rate, percent of calories received by the enteral and parenteral route, grams of protein and fat received by parenteral nutrition, cycle time and non-nitrogen calories per gram of nitrogen intake from parenteral nutrition.

Infant Data

Birth and neonatal variables were collected as outlined in **Appendix B**, including gestational age, birth weight, year of birth, neonatal conditions, primary surgical diagnosis, anatomic description of surgical resection including procedure performed, remaining bowel length, presence of multiple intestinal anastomoses, presence or absence of ileo-cecal valve, presence

and location of ostomy, timing of bowel reanastomosis, surgical gastrostomy feeding tube and medications. Diagnoses from cranial neuroimaging reports (ultrasound and MRI), abdominal ultrasound report and surgical operative notes will also be extracted. Any surgical procedures not related to the gastrointestinal tract that occurred during the hospital are also reported, including central line insertion.

Neurodevelopmental Data

IRB approval for this portion of the study is pending therefore data collection has not started. Outlined below is the plan for data collection related to neurodevelopmental outcome.

Age appropriate developmental assessments are performed by the Developmental Progress Clinic physical therapist and/or developmental psychologist based on adjusted age and/or developmental level. The developmental assessment tool used for infants < 12 months adjusted age is the Alberta Infant Motor Scale (AIMS). The Bayley Scales of Infant Development is used for infants > 12 months adjusted age. At each visit, the physician and/or nurse practioner performs a complete neurosensory examination to identify abnormalities of tone, posture or function. Neurodevelopmental outcomes will be compared based on achievement of enteral autonomy. Cases will also be matched for year of birth, race, gender and gestational age to control infants without a history of NEC who are also followed in the Developmental Progress Clinic.

Data management system:

A secure electronic Access based data management system was developed and developed. All patients are assigned a unique identifier and any patient health information is de-identified and handled in accordance with university HIPAA regulations and guidelines. The data is only accessible by study group members and each member has a unique login and password.

Study Definitions

Necrotizing Enterocolitis (NEC) is clinical or pathologic diagnosis associated with inflammation and necrosis of intestines with varying degrees of severity as defined by Bell. Diagnostic criteria for Short bowel syndrome (SBS) are reduced based on mucosal surface area due to surgical bowel resection or congenital syndromes leading to malabsorption. Enteral Autonomy (EA) is defined as the ability to achieve full enteral feeds by 12 months of age without need for parenteral nutrition. Intestinal Failure (IF) is defined as the need for parenteral nutrition ≥ 60 days. Chronic Lung Disease (CLD) is defined by oxygen requirement at 36 weeks postmenstrual age. Intraventricular Hemorrhage (IVH) is diagnosed as bleeding in the central nervous system using a grading system of severity as defined by Papile. Periventricular Leukomalacia (PVL) is defined as cystic echolucencies in the periventricular white matter seen on cranial ultrasound or MRI. Sepsis is defined as a positive blood culture with a known bacterial pathogen and treated with antibiotics for ≥ 5 days. Clinical sepsis is defined as having a negative blood culture but clinical symptoms consistent with sepsis syndrome and treated with antibiotics for ≥ 7 days and a documented diagnosis of clinical sepsis in the medical record. Cerebral Palsy (CP) is a non-progressive disorder of posture and tone affecting motor function of varying degrees of severity.

Severity scale as defined by the gross motor functional classification score (GMFCS) Moderate to severe CP if GMFCS ≥ 2.

IRB Approval

IRB approval for Study # 00017790 was obtained from Emory University and Children's Healthcare of Atlanta for phase one of this project which focused on identification of eligible subject, extraction of clinical, laboratory and patient data and development of the database. An IRB proposal to collect data regarding neurodevelopmental outcome among survivors has been submitted and is pending approval – Study # 0047422. **Appendix C.**

IRB approval is pending to Emory University School of Medicine for phase two of this pending for approval to evaluate patient data of neurodevelopmental outcome based on developmental evaluations performed at Emory Children's Center in the outpatient clinic. **Appendix D.**

Statistical Analysis

Data were analyzed using SPSS Statistical Software 18. Bivariate analyses were performed to compare demographic and mortality profiles based on achievement of enteral autonomy using chi-square for categorical variable and analyses of variance for continuous variables. I estimated the prevalence of the primary outcomes (1) intestinal failure, (2) enteral autonomy, (3) small bowel transplant and (4) death. Student's T-test or an ANOVA was used to compare differences in demographic profiles between those who achieved EA and those who did not. Binary logistic models were created to predict the primary outcomes of death or EA. The model included

variable expected to predict the outcome including r gestational age, birth weight, diagnosis, days on hyperalimentation, days of intralipid, peak SGPT and peak Direct Bilirubin levels.

Study Limitation/Delimitations

Both nutritional and neurodevelopmental outcomes vary based on characteristics of the clinical site secondary to institutional practice patterns and characteristics of the population which may not be generalizable to other centers. One of the specific goals of this study is to evaluate site specific outcomes which can be compared to data that has been published previously from other hospitals. Given that this is an exploratory study, investigators will compare growth and nutritional data to published norms; however, for evaluation of neurodevelopmental outcome, patients will be matched by gestational age and year of birth with control subjects who were also seen in the Developmental Progress Clinic but do not have a history of short bowel syndrome or intestinal failure. Patients who are referred for small bowel and liver transplantation have to physically relocate to another state for months to years therefore neurodevelopmental outcome data will not be available for the entire population of infants in this cohort.

Ethics of Research

Patient care management is determined solely by the attending neonatologist with/without the consultation of the gastroenterology service and is not altered or affected by this study. There are no ethical dilemmas related to his project. All patients with NEC meet eligibility criteria for referral to the Developmental Progress Clinic after hospital discharge because these infants are known to be at risk for developmental delay.

Chapter IV

Results

Study Population

During the study period between April 1, 2004 and July 31, 2009, 80 infants admitted to the Neonatal Intensive Care Unit at Children's Healthcare of Atlanta at Egleston met eligibility criteria. These infants represented 3.4% (80/2338) of the total admissions to the Neonatal Intensive Care Unit during this period. Primary outcome data for phase one of the study, which evaluates risk factors associated with reaching enteral autonomy, was available for all 80 infants.

Patient demographic characteristics are outlined in **Table 2**. The mean gestational age for infants in this cohort was 30.6 weeks (± 4.6 weeks) and their mean birth weight was 1490 grams (± 880 grams). Sixty percent were male; of whom, 50% were Black, 25% were White and 11% were Hispanic. Four infants (5%) were referred for intestinal transplant and 17 infants (21.3%) died prior to this analysis of data. The underlying diagnosis among those who died was NEC (67%), Gastroschisis (11%), Omphalocele (7%), Small Bowel Atresia (7%) and 11% with other GI syndromes. Those who died had similar gestational ages, birth weight and diagnoses as those who survived. Failure to achieve EA was negatively correlated with death (Pearson's coefficient -.73, p=.000). The date of death was known for 11/17 infants. Among those who died, the mean age of death was 279 ± 126 days (Range 121-574 days).

Nutritional outcomes

The majority (63.8%) of the infants identified with intestinal failure had a diagnosis of NEC. Other diagnoses associated with intestinal failure are listed in **Figure 4**. Overall, 60% of infants reached EA by 365 days; however, only 41% had reached full enteral feeds by 6 months of age. Peak serum AST levels (508 v. 324, $p<.004$) and days of parental nutrition and intralipid days (620 days v. 154 days, $p< .000$) were significantly higher among those who did not reach EA. Patients in both groups had similar peak serum levels of direct bilirubin and ALT. Patients who failed to reach EA were more likely to die. The percentage of eligible infants with IF who achieved EA increased with increasing birth year cohort. The patient diagnosis did not correlate with likelihood of reaching EA. Days of exposure to HAL (241 days ±62 days, $p<0.000$) and/or IL (243 days ± 81 days, $p<.000$) were significantly higher among those who failed to reach EA by 365 days. Additional data is currently being collected to analyze the exact amounts in terms of grams per kilogram body weight that the infant received in the parenteral nutrition.

Data regarding remaining bowel length postoperatively was not systematically recorded; therefore we were unable to evaluate this as a predictor of outcome. Data was recorded for 36/80 infants with a mean bowel length of 38 cm ± 7.3 cm. These data represent an ascertainment bias because the surgeon would be more likely to measure and document remaining bowel length on the patient requiring the more extensive resection.

Patient enrollment by year varied during the study period as a reflection of the fact that a dedicated intestinal rehabilitation team was implemented midway through the study period.

Overall, the percentage of patients who achieved EA increased during the study period reaching a peak of 93% in 2009; however, these differences were not statistically significant.

Additional analyses are being performed to explore differences in outcome based on surgical management, including time between initial surgery and reanastomosis, presence and use of mucous fistula for refeeds prior to reanastomosis and placement of gastrostomy feeding tube.

