2022

Splanchnic Oxygenation and Feeding Intolerance in the Very Low Birthweight Infant

Melissa C. Dollings
Virginia Commonwealth University

Splanchnic Oxygenation and Feeding Intolerance in the Very Low Birthweight Infant

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

Melissa C. Dollings
Bachelor of Science, Virginia Commonwealth University, 2004-2005
Master of Science in Nursing, Vanderbilt University, 2008-2009

Director: Lisa F. Brown, Ph.D., RN, School of Nursing

Virginia Commonwealth University
Richmond, VA
April, 2022

Dedication

This dissertation is dedicated to my husband, Gregg, who relentlessly supported, encouraged, and sometimes prodded me while I pursued my educational goals for most of our 18-year marriage. Also deserving of recognition are my daughters, Emma, Taryn, Taylor, Kayla, and Sierra who encouraged and supported their mom even whilst pursuing their own education.

Acknowledgment

Thank you to Dr. Lisa Brown for her tireless support, encouragement, and feedback. Thank you to Dr. Karen Hendricks-Munoz, Dr. Nancy Jallo, and Dr. Leroy Thacker for your support and expertise through this longer than expected process. I would like to acknowledge Sigma Theta Tau International and the Florida Association of Neonatal Nurse Practitioners for providing funding for my project. I extend great appreciation to my colleagues in the NICU who have shown me great support and assisted in my research through data collection and patient care. Above all, thank you to the parents who entrusted their precious babies to me in the pursuit of this research.

Table of Contents

List of Tables

List of Figures

Abstract

SPLANCHNIC OXYGENATION AND FEEDING INTOLERANCE IN THE VERY LOW BIRTHWEIGHT INFANT

By Melissa C. Dollings, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2022

Major Director: Lisa F. Brown, Ph.D., RN, School of Nursing

Background. Feeding intolerance is common in preterm infants but can be an ominous precursor of necrotizing enterocolitis, a life-threatening gastrointestinal disease. The definition and management of feeding intolerance vary widely. This research examined the relationship between feeding intolerance, intrauterine factors, extrauterine factors, and intestinal immaturity and circulatory immaturity in the premature, very low birthweight infant. It also explored the use of splanchnic oxygenation (a marker of intestinal perfusion) as an objective measure of feeding intolerance.

Methods. Near infrared spectroscopy (NIRS) monitoring (sensors that measure oxygenation of the tissues) was placed on 20 premature very low birthweight infants during the first few days of life and again if they developed feeding intolerance (n=6). Fractional tissue oxygen extraction (FTOE) was used as a marker for splanchnic oxygenation rather than splanchnic oxygenation (rSO2) alone as it measures the ability of the tissue to extract oxygen. Variables related to intestinal immaturity, circulatory immaturity, intrauterine factors and extrauterine factors were also collected.

Results. There was a significant difference between FTOE at baseline and FTOE during feeding intolerance. However, the FTOE during feeding intolerance was lower. The significant extrauterine and circulatory immaturity factors were the 10-minute Apgar and the presence of hypotension, respectively.

Conclusions. There was a significant difference in FTOE and feeding intolerance, albeit, in an unexpected direction. This may have been related to gut maturation between baseline and feeding intolerance measurements spanning from 2-4 weeks after birth. Further research with more frequent splanchnic oxygenation measurements may explain this finding.

Key Words: Premature infant, splanchnic oxygenation, fractional tissue oxygen extraction, feeding intolerance, necrotizing enterocolitis

Vita

Melissa Dollings, RN, NNP-BC
Doctoral Candidate
9631 Raven Wing Drive
Chesterfield, VA 23832
804-814-5193 (cell)
dollingsmc@vcu.edu

LICENSURE

1995 – present	Virginia Board of Nursing	RN	#0001141650
2008 – present	Virginia Board of Nursing	NP	#0024168081

EDUCATION

Date	**Institution**	**Degree**
2012 – present	Virginia Commonwealth University Dissertation phase, anticipated completion May 2022	Doctoral Candidate
2008	Vanderbilt University	MSN
2005	Virginia Commonwealth University	BS in Nursing
1995	Riverside School of Professional Nursing	Diploma

PROFESSIONAL EXPERIENCE

Children's Hospital of Richmond, VCU Health System, Neonatal NP 2008 - present
Richmond, VA

Chippenham-Johnston Willis Hospitals, Neonatal NP, Richmond, VA 2015-2017

Children's Hospital of Richmond, VCU Health System, Clinical Coordinator 2007-2008
Richmond, VA

Children's Hospital of Richmond, VCU Health System, Clinical RN III, Transport 2005-2007
Richmond, VA

Children's Hospital of Richmond, VCU Health System, Clinical RN II 2002 - 2005
Richmond, VA

Sentara Hampton General, RN, Team Leader, Intensive Care Unit 1996-2001
Hampton, VA

Sentara Hampton General, Registered Nurse, Medical-Surgical 1995-1996
Hampton, VA

PROFESSIONAL ACTIVITIES

Council of Advanced Practice Providers, Co-Chair, VCU Health System, 2022-present
Institutional Review Board Member Panel A, Member, VCU Health System, 2020-presnt
NICU Shared Leadership Team, member, VCU Health System, 2007- present
Pediatric APP/Resident Collaborative, VCU Health System, 2019 - present
NICU Oral Feeding Team, VCU Health System, 2017- present
NNP student preceptor for University of Virginia, Duke University & Old Dominion University

SPECIAL PROJECTS

Collaborated with interdisciplinary team members to establish unit specific clinical guidelines for blood transfusion, neonatal abstinence syndrome and initiation of bottle/breast feeding in the NICU.

PROFESSIONAL AWARDS AND HONORS

2020 VCU NICU Collaborative Practice Award
2014 Manuscript of Exceptional Merit, Neonatal Network
2008 VCU NICU RN Excellence in Leadership Award
2006 VCU NICU RN Excellence in Practice Award

PROFESSIONAL ORGANIZATIONS

National:

Academy of Neonatal Nursing, 2016-present
Sigma Theta Tau International Honor Society, 2005-2010, 2018-present
National Association of Neonatal Nurses, 2004-present

Regional:

Florida Association of Neonatal Nurse Practitioners, 2018-present
Central Virginia Association of Neonatal Nurses, 2005-present

Hospital Based:

Council of Advanced Practice Providers, Co-Chair, 2022-present
VCU Institutional Review Board Member, Panel A, 2020-present

PUBLICATIONS

Dollings, M. C. & Brown, L. F. (2016). An integrated review of intestinal microbiota in the very premature infant: Environmental factors, necrotizing enterocolitis, and late onset sepsis. *Neonatal Network*, 35 (4), 204-216.

FUNDED RESEARCH

Date: 2020-2022 Splanchnic Oxygenation and Feeding Intolerance in Very Low Birthweight Infants.

M. Dollings, Principal Investigator, Florida Association of Neonatal Nurse Practitioners, $4,560 and Sigma Theta Tau International, $4,560.

PODIUM PRESENTATIONS

Dollings, M. C., Reyna, B., McCafferty, B. (November, 2021). Cue Based Feeding, It's all about the infant! Virtual Podium Presentation. FOCUS…The Pediatric and Neonatal Care Conference, Richmond, VA.

Dollings, M. C. (April, 2019). *Near Infrared spectroscopy for prediction of feeding intolerance in the preterm infant*. Podium Presentation. Pediatric Academic Society, Baltimore, MD.

Dollings, M. C. (October, 2014). *An integrated review of the intestinal microbiota in very premature infants*. Podium Presentation. Florida Association of Neonatal Nurse Practitioners National Conference, Clearwater, FL.

Dollings, M. C. (October, 2013) Necrotizing Enterocolitis: Strategies for Improving Outcomes. Podium Presentation. FOCUS…The Pediatric and Neonatal Care Conference, Richmond, VA.

POSTER PRESENTATIONS

Dollings, M. C. (September, 2017). *A Comparison of splanchnic-cerebral oxygenation rations during various feeding states in one extremely low birth weight infant: A case presentation.* Poster Presentation. Academy of Neonatal Nursing National Conference, Las Vegas, NV.

Dollings, M. C. (October, 2014). *An integrated review of the intestinal microbiota in very premature infants*. Poster Presentation. Florida Association of Neonatal Nurse Practitioners National Conference, Clearwater, FL.

Chapter 1: Statement of the Problem

Necrotizing enterocolitis (NEC) is a life-threatening emergency associated with ulcerative inflammation and necrosis of the intestinal wall. It is usually associated with the administration of enteral (via the gastrointestinal tract) feeds and is rare in infants who have never had an enteral feeding (Muller et al., 2016). The occurrence of NEC varies widely among neonatal centers. Still, it has been reported to be between 7 -11 % of very low birth weight (VLBW) infants (weighing less than 1500 grams at birth), and occurrence is inversely related to gestational age (GA) at birth. Gestational age is the number of weeks since conception. Of those who develop NEC, a 10-50% mortality rate has been reported among VLBW infants. Of the infants who survive, 50% will have long-term gastrointestinal complications (*Necrotizing Enterocolitis | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program*, n.d.). In financial terms, the mean direct cost of caring for infants affected by NEC in the United States is estimated to be between $74,000 and $198,000 depending upon the severity, nearly 40% higher than healthy counterparts (Ganapathy et al., 2012; Mowitz et al., 2018).