A binary logistic regression model was created to predict the two primary endpoints, death and achievement of enteral autonomy. Expected predictors were entered into the model; however, variables known to be co-linear such as gestational age and birth weight and TPN days and IL days, were entered separately. Days of exposure to TPN and/or intralipids did not independently predict the risk of death or ability to achieve EA. Peak AST level independently predicted risk of death . **Table 8-10.**

Discussion

Necrotizing enterocolitis is a serious complication of prematurity that is associated with significant short and long term morbidity and mortality. In its most extreme clinical manifestations, affected infants require extensive bowel resection leaving them with surgical short bowel syndrome. The shortened bowel length may not be long enough to allow for sufficient amount of absorption of fluids and electrolytes to sustain normal growth and development. These infant have nutritional malabsorption syndrome and failure to thrive. Though initially life saving, the intravenous nutrition that initially sustains these infants becomes the primary source of the progressive cholestasis and liver failure in those who are unable to tolerate full enteral feedings. Furthermore, the adverse neurodevelopmental outcome of survivors highlights the importance of improving outcomes in this population. Improved understanding of the complex physiology and interrelationship with other co-morbid conditions and the interplay between nutrition and brain develop will allow researchers to improve nutritional and neurodevelopmental outcomes in these vulnerable neonates. This study evaluates the nutritional outcome of infants with intestinal failure in our clinical center.

Most premature infants have delayed tolerance of enteral feeding due to the immaturity of the preterm gastrointestinal tract. Animal studies have shown that the intestinal mucosa becomes atrophic when feedings are withheld for a prolonged period of time because the enzymes normally present on the intestinal villus are necessary to absorb nutrients. Most infants with NEC are critically ill during the immediate perioperative period and feedings are typically withheld for 2 weeks postoperatively to allow the tissues to heal. The ability to achieve enteral

autonomy is directly related to the severity of the underlying disease and the amount of remaining bowel length. How other aspects of our care and management affect this outcome are unclear and needs to be explored further.

Nutritional deprivation has been associated with poor neurological outcome even in children without underlying medical conditions.[38, 39] If one extrapolates these data to the preterm population, you would speculate the suboptimal nutritional intake in these infants contributes to their poor neurological outcome. Impaired somatic growth in preterm infants has been associated with poor neurological outcome in preterm in early infancy.[19] Clinicians are very concerned about the potential consequences of the poor nutritional intake in infants with short bowel syndrome. Frequently, the terminal ileum is involved and requires resection resulting in folate and B12 malabsorption. Infants with prolonged parenteral nutrition requirements typically develop cholestasis (stasis of bile in the liver) and have abnormal liver enzyme. In adult populations, CNS dysfunction and altered mental status are reported in patients with severe liver disease.[40, 41] The impact of the hepatic dysfunction/failure is unclear in the neonatal population. In our cohort, peak transaminases did not correlated with likelihood of reaching enteral autonomy. It will be intriguing to see the relationship of peak transaminases and neurodevelopmental outcome in phase two of this study.

The mean number of days of exposure to hyperalimentation and/or lipids did not correlate with the ability to achieve enteral autonomy. We speculate that using the number of days is not a

sensitive enough indicator; therefore additional data is being collected to calculate the exact amount in grams per kilogram of body weight of lipid emulsion the infants were exposed to. In addition, the relative percentages of carbohydrate and protein intake are also being collected. Case reports and animal data suggest that a lipid minimization strategy may decrease the risk of cholestasis in neonates requiring prolonged periods of parenteral nutrition. These data will also be used to correlate with neurodevelopmental outcomes.

The explanation for the extreme ranges of variability in incidence by center is unclear. This highlights the need for site specific surveillance and data collection regarding patient outcomes for patients with NEC and those with short bowel syndrome. Researchers are developing collaborative networks to identify "best practices" for the care and management of patients at risk for intestinal failure. Several centers report improved outcomes and even reversal of liver failure with aggressive management by a dedicated intestinal rehabilitation team to.[42-44]. During the study period we developed a dedicated intestinal rehabilitation team; however, it is no longer functional. We observed a decreasing trend of number of patients referred for small bowel transplant over time and an increased percentage of those at risk who reached enteral autonomy by one year of age. It will be important to monitor these trends now that this resource is no longer available.

Cytotoxic insults to the developing brain are a likely contributor to the adverse neurodevelopmental outcome previously reported in patients with surgical NEC.[9] These

infants are exposed to multiple episodes of cytokinemia both during the acute phase of NEC and also during subsequent episodes of bacterial sepsis. Cole, et al have reported an increased risk of blood stream infection and poor linear growth in infants with surgical short bowel syndrome.[10, 45] We speculate that this risk for repeated inflammatory insults is greatest in those with short bowel syndrome; however, currently there are limited data specifically evaluating regarding the neurodevelopmental outcome in this subgroup of patients. Neurodevelopmental outcomes for infants in our cohort will be explored in phase two of this study.

It is concerning that the incidence of NEC has remains relatively static over time. Overall, neonatal morbidity and mortality have decreased over time for low birth weight infants; however, we have not had a significant impact on preventing this disease. Those infants with intestinal failure typically have prolonged hospital inpatient lengths of stay and may require parenteral nutrition on a chronic basis after hospital discharge. They are frequently readmitted to the hospital secondary to feeding difficulties and bacterial sepsis, particularly in those with central venous lines receiving intravenous nutrition at home. The medical costs and psychosocial cost for the family are significant. The disruption in normal daily functioning for the affected child and their family must also be considered as an adverse outcome.

Variability in disease incidence and outcome suggests that there may be practice variations that are impacting the risk for liver disease and possibly even neurodevelopmental outcomes.

Center-based and collaborative research is needed to help answer these important questions. Our data represents the first attempt to critically evaluate the growth, nutritional and neurodevelopmental outcome of infants at risk for intestinal failure in our center. Our goal is to develop a multidisciplinary study group to perform clinical and basic science research and establish "best practice" guidelines for our center and also benchmark the outcome of these vulnerable infants to compare to similar academic centers. **Figure 5**

Figure 1: Infant with Necrotizing Enterocolitis

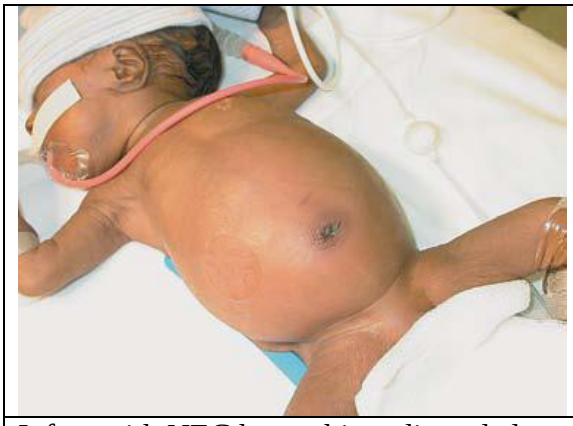	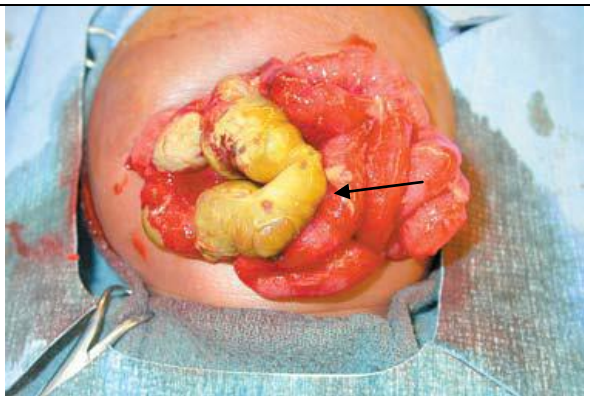
Infant with NEC has a shiny, distended abdomen with periumbilical erythema. (Photograph courtesy of Dr. David Kays Department of Pediatric Surgery, Univ of Florida	The arrow points to an area of necrotic bowel in a patient with necrotizing enterocolitis. (Photograph courtesy of Dr. David Kays Department of Pediatric Surgery, Univ of Florida

Figure 2: Neurodevelopmental Outcomes of Neonates with Surgical versus Medical Necrotizing Enterocolitis