Though we have not been able to eradicate NEC, we have learned that its occurrence involves a constellation of factors such as introducing enteral feedings, immature peristalsis, immature immunologic system, and susceptibility to hypoxic-ischemic injury (Sharma & Hudak, 2013). Necrotizing enterocolitis has a high mortality rate. There is a significant increased risk for severe neurodevelopmental delays, long-term feeding tube needs, and post-discharge surgeries for those who survive (Fullerton et al., 2017; Neu & Walker, 2011).

Due to the grave consequences of NEC, neonatal care providers pay close attention to feeding intolerance. Feeding intolerance, a symptom of NEC, is a common complication in very

premature infants since they have immature development and function of their gastrointestinal (GI) systems (Carlson, 2014). Feeding intolerance is a symptom that often precedes the diagnosis of NEC. Due to the serious implications of feeding intolerance, especially in the premature VLBW infant, it is taken seriously but managed very differently by neonatal care providers depending upon their personal or unit experiences (Fanaro, 2013).

The CDC reports that in the United States, 2.7% of births occur before the 34th week of gestation, and 1.34% are born weighing less than 1500 grams. This means that approximately 48,000+ babies are born prior to 34 weeks and weigh less than 1500 grams (Osterman et al., 2022). It is estimated that nearly one-third of these premature infants, more than 15,000 per year, experience feeding intolerance (Krishnamurthy et al., 2010).

Despite many infants suffering from feeding intolerance, no consistent definition is found in the literature (Fanaro, 2013). Feeding intolerance definitions usually include varying values for gastric residuals (GR), abdominal distention, quality of bowel sounds, frequency of feeding-related apnea and bradycardia episodes, presence of emesis and/or bloody stools as well as radiograph findings of intestinal dilation (Corvaglia et al., 2017; Dhingra et al., 2009; Moore & Wilson, 2011). In a concept analysis, Moore and Wilson (2011) suggested that the defining attributes of feeding intolerance include a "gastric residual of 50% of the previous feeding volume, abdominal distention, emesis, or a delay, decrease or discontinuation of enteral feedings" (p. 152). Later research done by Corvaglia et al. (2017) defined feeding intolerance as "the withholding of enteral feeding for $\geq$ 24 hours, due to the presence of at least two of the following signs: "abdominal distension, absent bowel sounds, persistent GR, GR volume >2 mL/kg of body weight or greater than half the volume of the previous feed, bilious or

bloody GR, and/or bloody stools" (p. 552). Despite similarities, definitions remain inconsistent. For the purposes of this research, the definition provided by Corvaglia et al. (2017) was used.

To further complicate the definition of feeding intolerance, recent research has focused on the utility of the gastric residual as an indicator of feeding intolerance and suggests that gastric residuals are an unreliable measure as it relates to the tolerance of enteral feeding (Parker et al., 2015; Riskin et al., 2017; Torrazza et al., 2015). Additionally, Moore and Pickler (2017) found that nursing assessment of emesis volume was inconsistent and inaccurate despite the level of Neonatal Intensive Care Unit (NICU) nursing experience. Thus, as new research findings are disseminated, the definition of feeding intolerance in premature VLBW infants evolves and changes over time. The assessment of its attributes continues to be subjective.

Since feeding intolerance can indicate developing NEC, it is important to identify the signs and symptoms as early as possible. Several tools have been developed for use at the bedside to assess developing symptoms. These include GutCheck, eNEC, and NeoNeeds© (Fox et al., 2015; Gephart, Spitzer et al., 2014; Gephart, Wetzel et al., 2014). GutCheck was developed through a research process that synthesizes the evidence, expert consensus building, and statistical modeling. In contrast, eNEC was developed by Christine Wetzel and Brittany Krisman as a quality improvement project (Gephart, Wetzel, et al., 2014). NeoNeeds© was developed through a retrospective review of the clinical symptoms of 297 patients (Appendix A). Five clinical categories for scoring were identified. A tool was developed, then evaluated with a sample of 72 infants and 532 observations, which had significant predictive value for intestinal dysfunction and positive and negative predictive values of 76% and 95%,

respectively (Fox et al., 2015). These tools require further clinical evaluation and validation. However, NeoNeeds© was used in this study since it was derived from clinical symptoms of a large sample size.

The morbidity, mortality, and cost of NEC underscore the need for improved management of enteral feeding and new diagnostic tools to recognize and manage feeding intolerance. Feeding intolerance is an important yet ill-defined symptom of prematurity with a wide range of management practices and many subjective attributes. Since feeding intolerance can be a warning sign for NEC and may delay the delivery of nutrition to the baby, it is important to learn more about feeding intolerance, develop more objective tools for its assessment and develop feeding interventions to minimize its occurrence.

Chapter 2: Conceptual Framework and Review of the Literature

Pathophysiology

To understand why premature infants are prone to feeding intolerance, we must understand how their anatomy and physiology differ from that of a term infant. The intestines of a premature infant are shorter than their term counterparts, with fewer villi to assist with the movement of food through the intestines (Brooks et al., 2013). Since adequate peristalsis and motility do not mature until 34 weeks, infants born earlier are at risk for prolonged intestinal exposure to enteral feeds (Corvaglia et al., 2014; Marin & Strickland, 2013). After introducing feeds, the potential outcomes range from feeding tolerance at one end to necrotizing enterocolitis at the other.

Not only are their intestines structurally different, but perfusion of the intestines is also compromised, at times, in the premature infant. A decrease in splanchnic oxygenation may result in malabsorption and play a role in feeding intolerance (Munshi & Clark, 2017). Some studies have shown that splanchnic oxygenation increases in response to bolus feeds but only after five weeks of age, while other studies have shown no association between splanchnic oxygenation and bolus feeds during anemia and post-transfusion (Balegar et al., 2020; Kuik et al., 2019). Decreased splanchnic oxygenation in the first few days of life may help predict which babies will develop NEC (Özkan et al., 2021; Palleri et al., 2020).

The ability to regulate blood flow to the intestine improves with gestational maturity, but the very premature infant has a higher propensity toward first auto-regulating cerebral blood flow, particularly after the first three days of life (Balegar et al., 2020; Elsayed & Fraser, 2017). This mechanism is immature and is affected by profound hypotension or hypertension in

the neonatal period (Vesoulis & Mathur, 2017). Data suggests that splanchnic blood flow is impacted by circulatory instability, potentially resulting in a silent hypoxic insult to the intestines (Cerbo et al., 2013; Marin & Strickland, 2013; Smith et al., 2022; Weaver et al., 2018).

Splanchnic Oxygenation

In terms of intestinal blood flow and splanchnic oxygenation, neonates have a lower resting vascular resistance than older children, allowing for increased blood flow and oxygen delivery. An increase in blood flow should create a physiologic boost to splanchnic oxygenation. However, some factors may interfere with the blood flow through the superior mesenteric artery, such as blood transfusions for anemia which may cause reperfusion injury to the bowel, and postnatal hypoxia caused by initial respiratory insufficiency. Additional factors include repeated hypoxic events associated with bradycardia/desaturation, which are common in premature infants, and the presence of patent ductus arteriosus (PDA), which may shunt blood away from the splanchnic organs (Elsayed & Fraser, 2017; Nankervis et al., 2008; Smith et al., 2022).

Near infrared spectroscopy (NIRS) has given researchers the ability to assess splanchnic oxygenation and oxygenation of the brain and kidneys. NIRS uses external sensors to measure total oxygen bound to hemoglobin in the tissues below the sensor, represented as regional oxygen saturation (rSO2). This number is derived from the measurement of oxygenated and deoxygenated hemoglobin (Marin et al., 2013; Martini & Corvaglia, 2018). Because premature infants' organs are so close to the surface, it is a good indicator of organ perfusion. However, there is no normative data or optimum ranges for splanchnic oxygenation in premature infants, likely because of the wide variability in risk factors and disease state of premature infants and

the relatively new use of NIRS for measuring splanchnic oxygenation. Infants within studies are compared to asymptomatic infants or some other baseline measurement and then evaluated in terms of “higher,” “lower,” or “more variability” in splanchnic oxygenation values (Bailey et al., 2012).

Various measurements have been used in research involving rSO2. The two most frequently encountered during this review are splanchnic cerebral oxygenation ratio (SCOR) and fractional tissue oxygen extraction (FTOE). SCOR uses cerebral oxygenation and splanchnic oxygenation and provides a ratio (Bailey et al., 2013; Fortune et al., 2001). The principle of cerebral autoregulation provides a relatively constant blood flow to the brain despite poor perfusion in other parts of the body (Vesoulis & Mathur, 2017). Therefore, comparing an infant’s splanchnic oxygenation to its own cerebral oxygenation may be more specific for splanchnic oxygenation than overall systemic oxygenation.

Another frequently used measurement derived from rSO2 is the FTOE. FTOE compares splanchnic oxygenation to systemic oxygenation as measured by pulse oximetry. The measurement compares splanchnic oxygen delivery with splanchnic oxygen consumption. Increasing FTOE indicates inefficient tissue oxygen utilization, while decreasing FTOE indicates adequate tissue oxygen utilization (Balegar et al., 2020). Measuring splanchnic oxygenation using NIRS and comparing it to systemic oxygenation (SpO2) via pulse oximetry (FTOE) is more economical than cerebral and splanchnic monitoring and may be quicker and easier at the bedside without sacrificing the quality of information.

There has been increasing use of splanchnic oxygenation as a measure of intestinal function in research, but it is still relatively new, and there is much to be discovered.

Considerable research related to splanchnic oxygenation has centered around transfusion associated necrotizing enterocolitis and anemia. Many studies have found an association between transfusions, anemia, and overall low splanchnic oxygenation readings with intermittent increases post transfusion associated with enteral feeding (Baserga et al., 2020; Braski et al., 2017; Goldstein et al., 2020; Martini et al., 2020). Other research reported no correlation between splanchnic oxygenation and anemia, although they did show a significant difference in cerebral and flank oxygen extraction (Mintzer et al., 2018).

The impact of PDA on splanchnic oxygenation has recently been explored, and findings suggest that the presence of PDA negatively impacts splanchnic oxygenation (Ledo et al., 2017; Smith et al., 2022). However, findings regarding the impact of PDA are inconsistent, as at least one study has suggested that there is no impact of PDA on splanchnic oxygenation at first enteral feed (Martini et al., 2019).

Within the last few years, more research has been aimed at the relationship between feeding intolerance or GI complications and splanchnic oxygenation. One study placed NIRS monitoring at the onset of GI symptoms and monitored for 48 hours. Ten days after the initial onset of symptoms, two physicians examined the evidence to determine if the symptoms were compatible with a diagnosis of NEC. The splanchnic oxygenation was then evaluated using SCOR for differences between NEC and non-NEC groups. It was determined that there was no significant difference in measurements between the two groups suggesting that NIRS was unable to detect the severity of GI complications (le Bouhellec et al., 2021). However, this study contradicts much of the research that shows some relationship between splanchnic oxygenation, NEC and/or GI complications. For example, a retrospective review looked at

splanchnic oxygenation and SCOR of infants <32 weeks GA and <1200 grams at birth with suspected NEC in the first three weeks of life. They compared those with Bell's Stage 2 or greater with those without NEC or Bell's < Stage 2. Their findings suggest that a high SCOR may confirm the presence of NEC, while high variability in splanchnic oxygenation may rule out NEC, which contradicts the aforementioned study (van der Heide et al., 2021). Similar findings from several studies showed that lower splanchnic oxygenation in the first week or two of life indicates an increased risk of developing feeding intolerance or NEC later (Corvaglia et al., 2017; Özkan et al., 2021; Palleri et al., 2020).

Further research has examined the time to full feeds after NEC diagnosis as a predictor of intestinal recovery. NIRS monitoring was initiated when the infant was suspected of having NEC and continued once daily for two hours until the infant reached full enteral feeds for at least 24 hours. Data analysis suggested that increases in intestinal rSO2 and associated range were associated with attaining full feeds within two weeks (Kuik et al., 2020). Kuik et al. (2020) also found post-prandial intestinal oxygenation increases in preterm infants in the fifth week of life, specifically when greater than 32 weeks post-menstrual age. They hypothesize that infants at younger gestational ages are physiologically unable to increase splanchnic oxygenation after feedings (Kuik et al., 2019). A look specifically at those infants who experienced absent or reversed end diastolic flow in utero suggested that infants with GI complications did show signs of lower splanchnic oxygenation and increased FTOE in response to enteral feeds both at the introduction of feeds and at the point of full enteral feeds (Martini et al., 2018). Type of feeding has also been investigated, and findings suggest that splanchnic oxygenation is decreased and

splanchnic FTOE is increased in those receiving preterm formula compared to those receiving breast milk or fortified breast milk feeds (Dani et al., 2021).

Research also suggests that infants, born at less than 32 weeks gestation, with cerebral oxygenation <70% within the first two days after birth are significantly more likely to develop NEC. This study also found that intestinal FTOE was higher in infants developing NEC but only in the last few measurements before the onset of NEC, which was approximately two days prior (Schat et al., 2019). This would seem to support a hypothesis that NIRS may be able to predict the severity of GI symptoms.

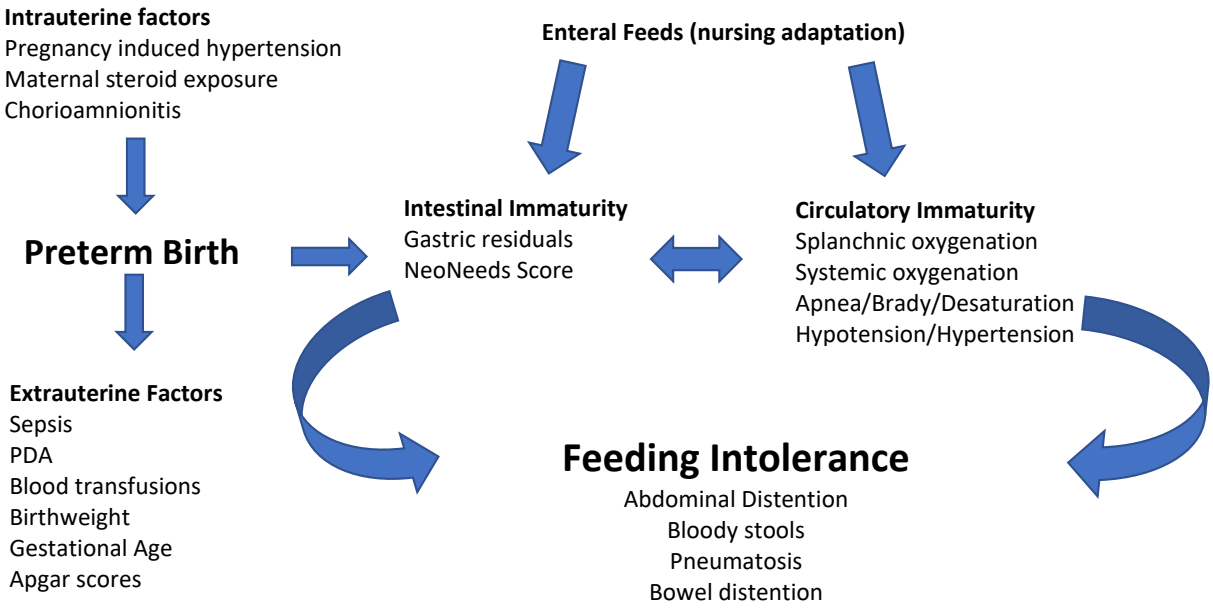
In summary, there is a paucity of research examining the relationship between feeding intolerance and splanchnic oxygenation outside of NEC and the blood transfusion/anemia focus. This research study addressed this gap by exploring the relationship between feeding intolerance, intrauterine factors, extrauterine factors, intestinal immaturity, and circulatory immaturity in the premature, very low birthweight infant. It also explored the use of splanchnic oxygenation as an objective measure of feeding intolerance.

Theoretical Framework

The Theory of Health Promotion for Premature Infants (Mefford, 2004) influences the framework for this research in terms of how prematurity and its associated interventions disrupt the homeostasis of the infant and provides a framework to develop and evaluate interventions aimed at minimizing the disruption and maintaining homeostasis for these fragile infants. As shown in Figure 1, the model begins with premature birth and the maternal and neonatal factors that play a role in intestinal and circulatory maturation and integrity beginning prior to birth and extending into the neonatal period. Their presence or absence may affect

homeostasis of the infant. These factors must be considered when examining relationships between enteral feeding and splanchnic oxygenation (a marker of intestinal perfusion) and are shown on the left-hand side of the framework.

Figure 1. Theoretical Framework



Intrauterine Factors

Pregnancy induced hypertension (PIH), a maternal vascular disorder during pregnancy that affects the placenta, has been shown to be an independent risk factor for NEC, although its treatment with magnesium sulfate has not been shown to impact the incidence of NEC (Bashiri et al., 2003; Gephart et al., 2012; Ghidini et al., 2001). A vascular disorder of the placenta such as PIH can cause poor growth in the fetus, affecting maturation and function of the intestines (Gephart et al., 2012).

Exposure to antenatal glucocorticoids has been shown to reduce multiple morbidities in the very premature infant, with NEC being one of those morbidities. There are two hypotheses regarding the mechanism. One hypothesis is that the exposure matures the cardiovascular system, thereby improving blood flow to the intestines, and the other hypothesis is that the steroid exposure facilitates organ maturation (Romejko-Wolniewicz et al., 2013; Smith et al., 2000).

Chorioamnionitis is associated with multiple morbidities in the neonate. In addition to sepsis, chorioamnionitis coupled with a vasculopathy was associated with low Apgar scores and, when coupled with maternal coagulopathy, was associated with NEC (Ogunyemi et al., 2003). The Apgar score assigns a value for heart rate, color, reflex irritability, tone, and respiration and serves as a measure of the transition to extrauterine life.

Extrauterine Factors

Patent ductus arteriosus (PDA) is an open vessel between the pulmonary artery and the aorta. Its persistence after birth results in decreased cardiac output and over-circulation of the lungs. The left ventricle of the heart increases output as a compensatory mechanism related to the presence of the PDA, but this supports cerebral blood flow and does not increase mesenteric blood flow (Elsayed & Fraser, 2017; Freeman-Ladd et al., 2005; Shimada et al., 2003). As mentioned earlier, there is some controversy in the current literature regarding the role of PDA in splanchnic oxygenation (Ledo et al., 2017; Martini et al., 2019; Smith et al., 2022)

There is evidence of greater variability in splanchnic tissue oxygenation during the transfusion of packed red blood cells, which may indicate a relative ischemia/reperfusion making the intestine more susceptible to transfusion-related gut injury (Bailey et al., 2015;

Marin et al., 2013). Although much research has been centered around transfusion-related NEC, anemia, and enteral feeding, there is no definitive answer on the safety of enteral feeds during and after transfusion or how it may relate to feeding intolerance outside of NEC (Balegar et al., 2020; Baserga et al., 2020; Clarke-Pounder et al., 2015; Goldstein et al., 2020; Kalteren et al., 2018; Killion, 2021; Martini et al., 2020; Mintzer et al., 2018; Sahin et al., 2020). Although blood transfusion has been associated with increased risk for NEC, it is unclear how it impacts feeding intolerance.