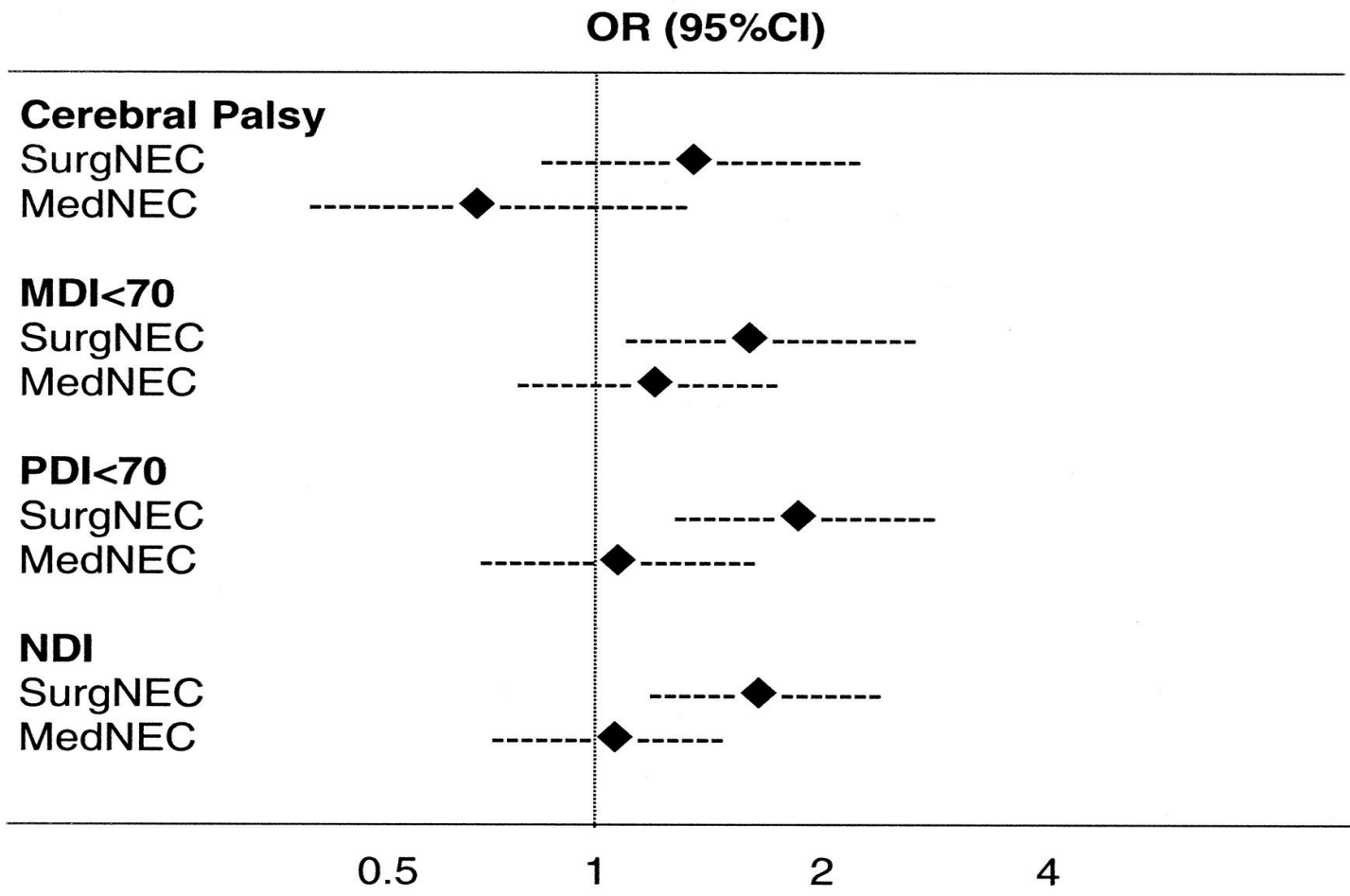

Figure 3: Estimated Time to in-hospital death for infants 401 to 1500 grams birth weight with Surgical Short Bowel Syndrome, Surgical NEC and Medical NEC[10]