Hashem et al. (2017) found that septic infants with feeding intolerance had lower peak systolic velocity and lower end-diastolic velocity (measured in the mesenteric artery) when compared to septic infants without feeding intolerance. These findings suggest that sepsis in a premature infant with feeding intolerance, which is one clinical sign of NEC, may put them at risk for further intestinal ischemia or damage. These neonatal factors must be accounted for when examining the relationship between splanchnic oxygenation and feeding intolerance.

This research addressed the above intrauterine and extrauterine variables. It also included facets of intestinal and circulatory immaturity related to feeding intolerance and splanchnic oxygenation. In the framework, these threats to homeostasis are then impacted by nursing interventions, which, in this case, is the administration of prescribed enteral feeding.

Intestinal Immaturity

Premature infants exhibit decreased intestinal length and lack of villi necessary for transit of enteral feeds, as well as the increased permeability of the intestinal wall. This affects both the movement of the food through the intestines and the absorption of nutrients (Brooks et al., 2013; Neu, 2007). Thus, when an infant is born during the second trimester or early in the

third trimester, these structures are not fully developed and have a decreased ability to digest food and absorb nutrients.

Intestinal peristalsis begins between 28- and 30-weeks GA and does not fully mature until the infant is between 33- and 40-weeks GA. Thus, infants born earlier are at higher risk for feeding intolerance and prolonged intestinal exposure to enteral feeds (Gardner et al., 2015; Marin & Strickland, 2013). Additionally, research suggests that abdominal NIRS readings correlated with motility; higher NIRS measurements correlated with increased motility (Akotia et al., 2016).

Junctions between the intestinal wall cells are not tight in the premature intestine allowing for bacteria to leave the intestine and enter the bloodstream resulting in late-onset sepsis (LOS), which is sepsis occurring >72 hours after birth (Sherman, 2010). Sepsis refers to a bacterial infection in the infant. LOS may lead to further GI dysfunction or damage to the intestinal wall through inflammation and hypoperfusion states, depending on severity (Wynn & Wong, 2010).

Currently, our best nursing bedside measures of intestinal immaturity are assessment of gastric residuals, emesis, and abdominal distention, all of which can be late signs of intestinal dysfunction. These assessment findings often lead to nil per os (NPO) periods due to NEC concerns, thus delaying enteral nutrition to the infant. Because of immature peristalsis and prolonged intestinal exposure to enteral feeds, the risk for NEC is increased. NEC may manifest itself like feeding intolerance in terms of gastric residuals and abdominal distention and may be accompanied by bloody stools, intestinal pneumatosis, and sepsis. Intestinal pneumatosis is gas within the bowel wall and can be seen on radiographs either as “train tracks” along the bowel

wall or bubbly lucencies. It is important to find more effective and objective ways to distinguish between feeding intolerance and NEC.

Intestinal immaturity may result in gastric residuals/emesis, abdominal distention, bloody stools, and pneumatosis. These are all symptoms included in our study definition of feeding intolerance. Gastric residuals and NeoNeeds© scores, a tool for assessing intestinal dysfunction, were explored to determine the relationship between intestinal immaturity and changes in splanchnic oxygenation.

Circulatory Immaturity

The sympathetic nervous system develops first in fetal development, followed by the parasympathetic nervous system. Thus, very premature infants are born before the parasympathetic nervous system is complete and are less able to maintain homeostasis in relation to breathing and circulation (du Plessis, 2009). Because the autonomic nervous system is immature, premature infants have less heart rate variability and are less able to control blood flow through changes in heart rate (Longin et al., 2006). The autonomic nervous system seeks first to auto-regulate blood flow to the brain and thus may impair blood flow to the intestines in this quest, particularly in times of illness or stress (Bailey et al., 2012; M. C. Baserga et al., 2003; Fortune et al., 2001; Greisen, 2005). Additionally, it has been suggested that bradycardia and apnea episodes, controlled by the immature autonomic system, may be associated with or symptoms of feeding intolerance (Lucchini et al., 2011).

As a measure of circulatory immaturity, splanchnic oxygenation and SpO2 were measured and recorded as well as apnea, bradycardia, desaturation, hypotension, and

hypertension episodes. Data obtained from these measures were examined against splanchnic oxygenation to determine the relationship between them.

Innovation

Most studies focused either on the early days of life or after NEC has been diagnosed. This study was innovative in using NIRS episodically for early concerns of feeding intolerance to evaluate the usefulness of the splanchnic NIRS and FTOE in this situation. This study may also provide additional validation to the Neo Needs tool, which has the potential to be an early warning tool for developing NEC.

Early objective differentiation between feeding intolerance solely related to an immature gut and feeding intolerance that is a symptom of NEC is important but, thus far, somewhat elusive. Therefore, this study examined the relationships between feeding intolerance, intrauterine factors and extrauterine factors, and intestinal and circulatory immaturity in the premature, very low birthweight infant. It also explored the use of splanchnic oxygenation (a marker of intestinal perfusion) as an objective measure of feeding intolerance.

Chapter 3: Methodology

Design

This prospective, descriptive observational pilot study with repeated measures examined the relationships between feeding intolerance, intrauterine and extrauterine factors, and circulatory and intestinal immaturity in the premature, very low birthweight infant. It also explored the use of splanchnic oxygenation as an objective measure of feeding intolerance.

Specific Aim 1. Examine the relationship between splanchnic oxygenation and feeding intolerance in VLBW infants born between 26- and 31-weeks GA

Specific Aim 2. Explore the relationship between splanchnic oxygenation and circulatory and intestinal immaturity factors in VLBW infants born between 26- and 31-weeks GA.

Specific Aim 3. Examine relationships between intrauterine and extrauterine factors and splanchnic oxygenation in VLBW infants born between 26- and 31-weeks GA.

Setting and Sample

The study was conducted in a 40 bed Level IV NICU located within an urban academic medical center. There are approximately 420 admissions to the NICU each year. The NICU is a single room design with four twin rooms. Infants are placed in heated incubators (GE Omnibed) equipped with scales. The staffing ratio is 2:1 for infants of this gestational age. All beside nurses are Registered Nurses (RN) who work rotating shifts of 4, 8, or 12 hours in length.

The study utilized a sample of VLBW infants born between 26 and 31 weeks completed gestation. The convenience sample was comprised of infants born at an urban academic

medical center and admitted to the Newborn Intensive Care Unit (NICU) whose parents provided consent for participation (Appendix B). Inclusion criteria included infants born between 26 0/7 and 31 6/7 weeks GA born at the study hospital or transferred to the study hospital within 24 hours of birth. Parents were English speaking. Exclusion criteria included infants with gastrointestinal anomalies, lethal anomalies, or genetic syndromes. Infants with these syndromes or abnormalities may have altered transit times beyond that of a normal VLBW premature infant. Infants who were not fed within the first week of life were also excluded since withholding feedings for this length of time typically represents a more critically ill infant.

Approximately 80 infants born at less than 1500 grams and less than 32 weeks are admitted to the study NICU each year. Very few infants born at this gestational age are born with the exclusion diagnoses; therefore, very few infants required exclusion. For this pilot study, we used a convenience sample of 20 infants, six of which developed feeding intolerance.

Measures and Instruments

Near Infrared Spectroscopy

We used Near Infrared Spectroscopy (NIRS) to measure the percentage of oxyhemoglobin and deoxyhemoglobin in organ tissue using an INVOS 5100C Cerebral/Somatic oximeter (Medtronic, Boulder, CO). The INVOS 5100C Cerebral/Somatic Oximetry Neonatal/Infant Sensors were placed in the infraumbilical area of the abdomen of study infants and connected to the oximeter. These sensors measure regional tissue oxygenation, and values reflect splanchnic tissue oxygen supply and demand (Massa-Buck et al., 2017).

Fractional Tissue Oxygen Extraction (FTOE)

Comparing splanchnic oxygenation with systemic oxygenation via pulse oximetry (SpO2) leads to fractional tissue oxygen extraction (FTOE). This is derived by subtracting the splanchnic oxygen value from the systemic oxygenation and then dividing by the systemic oxygenation. Splanchnic FTOE is useful in determining oxygen consumption and oxygen delivery to the splanchnic bed and has been increasingly used in exploring splanchnic oxygenation (Balegar et al., 2020; Cortez et al., 2011; Goldstein et al., 2020; Ilhan & Bor, 2021). The FTOE was calculated for each epoch using the splanchnic oxygenation readings and the SpO2 from pulse oximetry.

NeoNeeds©

NeoNeeds© is a bedside tool developed for detecting intestinal dysfunction with scores ≥ five or an increase of two over baseline warranting a discussion with the NICU provider team. The highest scores recorded for each 24 hours were used to calculate the means for analysis.

Demographic Data and Medical History

Data were collected from the infant's and mother's medical records (paper or electronic) to describe the sample and obtain information regarding intrauterine and extrauterine factors. Infant demographic information included the infant's gestational age at birth, birthweight, sex, and race. The infant's medical history obtained included treatment of PDA, blood transfusions, and sepsis. Maternal demographic information included age and race. Maternal history obtained included the presence of hypertension, steroid exposure, and diagnosis of chorioamnionitis.

Procedures

After IRB approval was obtained, in-services were held in the NICU for bedside nurses. The in-service included an explanation of the study, a demonstration of proper NIRS probe

placement and a detailed description, including the study definition of feeding intolerance and when to place the NIRS probe for feeding intolerance. Once the infant was enrolled, copies of the study protocol and feeding intolerance definition were placed in each infant's bedside binder.

Recruitment took place in the NICU prior to the achievement of 80 ml/kg/day of enteral feeds. The PI approached mothers of eligible infants, explained the study, and obtained written informed consent. After obtaining consent, demographic data were collected from the electronic medical record (EMR) and consented infants were immediately placed into the study. The study NICU had a feeding protocol for infants less than 1500 grams at birth, and this was followed regarding feeding type, volume, and rate of advancement.

Medical history and feeding tolerance were assessed daily for changes throughout the study duration which spanned birth to 34 weeks GA. Once infants tolerated between 40 and 80 ml/kg/day of feeds, sensors were placed in the infraumbilical area of study infants and connected to an INVOS 5100C Cerebral/Somatic Oximeter for a baseline measurement.

Using NIRS, splanchnic oxygenation was read continuously and recorded every 6 seconds. Data were retrieved from the oximeter, and FTOE was calculated in 15-minute epochs. The baseline measurement was approximately 24 hours in duration. Once it was obtained, the next measurement was done when feeding intolerance occurred and the decision to withhold feeds for 24 hours was made. Feeding intolerance was defined as "the withholding of enteral feeding for greater than or equal to 24 hours, due to the presence of at least two of the following signs: abdominal distension, absent bowel sounds, persistent GR, GR volume >2

mL/kg of body weight or greater than half the volume of the previous feed, bilious or bloody GR, and/or bloody stools" (Corvaglia et al., 2017, p. 552).

The NIRS sensors were applied by the PI or by the bedside nurse if the PI was not present at the time of feeding intolerance, and this measurement was approximately 48-72 hours in length. If the infant did not experience feeding intolerance, they received only one NIRS measurement of approximately 24 hours duration. If the infant did experience feeding intolerance, they received up to 3 NIRS measurements; one of 24 hours duration for baseline and one- or two of 48-72 hours duration depending upon the number of feeding intolerance episodes.

During the study period, data related to symptoms of intestinal and circulatory immaturity were collected and recorded onto data sheets every 24-72 hours by the PI. These included residual volumes, NeoNeeds© scores, apnea/bradycardia/desaturation events, and episodes of hypotension and hypertension. NeoNeeds© scores were documented every 8 hours by the bedside RN from the time of enrollment to 34 weeks gestation. These scores were documented on a data collection sheet kept in the bedside binder of each participant. All other variables related to intestinal and circulatory immaturity were obtained from the EMR.

Data Management Plan

Data were managed according to IRB requirements. All patient data were de-identified, and a key was kept in a secure, locked location in the PI's office, accessed only by the PI in compliance with HIPPA. Data were recorded on a datasheet kept in a binder at the patient's bedside. When removed from the bedside for entry into EXCEL, the datasheets were kept in a study binder in a secure, locked location in the PI's office. NIRS data were downloaded directly

to an EXCEL spreadsheet on a USB drive kept in a locked drawer in the PI's office separate from the key. The PI checked all data. Data checks for missing data were completed weekly, and corrective actions were taken if necessary.

Statistical Analysis

All analyses were done using JMP Pro 16 (SAS Institute Inc., Cary, NC, 1989-2022). Descriptive analyses were done to describe the sample. Comparisons were made between feeding tolerance and feeding intolerance to examine these potential relationships using a mixed linear regression model with repeated measures. We also used a mixed linear regression model with repeated measures to examine relationships between intrauterine and extrauterine variables, circulatory and intestinal immaturity, and splanchnic oxygenation (FTOE).

Attrition/Missing Data

One infant was withdrawn from the study, at parental request, during their baseline measurement. Their baseline data and remaining variables were still able to be used as per the consent. Another infant died while on study after a partial feeding intolerance measurement. Data were missing from residual and NeoNeeds© documentation at times. The impact of this was likely low since the study used the highest value from each 24 hours.

Chapter 4: Findings

This research study explored the relationships between feeding intolerance, intrauterine and extrauterine factors, and circulatory and intestinal immaturity in the premature, very low birthweight infant. It also explored the use of splanchnic oxygenation as an objective measure of feeding intolerance. Intrauterine variables included maternal hypertension, maternal steroid exposure, and chorioamnionitis. Extrauterine variables included sepsis, PDA, blood transfusions, birthweight, and gestational age. Circulatory immaturity was measured by systemic and splanchnic oxygenation, apnea/bradycardia/desaturations episodes, hypotension, and hypertension. Intestinal Immaturity was measured by the volume of gastric residuals and the NeoNeeds© scores.

Fifty-one infants between 26- and 31-weeks gestation weighing less than 1500 grams at birth were born during the enrollment period. A total of 20 infants were enrolled, six of those infants experienced feeding intolerance during the study period (Figure 2). Demographic data were collected and found to have mostly normal distribution with a slight skew in birthweight toward weights >1250 grams. Residuals, apnea/bradycardia/desaturation events, hypotension, hypertension and NeoNeeds scores were recorded as markers of circulatory and intestinal immaturity. Intra- and extra-uterine variables were also recorded (Table 1).

Table 1

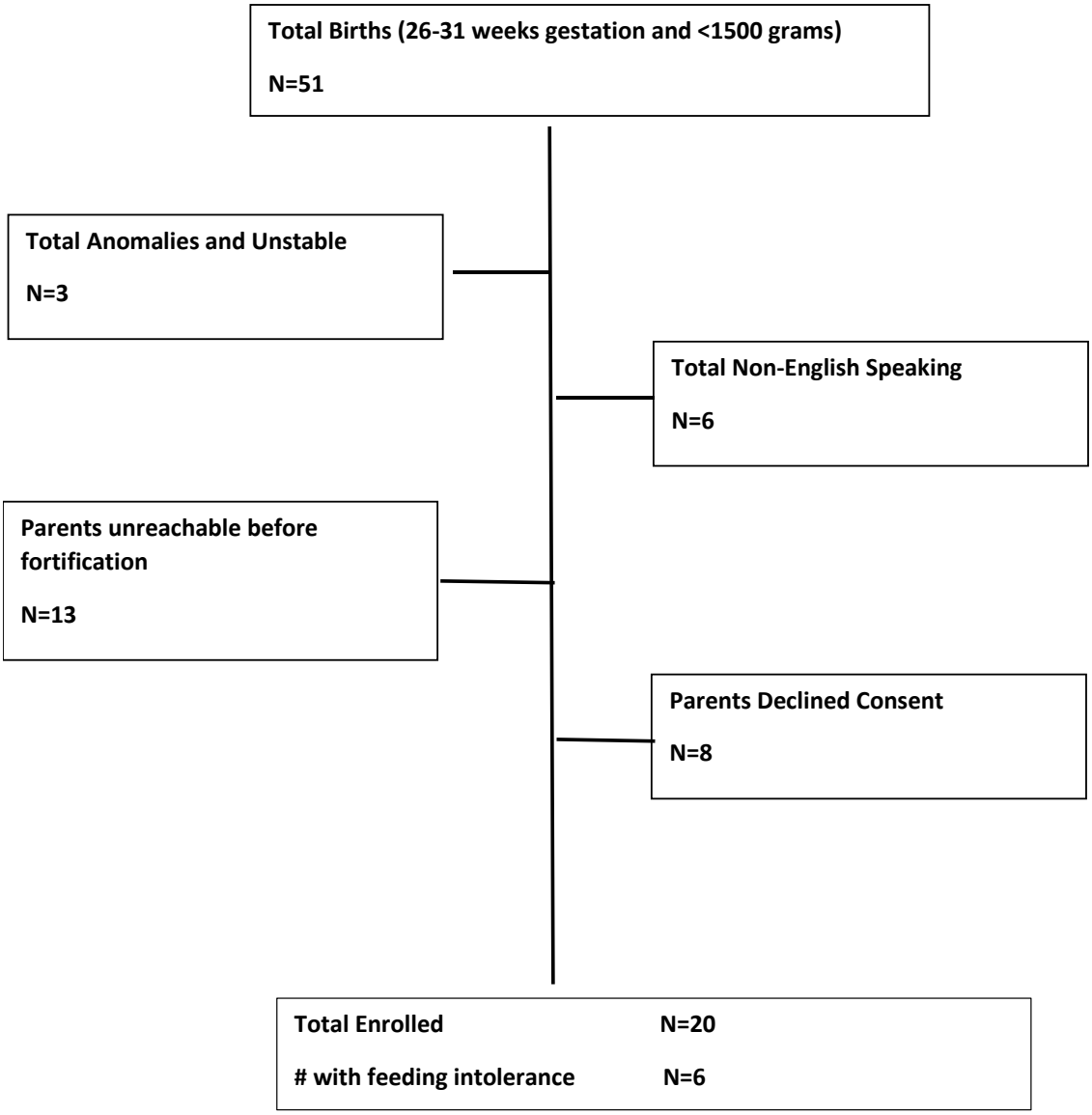
Intrauterine and Extrauterine Factors

Intrauterine Factors	n	%	**Extrauterine Factors**	**n**	**%**
Antenatal Steroids	14	0.70	Apgar scores		
Yes	2	0.10	1 minute (n=20)		
No	4	0.20	< 7	13	0.65
Inadequate			≥ 7	7	0.35
			7-10		
			5-minute (n=20)		
			< 7	4	0.20
			≥ 7-10	16	0.80
			10-minute (n=4)		
			< 7	1	0.25
			≥ 7	3	0.75
Chorioamnionitis			Culture positive sepsis		
Yes	2	0.10	Yes	1	0.05
No	18	0.90	No	19	0.95
Intrapartum Antibiotics	12	0.60	Documented PDA		
Yes	8	0.40	Yes	5	0.25
No			No	15	0.75
Maternal Hypertension	10	0.50	PDA Treatment (PDA n=5)	1	0.25
Yes	10	0.50	Yes	4	0.75
No			No		
			Number of blood transfusions	10	0.50
			0	5	0.25
			1-2	3	0.15
			3-4	2	0.10
			5-6		

Data collection, entry, and cleaning were the sole responsibility of the student investigator. Data were entered into and analyzed using JMP®.