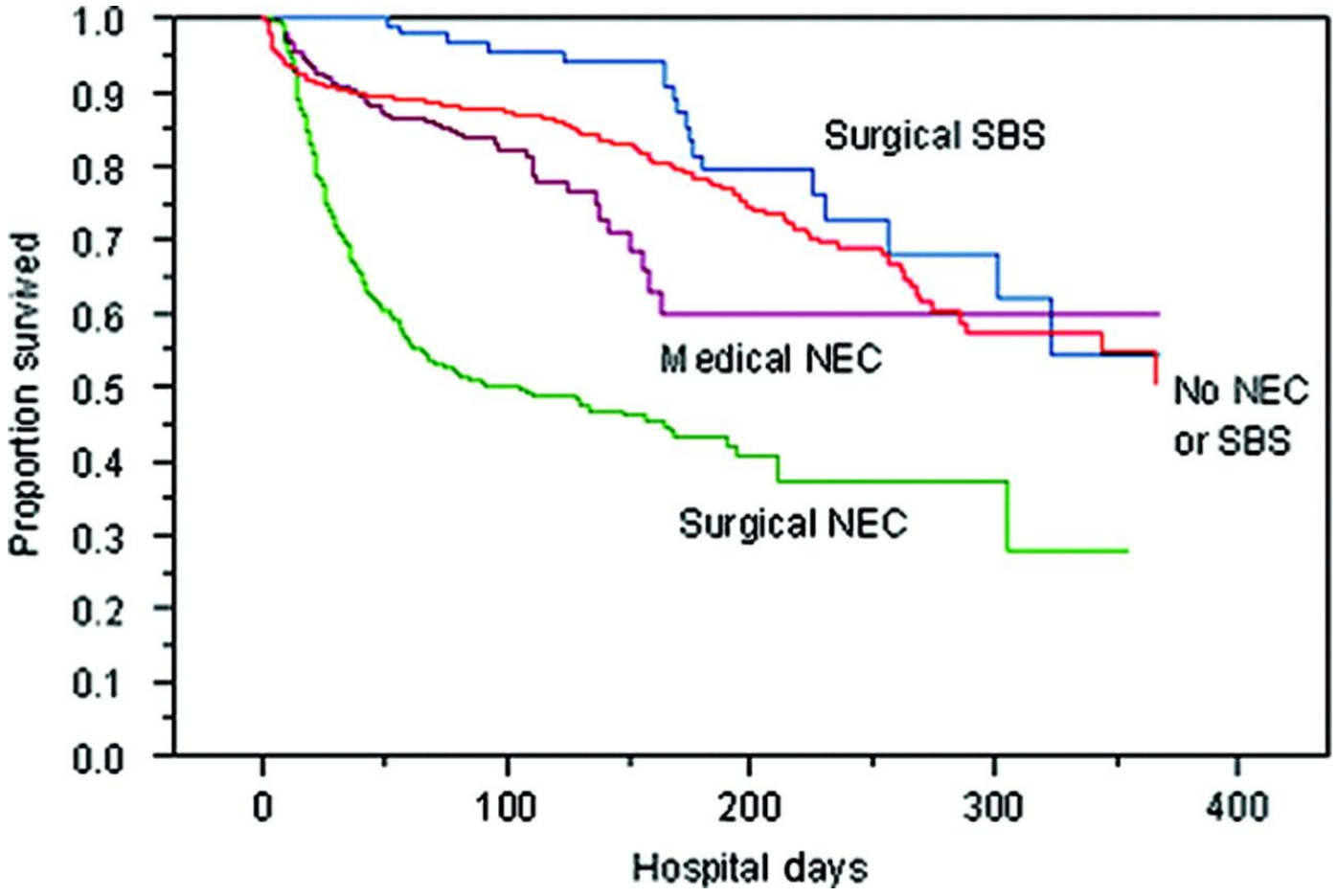

Figure 4: Diagnoses of Patients with Intestinal Failure

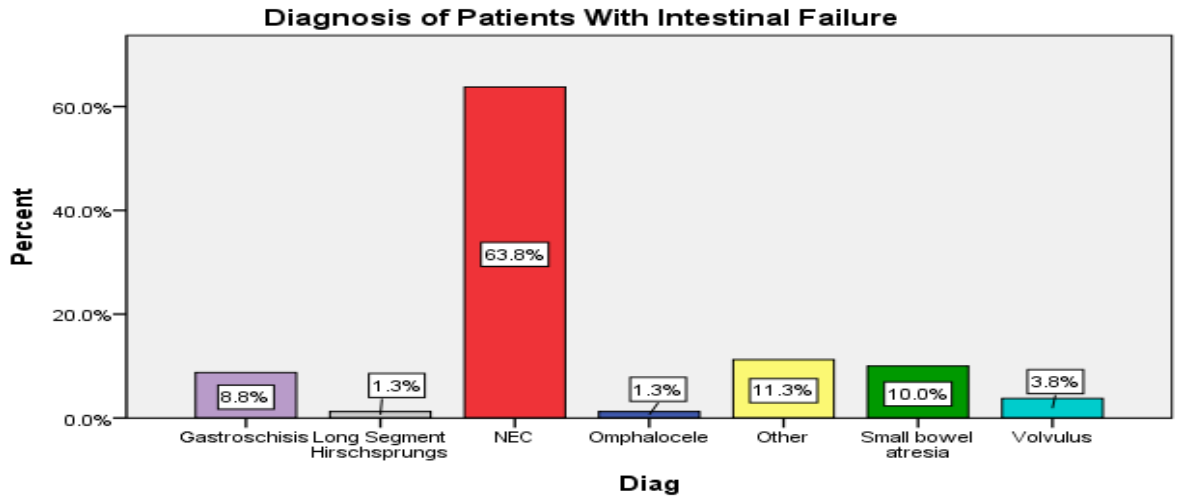

Figure 5: Nutrition, Neurodevelopment and Neuroimaging +

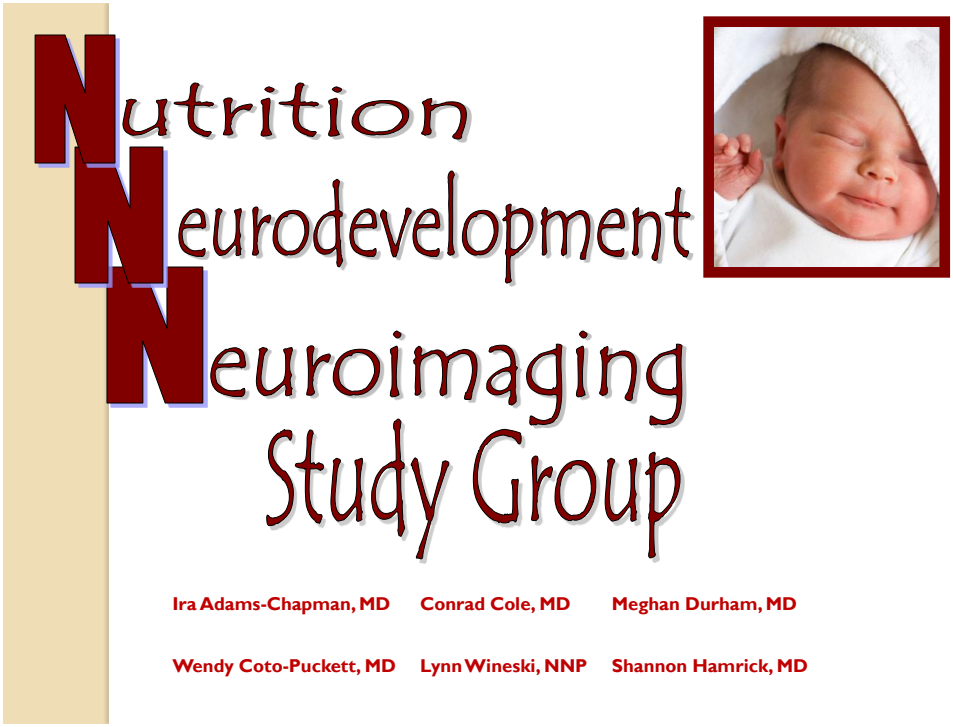

Table 1. Modified Bell's staging for NEC. (Adapted from Kleigman *et al.*)

Review of Bell's stages	***Clinical findings***	***Radiographic findings***	***Gastrointestinal findings***
Stage I	Apnea and bradycardia, temperature instability	Normal gas pattern or mild ileus	Gastric residuals, occult blood in stool, mild abdominal distention
Stage II A	Apnea and bradycardia, temperature instability	Ileus gas pattern with one or more dilated loops and focal pneumatosis	Grossly bloody stools, prominent abdominal distention, absent bowel sounds
Stage II B	Thrombocytopenia and mild metabolic acidosis	Widespread pneumatosis, ascites, portal-venous gas	Abdominal wall edema with palpable loops and tenderness
Stage III A	Mixed acidosis, oliguria, hypotension, coagulopathy	Prominent bowel loops, worsening ascites, no free air	Worsening wall edema, erythema and induration
Stage III B	Shock, deterioration in laboratory values and vital signs	Pneumoperitoneum	Perforated bowel

Table 2: Population Characteristics

	N = 80
Birth Weight	**1490 ± 880 grams**
Gestational Age	**30.3 ± 4.6 weeks**
Male	**48 (60%)**
Black	**40 (50%)**
White	**20 (25%)**
Hispanic	**9 (11%)**
Other	**11 (14%)**
Transplant	**4 (5%)**
Death	**18 (22.5%)**

Table 3: Comparison of Gestational Age and Birth weight by Enteral Autonomy Status

Test Statistic: T-Test
Interpretation: Mean birth weight and gestational age were not significantly different for those who achieved EA and those who did not.

Group Statistics

	EntAut	N	Mean	Std. Deviation	Std. Error Mean
Gestation	0	18	30.850	4.8458	1.1422
	1	62	30.127	4.6173	.5864
BWeight	0	18	1.44244	.868487	.204704
	1	62	1.49789	.890175	.113052

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gestation	Equal variances assumed	.156	.694	.578	78	.565	.7226	1.2498	-1.7656	3.2108
	Equal variances not assumed			.563	26.628	.578	.7226	1.2839	-1.9135	3.3586
BWeight	Equal variances assumed	.027	.871	-.234	78	.816	-.055443	.237082	-.527436	.416551

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gestation	Equal variances assumed	.156	.694	.578	78	.565	.7226	1.2498	-1.7656	3.2108
	Equal variances not assumed			.563	26.628	.578	.7226	1.2839	-1.9135	3.3586
BWeight	Equal variances assumed	.027	.871	-.234	78	.816	-.055443	.237082	-.527436	.416551
	Equal variances not assumed			-.237	28.220	.814	-.055443	.233848	-.534290	.423404

Table 4: Comparison of Peak Laboratory Values and Enteral Autonomy in Infants with Intestinal Failure

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PDbili	Equal variances assumed	.002	.961	1.466	78	.147	2.4915771	1.7000335	-.8929296	5.876083
	Equal variances not assumed			1.517	29.139	.140	2.4915771	1.6422002	-.8664046	5.849558
PAST	Equal variances assumed	7.237	.009	2.368	78	.020	174.319	73.627	27.740	320.89
	Equal variances not assumed			1.987	22.445	.059	174.319	87.716	-7.384	356.02
PALT	Equal variances assumed	.374	.542	.059	78	.953	2.991	50.429	-97.405	103.38
	Equal variances not assumed			.064	31.568	.949	2.991	46.423	-91.620	97.60

Table 5: ANOVA Comparing Peak Laboratory Values and Enteral Autonomy in Infants with Intestinal Failure

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
PDbili	Between Groups	86.601	1	86.601	2.148	.147
	Within Groups	3144.733	78	40.317		
	Total	3231.334	79			
PAST	Between Groups	423900.220	1	423900.220	5.606	.020
	Within Groups	5898468.530	78	75621.391		
	Total	6322368.750	79			
PALT	Between Groups	124.801	1	124.801	.004	.953
	Within Groups	2767124.686	78	35475.958		
	Total	2767249.488	79			

Table 6: Relationship Between Death and Peak Laboratory Values

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
PDbili	Between Groups	209.478	1	209.478	5.407	.023
	Within Groups	3021.856	78	38.742		
	Total	3231.334	79			
PAST	Between Groups	846191.976	1	846191.976	12.053	.001
	Within Groups	5476176.774	78	70207.395		
	Total	6322368.750	79			
PALT	Between Groups	75420.199	1	75420.199	2.185	.143
	Within Groups	2691829.289	78	34510.632		
	Total	2767249.488	79			

Table 7: Correlation Between Death and Achieving Enteral Autonomy in Infants with Intestinal Failure

Correlations

		EntAut	Death
EntAut	Pearson Correlation	1	-.713**
	Sig. (2-tailed)		.000
	N	80	80
Death	Pearson Correlation	-.713**	1
	Sig. (2-tailed)	.000	
	N	80	80

**. Correlation is significant at the 0.01 level (2-tailed).

Table 8: Binary Logistic Regression Model

Dependent Variable Death
BW * Days IL * Days HAL * Peak Dbili * Peak AST

Interpreation: Only Peak AST was independently associated with death.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	BWeight	-.363	1.318	.076	1	.783	.695
	DaysofIL	-.062	.037	2.758	1	.097	.940
	DaysofHAL	.059	.037	2.506	1	.113	1.061
	PDbili	.028	.111	.062	1	.803	1.028
	PAST	.005	.003	4.068	1	.044	1.005
	Constant	-5.178	2.778	3.474	1	.062	.006

a. Variable(s) entered on step 1: BWeight, DaysofIL, DaysofHAL, PDbili, PAST.

Table 9: Linear Regression Model
Dependent Variable – EA * Days HAL * IL

Interpretation: Days of HAL and Days of IL exposure were independently associated with diagnosis of EA as you would expect based on the definition of EA

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.849[a]	.721	.710	.19941

a. Predictors: (Constant), DaysofHAL, DaysofIL

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5.446	2	2.723	68.483	.000[a]
	Residual	2.107	53	.040		
	Total	7.554	55			

a. Predictors: (Constant), DaysofHAL, DaysofIL

b. Dependent Variable: entaut365

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.182	.042		28.277	.000
	DaysofIL	-.002	.002	-1.125	-.856	.396
	DaysofHAL	.001	.002	.276	.210	.834

a. Dependent Variable: entaut365

Table 10: **Linear Regression Model**

Dependent Variable Death * Days IL * Days HAL

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.227[a]	.052	.016	.225

a. Predictors: (Constant), DaysofHAL, DaysofIL

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.147	2	.073	1.443	.245[a]
	Residual	2.693	53	.051		
	Total	2.839	55			

a. Predictors: (Constant), DaysofHAL, DaysofIL

b. Dependent Variable: Death

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.036	.047		.756	.453
	DaysofIL	-.005	.003	-4.106	-1.695	.096
	DaysofHAL	.005	.003	4.085	1.687	.098

a. Dependent Variable: Death

Appendix A: Nutritional Outcomes Data Variables

PIFConID

PN

PN60

BrithYr

DEntry

IntTrans

DInTrans

Death

DDeath

DAlive

Gender

DOB

Latino

R_White

R_Asian

R_Haw

R_Black

R_AmIn

R_Unk

R_Other

R_Specify

Gestation

BWeight

BLength

Diag

DiagSpec

Atresia

Timefrom1stSurgtoRean

MultipleRean

DateOffTPN

DateOffIL

PIFConID_A

EntAut

Age

EntAutDate

LipidVol

PDbili

PAST

PALT

PGGT

PPT

DaystoEntAut

DaysofIL

DaysofHAL

entaut365

entaut183

Appendix B: Neonatal and Neurodevelopmental Outcome Data Variables

Patient Variables

Name

DOB

Gender (Male/Female/Ambiguous)