Figure 2.

Enrollment Algorithm



Descriptive statistics were employed to describe the sample, which was mostly comprised of 28–29-week male infants weighing >1250 grams. The mothers were in their early 30's and predominantly white. There were three sets of twins and one set of triplets, and the remainder were singletons. See Table 2 for details.

Table 2

Description of the sample

Demographics	n	%	Median	Range
GA at birth (weeks)			29	26-31
26-27	3	0.15		
28-29	12	0.60		
30-31	5	0.25		
Birthweight (grams)			1265	790-1440
500-749	1	0.05		
750-999	4	0.20		
1000-1249	4	0.20		
1250-1500	11	0.55		
Gender - male	14	0.70		
Maternal Age			31	20-38
20-24	1	0.05		
25-29	7	0.35		
30-34	10	0.50		
35-39	2	0.10		
Maternal Race				
Black	6	0.30		
White	11	0.55		
Latino	0	0		
Asian	2	0.10		
Other	1	0.05		

Results for Aim 1

The first specific aim examined the differences in fractional tissue oxygen extraction (FTOE) between the states of feeding tolerance and feeding intolerance. Using a mixed linear model with a fixed effect of tolerance and a random effect of subject, we compared the baseline FTOE with the FTOE during feeding intolerance for the six subjects experiencing feeding intolerance. The difference in the mean was statistically significant ($F_{1, 1766.9} = 792.08$, p-value <.001) The least square (LS) means for subjects in the feeding tolerant and intolerant states are presented in Table 3. The LS Mean difference between the two states is 0.2376 (0.0084) which is

significant different. When separately examining the intolerance FTOE of each infant and using their baseline as a control, all infants had differences in FTOE between the two states with all having higher FTOE when experiencing feeding tolerance, which further supports the findings of significance. Also statistically significant, was the subject variance with 35% of the variability being attributed to the subject. Using the likelihood ratio test this was statistically significant (= 732.2*,* 1 d.f., *p = <.001).*

Table 3

Comparison of baseline FTOE with intolerance FTOE in infants who experienced both (n=6).

Tolerance State	Estimate	Std Error	DF	Lower 95%	Upper 95%
Tolerance	0.79134	0.0466	5.1469	0.6725	0.9101
Intolerance	0.55378	0.0464	5.0645	0.4349	0.6726

Similarly, we compared the baseline measurements of those who developed feeding intolerance (n=6) with those who never developed it (n=14). Nearly 50% (46.5%) of the variability could be explained by subject, which was statistically significant using the likelihood ratio test (= 859.6*,* 1 d.f., *p=<.0001)*. However, there was no statistically significant difference in the mean FTOE at baseline between those that did and did not develop feeding intolerance ($F_{1,17.9}$ = 2.69, p = 0.1187). Baseline FTOE values for each group are presented in Table 4. Table 5 shows the results of the student's t-test, with the first line representing all baseline measurements and the second line representing only those babies who developed feeding intolerance; again, showing significance in the feeding intolerance group.

Table 4

Comparison: Baseline FTOE between infants who tolerated feeds and those with feeding intolerance

Groups	Estimate	Std Error	DF	Lower 95%	Upper 95%
Tolerance	0.7097	0.02557	17.92	0.65595	0.76346
Intolerance	0.7862	0.03906	17.91	0.704129	0.86833

Note. Tolerance = never developed feeding intolerance, Intolerance = developed feeding intolerance.

Table 5

Student's t All Pairwise Differences

Group	n	Difference	Std Error	t Ratio	Prob > t	Lower 95%	Upper 95%
All baseline	20	-0.076518	0.0466	-1.64	0.1187	-0.174653	0.0216166
Intolerance	6	-0.237566	0.008441	-28.14	**<.0001**	-0.254121	-0.221010

Results for Aim 2

Factors related to intestinal and circulatory immaturity (ABD events, residuals, hypotension, hypertension and NeoNeeds scores) were recorded and means calculated. Residual and NeoNeeds means were calculated by taking the highest value from each day and calculating the mean. Similarly, ABD events were counted daily, and the mean of the daily number was calculated. Mean arterial blood pressures less than the gestational age were recorded as hypotension, and systolics greater than 90 were recorded as hypertension. These two variables were recorded as yes/no.

Using multiple linear regression, these variables were examined in terms of a relationship with FTOE using subject as the random effect. Again, we assessed the group of all

baseline measurements and then tested against those who developed feeding intolerance (Table 6). Hypotension was the only variable tested for the intolerance group that showed statistical significance (*p > t* = .0267*)*. These variables were also tested using just the intolerance FTOE measurements from the babies who developed feeding intolerance with similar results.

Table 6

Fixed Effects Parameter Estimates: Intestinal and Circulatory Immaturity Variables

Variable Groups	Estimate	Std Error	DFDen	t Ratio	Prob>|t|	95% Lower	95% Upper
Residuals							
All	0.0770	0.1060	18.0	0.73	0.4769	-0.1457	0.2997
Intolerance	0.2665	0.1205	4.0	2.21	0.0917	-0.0684	0.6014
ABD episodes							
All	0.0274	0.0144	17.9	1.9	0.0743	-0.0030	0.0578
Intolerance	0.0300	0.0425	4.0	0.70	0.5203	-0.0884	0.1483
Hypotension							
All	0.0330	0.0221	18.0	1.49	0.1529	-0.0134	0.0794
Intolerance	0.1011	0.2947	4.0	3.43	**0.0267**	0.0191	0.1831
Hypertension							
All	-0.0017	0.0241	17.9	-0.07	0.9444	-0.0522	0.0488
Intolerance	-0.0581	0.0551	4.0	-1.05	0.3507	-0.2107	0.0945
NeoNeeds©							
All	0.0258	0.0224	18.0	1.15	0.2652	-0.0213	0.0729
Intolerance	0.0817	0.0515	4.0	1.59	0.1868	-0.0605	0.2240

Results for Aim 3

The relationship of intrauterine variables was examined through a mixed linear model using the FTOE means of all subjects at baseline measurement with each variable as a fixed effect and the subject as a random effect. We evaluated these variables against all baseline FTOE and the FTOE of those with feeding intolerance. None of the variables examined displayed

statistical significance (Table 7). These variables were also evaluated using just the intolerance FTOE measurements from the babies who developed feeding intolerance with similar results.

Table 7

Fixed Effects Parameter Estimates: Intrauterine variables

Intrauterine Variables Groups	Estimate	Std Error	DFDen	t Ratio	Prob>|t|	95% Lower	95% Upper
Antenatal Steroids							
All	0.0408	0.0523	16.9	0.78	0.4460	-0.0695	0.1511
Intolerance	-0.0229	0.0611	4	-0.38	0.7265	-0.1928	0.1469
Chorioamnionitis							
All	0.0521	0.0363	18.2	1.43	0.1687	-0.0242	0.1284
Intolerance	0.0486	0.0746	3.9	0.65	0.5505	-0.1596	0.2568
Maternal Hypertension							
All	0.0024	0.0229	17.9	0.11	0.9168	-0.0458	0.0506
Intolerance	0.0331	0.0563	4	0.59	0.5880	-0.1231	0.1893

Our attention was then turned to the extrauterine variables described in the theoretical model. Again, the variables were tested against all baseline measurements and against just the babies who experienced intolerance (Table 8). The relationship of many of the variables was not statistically significant. However, the 10-minute Apgar was statistically significant in the intolerance group ($p > t = 0.0268$). Since only two infants received 10-minute Apgar scores, this should be considered in terms of the reliability of this result. These variables were also tested using just the intolerance FTOE measurements from the babies who developed feeding intolerance with similar results.

Table 8.

Fixed Effect Parameters for Extrauterine variables

Extrauterine variables Groups	Estimate	Std Error	DFDen	t Ratio	Prob>|t|	95% Lower	95% Upper
BW							
All	0.0204	0.0246	17.9	30.16	0.4164	-0.0312	0.0721
Intolerance	0.0020	0.0786	4.0	0.03	0.9812	-0.2165	0.2205
GA							
All	0.0216	0.0229	18.0	0.94	0.3576	-0.0264	0.0696
Intolerance	0.1062	0.0578	4.0	1.84	0.1407	-0.0549	0.2673
Sepsis							
All	0.0485	0.0513	17.9	0.95	0.3572	-0.0594	0.1565
Intolerance	0.0954	0.0630	4.1	1.52	0.2028	-0.0779	0.2687
Blood Transfusion							
All	-0.0317	0.0254	17.9	-1.25	0.2291	-0.0850	0.0218
Intolerance	-0.1063	0.0578	4.0	-1.84	0.1406	-0.2674	0.0548
PDA							
All	0.0227	0.0259	17.9	0.88	0.3931	-0.0318	0.0772
Intolerance	0.0075	0.0585	4.0	0.13	0.9045	-0.1551	0.1700
Apgar 1 min							
All	-0.0435	0.0470	17.9	-0.93	0.3671	-0.1423	0.0553
Intolerance	-0.0387	0.0762	4.0	-0.51	0.6384	-0.2506	0.1732
Apgar 5 min							
All	-0.0348	0.0568	17.9	-0.61	0.5479	-0.1541	0.0845
Intolerance	0.0387	0.05533	4.0	0.70	0.5229	-0.1150	0.1924
Apgar 10 min							
All	-0.086	0.0813	2.0	-1.06	0.4014	-0.4363	0.2643
Intolerance	-0.2824	0.0220	420	-12.82	**<.001**	-0.3257	-0.2391

Chapter 5: Discussion

Splanchnic Oxygenation and Feeding Intolerance

This study examined the relationships between feeding intolerance, intrauterine and extrauterine factors, and circulatory and intestinal immaturity in premature, very low birthweight infants. It also explored the use of splanchnic oxygenation as an objective measure of feeding intolerance.

Studies have shown either no difference in fractional tissue oxygen extraction (FTOE) between feeding tolerance and feeding intolerance or the FTOE has been higher during feeding intolerance (Corvaglia et al., 2017; le Bouhellec et al., 2021; Özkan et al., 2021; Palleri et al., 2020; van der Heide et al., 2021). When the rSO2 is low and the SPO2 is high, it creates a higher FTOE indicating that the tissue is inefficient at extracting oxygen from the bloodstream. This study found that FTOE was lower, and regional splanchnic oxygenation (rSO2) was higher during times of feeding intolerance when compared to feeding tolerance. This indicates adequate tissue oxygen utilization during the feeding intolerance episodes which was an unexpected finding. The lowest oxygen level the NIRS oximeter can register is 15%. During the baseline measurements, there were many times the oximeter was reading 15% for extended periods of time or would lose the signal altogether. A possible explanation for these unexpected findings is the maturation of the GI system. Baseline measurements were taken between the 5th and 11th days of life during a time when the gut is still undergoing maturation and may still contain meconium in the preterm infant. The intolerance measurements were taken between days 14 and 39, at which time the gut was more mature with more stable blood flow and likely better able to utilize oxygen. During this study, all infants experiencing feeding

intolerance did so between 30- and 33-weeks gestation, a time when they may be approaching improved tissue oxygen utilization. This finding is consistent with previous findings showing increased postprandial oxygenation in the 5th week of life, specifically after 32 weeks gestation (Kuik et al., 2019).

There was no significant difference in the FTOE means at baseline between infants who developed feeding intolerance and those who did not develop feeding intolerance. Studies have shown lower baseline rSO2 measurements in infants who develop NEC but have not been examined regarding feeding intolerance (Corvaglia et al., 2017; Özkan et al., 2021; Palleri et al., 2020). One infant in the study did develop NEC and only received a few hours of intolerance measurement due to critical illness requiring exploratory laparotomy. That infant died within 24 hours of the intolerance measurement, but even in that infant, the baseline FTOE was higher than the intolerance FTOE.

Circulatory and Intestinal Immaturity

Hypotension was the only circulatory variable that showed significance. This finding is supported by research showing that splanchnic blood flow is impacted by cardiovascular instability such as hypotension and hypertension (Cerbo et al., 2013; Marin & Strickland, 2013; Smith et al., 2022; Vesoulis & Mathur, 2017; Weaver et al., 2018). Neither of the intestinal immaturity variables, NeoNeeds© or residual means, were significant when compared to FTOE of the six infants who experienced feeding intolerance. However, when analyzed individually using their own FTOE measurements, two subjects were found to have significant relationships between FTOE and NeoNeeds, residuals, and apnea/bradycardia/desaturations (ABD). This is anecdotal only as the probability of a Type 1 error is high and statistical significance cannot be

claimed. During this study, hypertension occurred late in the study period after all NIRS measurements were completed. It cannot be ascertained whether hypertension in the early period would have been significant in this study.

Intrauterine and Extrauterine Variables

There were no significant differences in the intrauterine variables. Maternal hypertension, steroid exposure, and chorioamnionitis did not show significance compared to baseline or feeding intolerance FTOE. While these factors have been associated with increased risk for NEC, there was no relationship with feeding intolerance in this study (Gephart et al., 2012; Ogunyemi et al., 2003; Romejko-Wolniewicz et al., 2013; Smith et al., 2000).

Apgar at 10 minutes of life was the only extrauterine variable of statistical significance. Only two infants required a 10-minute Apgar, which may have affected the significance of the variable. An Apgar at 10 minutes of life is required if the Apgar at 5-minutes of life was less than seven. Thus, infants requiring a 10-minute Apgar usually show poor response to resuscitation efforts which may affect circulation and blood flow to the intestines in those very early minutes of life and beyond.

Only one infant was diagnosed with PDA in the feeding intolerance group (N=6)and four were diagnosed with PDA amongst all subjects (n=20). Similarly, only one infant in the entire sample developed culture proven sepsis. This greatly impacts our ability to determine the significance of these variables.

Four infants received blood transfusions before their baseline measurements. Three of those receiving a blood transfusion developed feeding intolerance, one with two episodes of feeding intolerance. They were each transfused again between one and seven days prior to the

diagnosis of feeding intolerance. Transfusion-related NEC occurs within 48-hours of a transfusion, and some studies have focused on the utility of withholding feeds during transfusion. The only infant who developed NEC was transfused as they became critically ill less than 24-hours before necrotic bowel was found. In this case, this is likely not transfusion related NEC. There is no consensus regarding withholding enteral feeding for transfusions or whether blood transfusions are precursors to feeding intolerance without NEC.

Limitations

The most obvious limitation is our small sample size of 20, with only seven feeding intolerance measurements. Due to this small sample size, our findings are not generalizable to the larger population, but this small pilot study provides an impetus for future investigation. Detailed data were collected but required recoding into two variable answers due to the sample size. The impact of variables was not able to be determined but we were able to look for relationships through linear regression on repeated measures.

The lack of measurements between baseline and intolerance is another limitation. Because there was no measurement in the days leading up to the intolerance measurement, we cannot be certain if there was a change in FTOE when the infants began experiencing intolerance. The interim FTOE readings may have explained the FTOE readings obtained during feeding intolerance. It is unclear why there is a rSO2 signal drop out on the oximeter, particularly during the early measurements. It may be due to immature bowel with fewer capillaries for gas exchange or changes in vascular tone and blood flow. In times of hypotension, cerebral auto-regulation kicks in and protects the brain from hypoxia, thereby rendering other organs more susceptible to hypoxia and/or compromised blood flow.

Additionally, measuring baseline FTOE in the first 10 days of life may have been complicated by the presence of meconium. Meconium is dark and may have interfered with the accuracy of oxyhemoglobin and deoxyhemoglobin readings.

Missing nursing documentation was a limitation to collecting data for NeoNeeds, residuals and apnea/bradycardia/desaturation (ABD) events. Although there were reminders on the incubator, in the EMR, and in the bedside binder, there were times when residuals and NeoNeeds were not charted. Additionally, the ABD documentation sometimes had a comment reading “several desaturations per hour over the past 12 hours” rather than individual documentation of events. Thus, when recording events, the principal investigator chose either 10 or 20 based upon the comments in the documentation. Where there was no comment, the actual number of events documented was recorded. Even in this situation, some events go undocumented, so the true cardiorespiratory instability of the infant is difficult to ascertain.

Limitations of examining intrauterine and extrauterine variables are related to sample size. Data availability and accuracy were adequate and not a concern for this portion of the study. Although detailed data were collected, such as different types of maternal hypertension, the variables were reduced to two responses due to the small sample size. The likelihood of a Type 1 or Type 2 error is high due to the small number of infants experiencing feeding intolerance despite having repeated measures.

Another limitation was the lack of research staff to help monitor and collect the large amount of data generated in the study. Several times the PI was unable to meet face to face with the family to obtain consent within the desired timeframe. Due to the consent being required early in the infant’s life and maternal stress, the PI did not feel it appropriate to

attempt phone consent. Competing demands on nursing and new or rotating staff from other units sometimes compromised data collection, creating missing data. Technical difficulties with the oximeter itself were encountered, such as the memory filling up and stopping in a middle of a recording or the monitor becoming unplugged and not turned back on during a shift change also created some missing data. Attempting recruitment at a time when mothers are emotional and overwhelmed with what is usually an unexpected premature delivery is also challenging. The PI attempted to mitigate this by emphasizing the non-invasive nature of the study.

Implications for Future Research

Future research should include long-term monitoring of infants from birth to 34 weeks to further define normal or preferred ranges and determine whether or how soon NIRS can detect a change in intestinal function. Weekly or biweekly monitoring would be useful in recognizing patterns that are indicative of impending intolerance and allow the provider to establish a clear baseline for the infant through maturation. The development of a smaller NIRS oximeter sensor would be beneficial in localizing measurements in very small infants.

The utility of an early intestinal dysfunction tool is noteworthy and deserves more research regarding reliability and validity as well as inter-rater reliability testing. Scoring symptoms across several physiologic systems may provide a complete picture and help raise suspicions when infants begin showing more non-specific symptoms.