Race

Gestational Age

Birthweight

Birth hospital

Discharge Hospital

Mode of delivery (Vaginal/C-section/Assisted)

Apgar Scores (1 minute and 5 minutes)

Pregnancy complications

- Premature
- Pregnancy Induced Hypertension
- Abruption
- Chorioamnionitis
- Maternal Condition – other
- Fetal Distress

Neonatal Complications

- Respiratory Distress Syndrome
- Chronic Lung Disease
- Patent Ductus Arteriosus (Indomethacin/Ibuprofen/Surgical Ligation)
- CNS Imaging (None/Cranial Ultrasound/MRI/CT Scan)
- Intraventricular hemorrhage (None/Grade 1/Grade 2/Grade 3/Grade 4) (unilat/bilat)
- Periventricular Leukomalacia (Yes/No)
- Hearing Status at discharge
  - Normal/Referred/Abnormal
- Retinopathy of Prematurity
  - Unilateral or Bilateral
  - Highest Stage in either eye
  - Laser surgery required
- Early Onset Sepsis (within first 3 days)
  - If yes, pathogen type

E. coli

Group B Strep

Enterococcus

Staph species

Klebsiella

Candida species

Late Onset Sepsis (after first 3 days) – may have multiple infections and each needs separate entry

If yes, pathogen type

E. coli

Group B Strep

Enterococcus

Staph species

Klebsiella

Candida species

Serratia species

Pseudomonas species

If yes, was this a catheter associated infection?

Pneumonia

Pulmonary Hemorrhage

Pneumothorax

Necrotizing Enterocolitis

If yes, Bell Stage (Stage 1/Stage 2/Stage 3)

Surgical Procedure Performed

Laparotomy

Ileostomy

Jejunostomy

Mucous fistula

Hartmann's Pouch

Resection with end-to-end anastomosis

Penrose Drain

Primary Surgeon

Remaining bowel length

Peritoneal cultures

Not performed

Negative

Positive (If so, pathogen type)

Surgical Complications

Wound dehiscence

Cholestasis

If yes, peak direct bilirubin

Neurodevelopmental Outcome Variables (data recorded at each visit)

Chronological Age

Adjusted Age

Weight

Length

Head Circumference

Assessment Tool Used

Alberta Infant Motor Scale (AIMS)

Raw Score for AIMS

Percentile Score (for AIMS)

Normal/Suspect/Abnormal

Bayley Scales of Infant Development –III

Cognitive Raw Score

Language Raw Score

Motor Raw Score

Normal/Suspect/Abnormal

Neurological Exam

Normal/Suspect/Abnormal – if suspect or abnormal:

Hypertonia

Hypotonia

Ataxia

Cerebral Palsy

GMFC Score

Blindness

Deafness (if yes, type of augmentation)

Autism?? screen done at 18 month visit

Behavior Problems

Language Delay

Developmental Therapies (Recommended/Receiving)

Physical Therapy

Speech Therapy

Occupational Therapy

Feeding Therapy

Special Needs Preschool Services

Nutritional Status

At Discharge

At Each Follow-Up Visit

Parenteral Nutrition (include percentage of total nutrition)

Tube fed (NG/Gastrostomy tube)

FTT

Nutritional supplements (If yes, which type)

SES Information

Primary caregiver (mother/father/both/grandparent/foster care/hospitalized)

Highest educational level completed by primary careprovider

Average household income in past year

Appendix C: IRB – Children's Healthcare of Atlanta

Short bowel syndrome and intestinal failure in children:

A contemporary review

Principal Investigator: Ira Adams-Chapman MD

Division of Neonatology

Department of Pediatrics

Emory University School of Medicine

Co-Investigators

Wendy Coto-Puckett MD

Department of Pediatrics

Division of Neonatology

Emory University School of Medicine

Megan Durham MD

Division of Pediatric Surgery

Department of Pediatrics

Emory University School of Medicine

Sub-Investigator

Yvonn Sarson

Department of Pharmacy and Nutrition, Egleston

Children's Healthcare of Atlanta

Study Coordinator

Kerrie Fields, MBA, BSN, RN

Senior Research Nurse

Clinical Research Department, Egleston

Children's Healthcare of Atlanta

Background:

The current medical literature is insufficient to determine factors that predict outcome in patients with intestinal failure(IF) and short bowel syndrome (SBS) as too few patients are seen at any one center in a short enough time that medical, nutritional, surgical, and transplant options are similar. The four largest studies are retrospective, single site studies that covered periods of 12, 18, 25, and 26 years and identified 30, 87, 78, and 102 patients, respectively[1-4]. Our recent evaluation of prospectively collected data by a multicenter neonatal consortium revealed that the incidence of surgical SBS in infants with birth weight between 401-1500 g was 7/1,000 [5]. A major obstacle to understanding outcomes is that there are no comprehensive, multi-center studies, nor large prospective studies in the field of pediatric IF/SBS. Hence, a consortium, comprised of pediatric centers with an established interest in IF/SBS should be initiated.

This study will allow us to participate in a multicenter retrospective study which is necessary to plan and collect data for a multicenter collaborative prospective study. It will also allow us to assess the clinical outcomes of the patients and develop testable hypothesis.

Hypotheses or questions: This is a retrospective study that we allow us to build on the following hypothesis generated from a review of the literature.

We hypothesize that:

a. The frequency of blood stream infections is associated with mortality or need for intestinal transplant.

b. Development of cholestasis in children with IF/SBS will be directly related to the amount of intravenous lipid that the infant receives.

c. Prolonged dependence on parenteral nutrition (more that 360 days) is associated with identifiable risk factors including lower birth weight, shorter length of residual small intestine, longer time without intestinal continuity, and absence of the ileocecal valve.

d. Variability exists among centers with respect to several important practice patterns in IF management and patient monitoring.

Specific Aims: To perform a retrospective review of the contemporary management and outcome of infants and children with IF and SBS at our institution and make this data available among the collaborative sites (see list of collaborative sites in appendix) to identify risk factors for long-term parenteral nutrition, cholestasis, intestinal transplant, and death with the ultimate goal to design a prospective study.

Summary of Procedures

Study Design:

A retrospective chart review of a cohort of infants and children with IF/SBS managed at Children's Healthcare of Atlanta at Egleston and Scottish Rite. Patients will be identified by reviewing the medical charts of patient with neonatal surgery. Information will be retrieved from the charts on patient demographic, clinical, and nutritional risk factors that will predict the following critical outcomes: (1) need for long-term PN (> 360 days), (2) discontinuation of PN, (3) development of cholestasis, (4) need for intestinal transplant, and (5) death. We will use the data collected and the experiences gained from the retrospective study to determine the feasibility of a consortium to conduct a multi-centered, prospective study of children with IF and to conduct randomized, controlled therapeutic trials. If successful, these data will be utilized for a future UO1 application.

a) Participant Inclusion criteria:

Infants who are < 12 months of age and have received PN for at least 60 days as a consequence of IF/SBS will be included in this study. For specific aim #1 we will recruit patients who are diagnosed between January 1, 2002 through December 30, 2006.

b) Participant exclusion criteria*:*

Children >12 months of age before they received a full 60 days of PN will be excluded.

c) Enrollment criteria and definitions

Patients will be selected by a retrospective review of medical records. Investigators will identify those children who were on PN for at least 60 days between January 1, 2002 and December 31, 2006. Demographic, clinical, biochemical, and outcome data will be collected at each site in a de-identified fashion. Data collected through December 31, 2008 will allow for at least a two year follow-up for all children. Included patients will have required PN on a continuous basis for the first 60 days after the onset of the diagnosis of IF. Interruptions of PN are permitted due to surgical procedures, loss of central access, or infections. If the cumulative number of days PN is interrupted is not greater than 14, then the patient will be included in the study. Hence, patients who received at least 60 days of PN over no more than a 74 day period ending on or before their first birthday are to be enrolled If the patient has established enteral autonomy for more than 14 days, but then loses tolerance, then the 60 day period restarts when PN is reinstituted.

All identifiable patients who meet entry criteria will be included in the study. Eligible patients may have a varied management course. Examples of potential differences among the patients include: (1) initial diagnosis, surgery, PN management, and follow-up, (2) initial surgery, follow up surgery and all subsequent medical and surgical management might not have occurred at Egleston or Emory Children's Center and Scottish Rite or the Children's Center for Digestive Health.

Confidentiality:

Patient confidentiality will be maintained at all times. Only healthcare professionals working within the Department of Pharmacy and Clinical Nutrition, and research Department of CHOA and the Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Emory University School of Medicine will be collecting this data. All qualifying patients will be assigned a unique study number. This study number rather than patient names will be on the case report form and database. Names and other facts that might identify patients will not appear when we present this data, establish new protocols, or publish its results.

Data Collection

See case report forms attached

Risks

This study poses no known additional physical risks directly to the patient.

There is minimal risk which may be related to a breach of confidentiality since this involves the analysis of existing data.

In order to protect the personal health information of patients, all data collected will be entered into a password protected access database located on the network drive of the Division of Pediatric Gastroenterology. Only personnel identified in this proposal will have access to the database. The hard copies of the case report forms will be stored in file cabinets within the PIs office in the Department of Pediatrics. These file cabinets have locks and the keys are kept by the study coordinators.

All qualifying patients will be assigned a unique study number. This study number rather than patient names will be on the case report form and database. Names and other facts that might identify patients will not appear when we present this data, establish new protocols, or publish its results.

Potential benefits

The patient's whose data will be analyzed will have no direct benefits from this study. However, knowledge gained from this stud will have a potential impact on the management of children on home parenteral nutrition.

Informed consent process

Written informed consent will not be sought or documented from these patients because:

1. The research involves no more than minimal risk to the subjects. This is a retrospective analysis of already existing data. There will no be any direct patient contact involved.
2. The waiver or alteration does not adversely affect the rights and welfare of the patient
3. The research process cannot be practically carried out without the waiver of the written informed consent, assent or permission requirements. This is a retrospective study and it would be very difficult to contact all of the patients who were on home TPN during the stated study period. Addresses and phone numbers of the families might have changed and current contact information would not be available. If a large proportion of former patients are missing then the analysis would be biased and the results would be difficult to interpret.
4. Whenever appropriate, the subjects will be provided with additional pertinent information

Data Analysis:

The first major aim is to determine the feasibility of a future, prospective study. To provide information, we will examine frequencies of missing data, across the entire cohort and within our site. Percentages of missing data and reasons for missing will be computed for each variable.

The retrospectively collected data will be used to perform a sample size calculation to determine whether the sample size is adequate and the amount of data available is appropriate to answer the question(s) with adequate statistical power (e.g., 80%) for the prospective multicenter study. To examine whether length of parenteral nutrition is associated with various risk factors, we will initially examine the association of the dichotomous outcome (1 year or less vs. more than 1 year of parenteral nutrition) with potential risk factors using chi-square or exact tests of association for categorical (e.g., sex, presence/absence of ileocecal valve) data, or tests of trend for ordinal risk factors (e.g., length of residual small intestine), or tests for differences in distribution (t-test or Wilcoxon rank sum test) for continuous variables (e.g., birth weight). Should death or transplantation occur prior to 1 year of parenteral nutrition, such patients will be included in the category of longer parenteral nutrition, thus functionally creating a composite endpoint.

With variable follow-up and censored data likely for some critical outcomes the main analytical method will be survival analysis. Because de-identification will preclude obtaining exact dates for certain data elements, we will utilize discrete time versions of survival analytical techniques. We could instead actually collect the time to various events rather than dates, protecting confidentiality, but the burden on the data collector would be increased substantially. Estimates of time to each event (death, intestinal transplant, intestinal failure, cholestasis) will be estimated for the entire cohort and separately for subgroups defined by length of parenteral nutrition (no more than 1 year vs. more than 1 year), number of BSI, the amount of daily intravenous lipid received, and whether or not an intestinal lengthening procedure was performed.

We recognize that the numerous analyses proposed will increase the experiment-wide error rate, but inasmuch as these will be exploratory analyses to help guide a future, prospective study in which more precisely defined hypotheses will be tested, we will not account for the multiple comparisons.

References

1. Andorsky DJ, Lund DP, Lillehei CW, Jaksic T, Dicanzio J, Richardson DS, Collier SB, Lo C, Duggan C. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001;139:27-33.

2. Goulet OJ, Revillon Y, Jan D, De Potter S, Maurage C, Lortat-Jacob S, Martelli H, Nihoul-Fekete C, Ricour C. Neonatal short bowel syndrome. J Pediatr 1991;119:18-23.

3. Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N, Vargas JH. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr 2004;145:157-63.

4. Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, Kuzma-O'Reilly B, Teitelbaum DH. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg 2005;242:403-9; discussion 409-12.

5. Cole CR, Hansen NI, Higgins RD, Ziegler TR, Stoll BJ, for the Eunice Kennedy Shriver NNRN. Very Low Birth Weight Preterm Infants With Surgical Short Bowel Syndrome: Incidence, Morbidity and Mortality, and Growth Outcomes at 18 to 22 Months. Pediatrics 2008;122:e573-582.

EMORY
UNIVERSITY

10: IRB00047422

Date: Thursday, April 21, 2011 4:05:27 PM

Study Identification Information

1.0 * Enter the Full title of the study (include any version dates from the sponsor)

Nutrition and Neurodevelopmental Outcomes of Children with Surgical Short Bowel Syndrome at a Regional Center

2.0 * Enter a SHORT identifying title for tracking purposes:

Nutrition and NO Outcome and SBS

3.0 What is the estimated start date of this study:

01-Mar-11

4.0 What is the estimated completion date of this study:

31-Mar-12

5.0 * Enter the name of the Principal Investigator (There can only be ONE Principal Investigator and the Principal Investigator must have an Emory affiliation):

Ira Adams-Chapman DeptNeonatology

6.0 Enter the name of Emory Co-Investigators: (this includes Emory personnel and non-Emory persons with a sponsored account)

Last	First	Dept
Coto-Puckett	Wendy	RTP
Swan	Deanne	Behavioral Science
Wineski	Lynn	Neonatolog

7.0 Enter the name of Emory Study Coordinators: (this includes Emory personnel and non-Emory persons with a sponsored account)

Last	First	Dept
There are no items to display		

8.0 Enter the names of other Emory Study Staff (other than PI, Co-I's and Coordinator's): (this includes Emory personnel and non-Emory persons with a sponsored account)

Last	First	Dept	Type
There are no items to display			

9.0 **Enter information on Non-Emory Study Staff:** (this is for non-Emory personnel who will not be logging into eIRB)

Name	Affiliation	Type
[View] Conrad Cole	Research collaborator	Collaborator

10: IRB00047422

Required Reviews

*All Studies **MUST** have the approval of the Department Chair **OR**Faculty Advisor, which ever one is applicable. eIRB auto populates the Department Approver based on the Principal Investigator's affiliation. If the listed Dept is not responsible for overseeing your research study then please remove it. Having additional Dept Approvers listed or incorrect Dept Approvers listed will cause delays in the review of the study.*

1.0 **DepartmenUdivision Approvals Required - this is determined by the primary department for the PI according to HR. Add any additional DepUDiv approvals that may apply to the PI:**

Department Name
Pediatrics - Main

2.0 * **Are you are a Student Researcher at Emory College, School of Public Health, School of Law, School of Nursing, Business School, Graduate School or School of Theology?**

'" r**Yes** r. **No**

If yes, add your Faculty Advisor:

You must remove the department/division approval in 1.0 if yOU have chosen facultv advisor C1Pproval for this study.

3.0 *If a committee is listed, you must apply to each of the listed committees using their current and separate application process.*

10
There are no items to display

4.0 * **Will there be any professional or technical charges for drugs, devices, items, services, or procedures during the course of this study that may be billed to study accounts or third party payors?**

* r**Yes** r. **No**

10: IRB00047422

Study Sites

- A site is where recruitment will occur
- A site is where the research will take place

- A site is data collection will take place
- A site is where data analysis will take place
- A site is where data will be stored

1.0 * Indicate all locations where the Emory Investigator will conduct this study:

Emory Children's Center
Hughes Spalding Children's Hospital
Children's Healthcare of Atlanta (CHOA)

2.0 If "Other - ", list all other locations where the Emory Investigator will conduct the study:

Name of the Site	IRS of record for this site
There are no items to display	

ID: IRS00047422

Funding

1.0 * Choose the funding status of this study:

There are no plans to pursue funding for this study

2.0 For each sponsor providing funding for this study:

Sponsor	Type	Grant	OSP UPN
There are no items to display			

ID: IRS00047422

Research Design

1.0'# Enter or Upload a Lay Summary. This should be a non-scientific summary of the research.

Name	Modified	Version
Lay SummarLIRS_NND.doc	*2/7/2011* 5:20 PM	0.01

2.0'# Upload scientific protocol documentation:

Name	Modified	Version
Methods IRS NND.doc	*2/9/2011* 3:06 PM	0.01

NNOJRB_Submission[1j with abstract.doc *2/24/2011* 9:38 AM 0.01

10: IRB00047422

Type of Research

Research is defined by the regulations as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge".

Human subjects are defined by the regulations as "living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Federal requirements to protect human subjects apply to a much broader range of research than many investigators realize, including reserach that uses human specimens (such as cells, blood and urine), residual diagnostic specimens and medical information.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

Answer the following questions to help determine the type of research being conducted (Social or Biomedical):

1.0 '* Does this study involve any type of medical or physiological interventions with human subjects? See above for definitions of "Human Subjects" and "Intervention"

○ Yes ◉ **No**

2.0'* Is this a biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices)?

C Yes (i **No**

3.0 '* Is this secondary data analysis of existing data, no interaction, no observation? ("No Subjects" study) See above for definition of "Human Subjects" and "Interaction"

Ie **Yes** **No**

10: IRB00047422

Social, Humanist and Behavioral Research

Social! Humanist! Behavioral Research involves observational and survey research, work with population and/or epidemiological studies. This type of research does not involve any drugs or devices (investigational or marketed).

Psycho physiological testing - measurement of physiological bases of psychological processes

Psychometric testing - measurement of "psychological aspects" such as knowledge, skills, abilities or personality

Deception - the subject, at the time of the data collection, is not fully informed of the nature and purpose of the research in which they are involved so as to prevent potentially biased reporting of data/information.

1.0'* Check all below that apply:

Psychometric testing
Chart Review

If other, please describe:

2.0 Upload any surveys, Questionnaires or any other Research Instruments:

Name	Modmed	Version
There are no items to display		

3.0 !* Does the research design require subjects to be deceived?

Yes {i **No**

If yes, describe and justify:

4.0 " Will the subjects be exposed to any stress?

Yes (e' **No**

If yes, describe and justify:

5.0 Select any Keywords that describe your study:

Behavioral/Social
Brain Damage
Digestive Disease and Disorders
Gastrointestinal Disorders
Liver Diseases
Neonatal
Nutrition/Dietics
Pediatrics
Psychology, Developmental
Psychometrics

10: IRB00047422

HIPAA Determination

The "RWHSC" is comprised of the School of Medicine (SaM), School of Nursing (SON), School of Public Health (SPH), Yerkes Primate Center (YPC), Student Health Services (SHS), Psychological Center (PC), University Counseling Center (UCC), and the Oxford Col/ege Student Health & Counseling Center.

For a list of PHI identifiers, go to
http://www.irb.emory.edu/researchers/formstools/docs/otherIphi_identifiers.pdf

1.0 * Will you be receiving or disclosing any information about a person's health, healthcare or payment for healthcare that has any associated identifiers?

e Yes r. No

2.0 * Is there any person on the study (Study Staff) that is part of the "RWHSC Covered Entity"?

(i Yes C No

3.0 * Will any protected health information (PHI) be provided by any component of the "RWHSC Covered Entity"?

Ie Yes r No

10: IRB00047422

Protected Health Information (PHI)

1.0 * What are your sources of PHI? (Choose all that apply)

Physician
records
Hospital records
Clinical records
Laboratory
results
Pathology results
Radiology results
Other - please describe
below

If other, please describe:

Developmental Testing Data will be used for this

study

If using data previously collected, enter the last date of collection:
30-Dec-10

2.0 * You will require access to PHI for the following reasons: (Choose all that apply)

The identification of eligible subjects: Ie Yes C No

The conduct of the study: r. Yes r No

3.0 Do you need access to the entire medical record and/or health information database for recruitment?
r. Yes r No

If not, list portions of the medical record and/or health information database for which you will require access for recruitment:

4.0 Do you need access to the entire medical record and/or health information database for conduct of the study?
(. Yes r No

If not, list portions of the medical record and/or health information database for which you will require access for conduct of the study:

5.0 * It is assumed that all personnel currently associated to this study will request and/or use the collected PHI. Do you plan to use any other persons to request or collect the PHI?

r Yes(i No .!f.yes, be sure to uQdate the PERSONNEL section of this aQ.Qlication!

Have all persons associated with this study completed Emory's approved CITI training course?
r. Yes r No

6.0 * PHI will be shared with the IRB. Please identify any other person or group with whom the PHI will be shared or disclosed:

IRB other than the Emory IRB

If Other - please describe:

Children's Healthcare of Atlanta IRB

7.01< Provide the date and/or event by which you will no longer need to use the collected PHI:

Date: 29-Mar-12

Event: Anticipate end of data analysis in March 31, 2012

10: IRB00047422

HIPAA part 1

1.0'* Will you be using data with the following HIPAA identifiers? (Choose all that apply)

Name or initials
All elements of dates such as DOB, admission date, etc. (except year)
Medical records numbers

2.0'1< Check the HIPAA Authorization Type you will be utilizing:

Not Applicable

3.0 * Check the type of HIPAA Waiver you are requesting:

Complete HIPAA waiver for the entire study

10: IRB00047422

HIPAA part 2

1.0'" Describe why the research cannot be practicably conducted without authorized access to PHI?

The study is a retrospective chart review. Patients are identified as eligible for inclusion based on name and medical record number. Specific demographic variables including birth weight, gestational age, age at time of surgery, age at time of various time points for data collection, will be critical to this analysis because they infleunce the risk of developing certain outcomes and the data will need to be adjusted for these variables.

2.0'* Describe how the privacy of the PHI will be protected:

Each patient will be assigned a unique identifier instead of using PHI. A secure Access database will be utilized that is password protected. Only members of the study will be able to view the research database. No PHI will be reported. Data will be published as aggregate data without specific reference to any individual patient or their PHI. All PHI will be supressed in the database and data elements will be only be identified by study number.

3.0 * The investigator believes the use or disclosure of the PHI for this study represents no more than a minimal risk to the privacy of the subject because:

Identifiers are protected against improper use or disclosure by the following means: (Choose all that apply)

Information will not be disclosed unless it is scrubbed of all identifiers

Only coded data will be disclosed, and agreement is in place where only Covered Entity will have coding list.

Identifiers will be destroyed upon completion of: (Choose all that apply)

Data analysis

If other, please describe:

4.0 If identifiers will NOT be destroyed, then explain why they must be retained (e.g., longitudinal study; specific federal requirements, etc ...)

ID: IRB00047422

Miscellaneous Documents

The Lay Summary should be uploaded in the Research Design section

All Protocol and Scientific documents should be uploaded on the Research Design section

All Funding documents should be uploaded in the Funding section

All Consents, Assents, and HIPAA documents should be uploaded in the Consent/Assent section

All Clinical Investigator's Brochure for Devices should be uploaded in the Device section

All Clinical Investigator's Brochure for Drugs should be uploaded in the Drug section

All Social Surveys, Questionnaires and other Research Instruments should be uploaded in the Social section

All Recruitment and Advertisement documents and files should be uploaded in the Recruitment section

You may navigate to any of the above listed pages by using the .. ..Lump To" drop down at the top and bottom of this page.

1.0 Upload any addtional documents including:

- Radiation Summary form (for procedures with human subjects)
- Protocol Summary for Committee I
- Biosafety Notice of Intent form

Name	Modified	Version
There are no items to display		

2.0 Upload CITI Certification for all study staff:

Name	Modified	Version
citi certification_choa_adamschapman.doc	*2/9/2011 3:08* PM	0.01
CITI_Cole_2.9.11 [1].pdf	*2/9/2011 4:01* PM	0.01
CITI_ Collaborative_emory[1]wineski.doc	*2/28/2011 7:48* AM	0.01
CITI_Refresher _ Completion_Report_DSwan [1].pdf	*2/24/2011 8:44* PM	0.01
Coto-Puckett citi training	*11/4/20101:22* PM	0.01

ID: IRB00047422

Conflict of Interest

- **For more information about Emory COI policies, click here.**

1.0 * **Institutional Financial Interest**
Is any licensed Emory intellectual property used in this project?
- *r* Yes Ie **No**

2.0 ," **Investigator Financial Interest**
Do you or any member of your research team (including spouse and dependent children, individually or in aggregate) have any of the following financial relationships with (a) the study sponsor or a direct competitor of this sponsor; (b) a company whose products or services are used or studied in the research; (c) the technology being studied?

" eYes 𝒾 **No**

Check YES if any of the following apply:

- **Payments of $10,000 or more including salary, consulting fees, royalty or licensing payments from intellectual property, honoraria and/or gifts received within the past 12 months or anticipated for the next 12 months (excluding salary and other payments for services from the University)**
- **Equity interest worth $10,000 or more or equity interest greater than 1% of the business entity as determined by reference to its publicly listed price (excluding mutual funds)**
- **Any equity interest if the value cannot be determined by reference to publicly listed prices (e.g., start-up companies)**
- **A position as director, officer, partner, trustee, employee, or any other position of management**
- **Patent rights or royalties from such rights whose value may be affected by the outcome of the research, including royalties under any royalty-sharing agreements involving the University**
- **Any other financial interest whose value may be affected by the outcome of the research**

ID: IRB00047422

FINAL PAGE

You have completed your application!

Please click "Finish" to finalize and exit the application. The application will still be editable until it is submitted by the Principal Investigator. "Finish" will NOT submit the application for review.

Please.note that a submission may only be forwarded for review by the Principal Investigator. To do thili, the Principal Investigator must select "SUBMIT" in the study worksgace.

You can track the ongoing status of your submission by logging into the study workspace.

Please feel free to contact the IRB (irb@emory.edu or 404.712.0720 or http://www.emory.edu/irb) with any questions or concerns.

Things to remember:

- If your study needs Conflict of Interest, Radiation Safety or BioSafety approval, you must apply to those committees separately using the process in place for those com

- mittees. You must also note this on the "Required Reviews" section.
- If your study needs Human Emybronic Stem Cell Committee approval, you must apply to the HESC separately using the process in place for the HESC. You must also note this on the "Required Reviews"

section.

- If your study is to be conducted at the VAMC, you must apply to the VA R&D Committee separately using
  the process in place for the VA R&D Committee.
- If your study is to be conducted at Grady Health Systems, you must apply to the Grady Research Oversight Committee separately using the process in place for the Grady Research Oversight Committee.
- If your study is a Clinical Trial, you must ensure the sponsor has registered this trial at Clinicaltrials.gov and
  you must enter this trial into SiteMinder. For more information on SiteMinder, contact Emory Univeristy's CTa office.

Appendix E: SSP Proposal Form

Acknowledgements:

Conrad Cole, MD, MPH Gastroenterology	Children's Hospital Medical Center Department of Pediatrics Cincinnati, OH
Meghan Durham Pediatric Surgeon	Emory University Department of Pediatrics/Division of Pediatric Surgery Atlanta, GA
Lynn Wineski, NNP Nurse Practioner	Developmental Progress Clinic Emory University School of Medicine Department of Pediatrics/Division of Neonatology Atlanta, GA
Wendy Coto-Puckett, MD Neonatology Fellow	Emory University School of Medicine Department of Pediatrics/Division of Neonatology Atlanta, GA
Yvonne Sarnes Nutritionist	Children's Healthcare of Atlanta Atlanta, GA

Many thanks to the staff of the Developmental Progress Clinic who perform the various components of the medical and developmental assessment. Our administrative support team is instrumental for clinical operations.

Medical Providers	Linda Black, MD Ojuro Osunkoya, MD Gloria Smikle, NP Emory University School of Medicine Atlanta, GA
Physical Therapist	Laura Tarrago, PT Children's Healthcare of Atlanta Rehabilitation Services
Psychologist	Sheena L. Carter, PhD Sobha Fritz, PhD Emory University Department of Pediatrics Atlanta, GA
Developmental Specialist	Maureen Mulligan LaRossa, RN Emory University Department of Pediatrics/Division of Neonatology Atlanta, GA
Jacqueline Walton	DPC Clinic Manager
Vickie Reid	Administrative Assistant

Special thanks to my SSP Committee for your insight and guidance during this process.

Silke von Esenwein, PhD	Committee Chair
DeAnne Swann, PhD	Committee Member and Statistical Support
Theresa Gauthier, MD	Field Advisor
Walter Burnett, PhD	Health Care Outcomes Track Advisor

REFERENCES

1. Hack, M., et al., *Outcomes in young adulthood for very-low-birth-weight infants.* N Engl J Med, 2002. **346**(3): p. 149-57.
2. Hack, M., et al., *Chronic conditions, functional limitations, and special health care needs of school-aged children born with extremely low-birth-weight in the 1990s.* JAMA, 2005. **294**(3): p. 318-25.
3. Synnes, A.R., et al., *School Entry Age Outcomes for Infants with Birth Weight <=800 Grams.* The Journal of pediatrics. **157**(6): p. 989-994.e1.
4. Vohr, B.R., et al., *School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial.* Pediatrics, 2003. **111**(4 Pt 1): p. e340-6.
5. Vohr, B.R., 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**(6): p. 1216-26.
6. Hintz, S.R., et al., *Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era.* Arch Dis Child Fetal Neonatal Ed, 2005. **90**(2): p. F128-33.
7. Shankaran, S., et al., *Outcome of extremely-low-birth-weight infants at highest risk: gestational age < or =24 weeks, birth weight < or =750 g, and 1-minute Apgar < or =3.* Am J Obstet Gynecol, 2004. **191**(4): p. 1084-91.
8. Stoll, B.J., et al., *Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network.* Pediatrics. **126**(3): p. 443-456.
9. Hintz, S.R., et al., *Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis.* Pediatrics, 2005. **115**(3): p. 696-703.
10. Cole, C.R., et al., *Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months.* Pediatrics, 2008. **122**(3): p. e573-82.
11. Schwartz, M.Z. and K. Maeda, *Short bowel syndrome in infants and children.* Pediatr Clin North Am, 1985. **32**(5): p. 1265-79.
12. Lin, P.W., T.R. Nasr, and B.J. Stoll, *Necrotizing enterocolitis: recent scientific advances in pathophysiology and prevention.* Semin Perinatol, 2008. **32**(2): p. 70-82.
13. Hunter, C.J., et al., *Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC).* Pediatr Res, 2008. **63**(2): p. 117-23.
14. Neu, J. and W.A. Walker, *Necrotizing Enterocolitis.* New England Journal of Medicine. **364**(3): p. 255-264.
15. Bell, M.J., et al., *Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging.* Ann Surg, 1978. **187**(1): p. 1-7.
16. Hunter, C.J., N. Chokshi, and H.R. Ford, *Evidence vs experience in the surgical management of necrotizing enterocolitis and focal intestinal perforation.* J Perinatol, 2008. **28 Suppl 1**: p. S14-7.
17. Hunter, C.J., et al., *Evidence vs experience in neonatal practices in necrotizing enterocolitis.* J Perinatol, 2008. **28 Suppl 1**: p. S9-S13.
18. Hintz, S.R., et al., *Neurodevelopmental and Growth Outcomes of Extremely Low Birth Weight Infants After Necrotizing Enterocolitis.* Pediatrics, 2005. **115**(3): p. 696-703.
19. Stoll, B.J., et al., *Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection.* JAMA, 2004. **292**(19): p. 2357-65.

20. Castillo, R.O., et al., *Pediatric Intestinal Transplantation at Packard Children's Hospital/Stanford University Medical Center: Report of a Four-Year Experience.* Transplantation Proceedings. **38**(6): p. 1716-1717.
21. Gura, K.M., et al., *Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management.* Pediatrics, 2006. **118**(1): p. e197-201.
22. de Meijer, V.E., et al., *Parenteral fish oil as monotherapy for patients with parenteral nutrition-associated liver disease.* Pediatr Surg Int, 2009. **25**(1): p. 123-4.
23. Gura, K.M., et al., *Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease.* Pediatrics, 2008. **121**(3): p. e678-86.
24. Bines, J.E., *Intestinal failure: A new era in clinical management.* Journal of Gastroenterology and Hepatology, 2009. **24**: p. S86-S92.
25. Beath, S., et al., *Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation.* Transplantation, 2008. **85**(10): p. 1378-84.
26. Piedra, P.A., D.M. Dryja, and L.J. LaScolea, Jr., *Incidence of catheter-associated gram-negative bacteremia in children with short bowel syndrome.* J Clin Microbiol, 1989. **27**(6): p. 1317-9.
27. Kurkchubasche, A.G., S.D. Smith, and M.I. Rowe, *Catheter sepsis in short-bowel syndrome.* Arch Surg, 1992. **127**(1): p. 21-4; discussion 24-5.
28. Hintz, S.R. and M. O'Shea, *Neuroimaging and neurodevelopmental outcomes in preterm infants.* Semin Perinatol, 2008. **32**(1): p. 11-9.
29. Rezaie, P. and A. Dean, *Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system.* Neuropathology, 2002. **22**(3): p. 106-32.
30. Schulzke, S.M., G.C. Deshpande, and S.K. Patole, *Neurodevelopmental Outcomes of Very Low-Birth-Weight Infants With Necrotizing Enterocolitis: A Systematic Review of Observational Studies.* Arch Pediatr Adolesc Med, 2007. **161**(6): p. 583-590.
31. Inder, T.E., et al., *White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term.* AJNR Am J Neuroradiol, 2003. **24**(5): p. 805-9.
32. Mirmiran, M., et al., *Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants.* Pediatrics, 2004. **114**(4): p. 992-8.
33. Woodward, L.J., et al., *Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants.* N Engl J Med, 2006. **355**(7): p. 685-694.
34. Back, S.A., et al., *Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury.* J Neurosci, 2001. **21**(4): p. 1302-12.
35. Adams-Chapman, I., *Insults to the developing brain and impact on neurodevelopmental outcome.* J Commun Disord, 2009. **42**(4): p. 256-62.
36. Martin, C.R., et al., *Neurodevelopment of Extremely Preterm Infants who had Necrotizing Enterocolitis with or without Late Bacteremia.* The Journal of pediatrics. **157**(5): p. 751-756.e1.
37. Vennarecci, G., et al., *Intestinal Transplantation for Short Gut Syndrome Attributable to Necrotizing Enterocolitis.* Pediatrics, 2000. **105**(2): p. e25-.
38. Fanjiang, G. and R.E. Kleinman, *Nutrition and performance in children.* Curr Opin Clin Nutr Metab Care, 2007. **10**(3): p. 342-7.

39. Walker, S.P., et al., *Early Childhood Stunting Is Associated with Poor Psychological Functioning in Late Adolescence and Effects Are Reduced by Psychosocial Stimulation.* The Journal of Nutrition, 2007. **137**(11): p. 2464-2469.
40. Norenberg, M.D., *The role of astrocytes in hepatic encephalopathy.* Neurochem Pathol, 1987. **6**(1-2): p. 13-33.
41. Tarter, R.E., A.M. Arria, and D.H. Van Thiel, *Hepatic encephalopathy coexistent with alcoholism.* Recent Dev Alcohol, 1991. **9**: p. 205-24.
42. Cowles, R.A., et al., *Reversal of intestinal failureâ€“associated liver disease in infants and children on parenteral nutrition: experience with 93 patients at a referral center for intestinal rehabilitation.* Journal of Pediatric Surgery. **45**(1): p. 84-88.
43. Sigalet, D., et al., *Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease.* Eur J Pediatr Surg, 2009. **19**(6): p. 348-53.
44. Nucci, A., et al., *Interdisciplinary management of pediatric intestinal failure: a 10-year review of rehabilitation and transplantation.* J Gastrointest Surg, 2008. **12**(3): p. 429-35; discussion 435-6.
45. Cole, C.R., et al., *The rate of bloodstream infection is high in infants with short bowel syndrome: relationship with small bowel bacterial overgrowth, enteral feeding, and inflammatory and immune responses.* J Pediatr. **156**(6): p. 941-7, 947 e1.