Future research should continue to examine factors related to pregnancy and the transition to extrauterine life. Although this study did not show significance in most of the variables investigated, the sample was small, and there is still a possibility that these factors impact future feeding intolerance. Researchers should continue to examine the role of enteral

feeds in transfusion-related NEC and the possibility of transfusion-related feeding intolerance and management. Identifying significant factors will allow researchers to investigate mitigating interventions. Feeding intolerance is a common occurrence in the premature population. Because it can be a symptom of life-threatening gastrointestinal complications it is a key area of neonatal research.

Appendix A

Neonatal Necrotizing Enterocolitis Early Detection Score (NeoNEEDS) Please score q8 hours

Parameter	Criteria & Score		Date/Time	Date/Time	Date/Time	Date/Time	Date/Time	Date/Time
Behavior	Appropriate	0						
	Drowsy. Decreased activity, but responds appropriately to stimulation.	1						
	Lethargic. Decreased activity with minimal response to stimulation.	2						
Cardiovascular	Capillary refill <2 sec HR btw 110-160 and MAPs stable.	0						
	Capillary refill <5 sec **OR** HR>160 for 1 hr **OR** MAP <10% from prior 24 hrs.	1						
	Capillary refill >5 sec **OR** HR>160 for 2 hr **OR** episode HR <100 **OR** MAP unstable requiring pressors.	2						
Respiratory	No Apnea/Desat episodes. No changes in current settings or RR rate.	0						
	Apnea/Desat self-limited **OR** RR >60 for 1 hr **OR** using accessory muscles **OR** increase periodic breathing **OR** increase FiO_2 level >10% from prior 24 hrs.	1						
	Apnea/Desat requiring stimulation/bagging **OR** increasing RR (ie ≥ 80) ± retractions **OR** increase respiratory support (ie increasing vent pressures or method of ventilation- such as change from nasal cannula to cpap).	2						
Abdominal	Soft, non-distended, non-tender, normoactive bowel sounds.	0						
	Slightly distended abdomen (1 cm from baseline) **OR** Hypoactive bowel sounds for 2 mins.	1						
	Distended abdomen (>3 cm from baseline) **OR** No bowel sounds for 5 mins **OR** guarding/tender **OR** heme + stools.	2						
Feeds	Not feeding **OR** tolerating bolus, *no residuals, no emesis.*	0						
	Emesis/Residuals >10% volume, partially digested.	1						
	Emesis/Residuals >20% volume **OR** discolored (bilious) residuals/emesis.	2						
Add 1 for each additional risk factor: a) BW < 1000g **OR** GA <28 wks ; b) Formula feeds								
	Total Score:							
	Initials:							

Scoring Directions (0 to 2)-

Score by starting with the most severe parameters first

Contact Provider for SCORE ≥5 OR Change in Baseline Score ≥2 for clinical assessment & consider ABD XR

Initials/ Signatures:

Participant

Neonatal Necrotizing Enterocolitis Early Detection Score (NeoNEEDS)

Appendix B

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE: Splanchnic oxygenation and feeding intolerance in the very low birthweight infant

VCU INVESTIGATORS: Melissa C. Dollings, PhD(c), RN, NNP-BC (804-814-5193) & Lisa F. Brown, PhD, RN (804-828-5114)

SPONSOR: Florida Association of Neonatal Nurse Practitioners and Sigma Theta Tau International

NOTE: If you are a parent or legal guardian, please remember that "you" refers to the parent and "your child" refers to the child study participant.

ABOUT THIS CONSENT FORM

You and your child are being invited to participate in a research study. **It is important that you carefully think about whether being in this study is right for you and your child and your situation.**

This consent form is meant to assist you in thinking about whether or not you and your child want to be in this study. **Please ask the investigator or the study staff to explain any information in this consent document that is not clear to you.** You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision. If you wish to participate, consent must be obtained prior to your baby's first feeding.

Participation in this research study is voluntary. You may decide not to allow your child to participate in this study. If your child does participate, you may withdraw your child from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you or your child are otherwise entitled.

AN OVERVIEW OF THE STUDY AND KEY INFORMATION

Why is this study being done?

The purpose of this research study is to learn more about how the oxygen levels in intestines of premature babies affects their ability to digest food. You are being asked to allow your child to participate in this study because your child was born premature.

Problems with digesting food can be a sign of a more serious disease call Necrotizing

Enterocolitis (an inflammation of the intestines). Findings from this study may help us tell the difference between Necrotizing Enterocolitis and digestive problems simply related to prematurity.

What will happen if I participate?

In the first few days after your baby begins receiving feeds, a small, light emitting probe will be placed on your child's abdomen to measure oxygen of the intestines. It will be kept in place for 24 hours and then removed. The next time it will be applied is when the doctors decide to stop the feeds due to your baby having difficulty digesting the feeds. At this time, the probe will remain in place between 24 and 48 hours depending upon the length of the feeding difficulties. The probe may be placed up to a total of 4 times during the study depending upon how your baby tolerates the feeds. The probes will not be placed more often than 2 times per week.

Your child will receive the usual care according to his or her age (in weeks) at birth. The only difference will be the addition of the probes to measure oxygen levels.

In this study, you (the parent) will be asked to do the following things:

1. Give permission for the researchers to collect information about your pregnancy history, your infant's hospitalization, and your and your infant's demographic information from your and your infant's medical records.

Your child's participation in this study will last up to the point when your child is 34 weeks from conception. This may be 2-8 weeks depending upon how early your child was born. Approximately 25 children and their mothers will participate in this study.

What are the risks and benefits of participating?

There are both risks and benefits of participating in research studies. We want you to know about a few key risks right now.

Risks and Discomforts	Benefits to You and Others
Risk of skin irritation from probe Participation in research might involve some loss of privacy. There is a small risk that someone outside the research study could see and misuse information about you.	This is not a treatment study, and your child is not expected to receive any direct medical benefits from your participation in the study. The information from this research study may lead to a better treatment in the future for premature babies.

WHAT ALTERNATIVE TREATMENTS OR PROCEDURES ARE AVAILABLE?

There are no alternative treatments or procedures available. If you decide not to enter this study, your child will still receive the usual care that he/she would receive even if he/she were in the study.

WHAT ARE THE COSTS?

There is no cost to you for your child's participation in this study.

CAN I STOP BEING IN THE STUDY?

You can stop your child's participation in this research study at any time. Leaving the study will not affect your child's medical care. Tell the study staff if you are thinking about stopping or decide to stop. Data collected prior to withdrawal may still be used by the investigators unless you request in person or by email to withdraw the data also.

Your participation in this study may be stopped at any time by the investigator without your consent. The reasons might include:

- Significant skin irritation from study probes
- administrative reasons require your withdrawal
- Significant illness

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

Identifiable information in these databases is not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed.

Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring, and overseeing this study:

 Representatives of VCU and the VCU Health System

Study Results

In general, we will not give you any individual results from the study. If we find something of medical importance to your child, we will inform you although we expect that this will be a very rare occurrence.

Future Research Studies

In the future, identifiers will be removed from the information collected during this study, and after that removal, the information could be used for other research studies by this study team or another researcher without asking you for additional consent.

HOW WILL MY HEALTH INFORMATION BE USED AND SHARED DURING THIS STUDY?

As part of this research study, we will ask you to share identifiable health information with us and/or permit us to access existing information from your healthcare records. New health information may also be created from study-related tests, procedures, visits, and/or questionnaires. This type of information is considered "Protected Health Information" that is protected by federal law.

What type of health information will be used or shared with others during this research?

The following types of information may be used for the conduct of this research:

☒ Complete health record	☒ Diagnosis & treatment codes	☐ Discharge summary History
☒ and physical exam	☐ Consultation reports	☒ Progress notes
☒ Laboratory test results X-	☒ ray reports X-ray films /	☒ images
☐ Photographs, videotapes	☐ Complete billing record	☐ Itemized bill
☒ Information about drug or alcohol abuse	☒ Information about Hepatitis B or C tests	
☐ Information about mental health	☒ Information about sexually transmitted diseases	
☐ Other physical or mental health information (specify):		

Who will use or share protected health information about me?

VCU and VCU Health are required by law to protect your identifiable health information. By consenting to this study, you authorize VCU/VCU Health to use and/or share your health information for this research. The health information listed above may be used by and/or shared with the following people and groups to conduct, monitor, and oversee the research:

- Principal Investigator and Research Staff
- Study Sponsor
- Health Care Providers at VCU Health
- Research Collaborators
- Institutional Review Boards
- Others as Required by Law

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

When will this authorization (permission) to use my protected health information expire? This authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

Statement of Privacy Rights

You may change your mind and revoke (take back) the right to use your protected health information at any time. However, even if you revoke this authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization, you may no longer be allowed to participate in the research study. To revoke this Authorization, you must contact the Principal Investigator at Melissa C. Dollings, 1213 E. Clay Street, PO box 985912, Richmond, VA 23219 or 804-814-5193 **WHOM SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?**

The investigator named below is the best person to contact if you have any questions, complaints, or concerns about your participation in this research: Melissa C. Dollings, PhD(c), RN, NNP-BC

By phone: 804-814-5193 or

By email: Dollingsmc@vcu.edu

If you have general questions about your rights as a participant in this or any other research, or if you wish to discuss problems, concerns or questions, to obtain information, or to offer input about research, you may contact:

Virginia Commonwealth University Office of Research
800 East Leigh Street, Suite 3000, Box 980568, Richmond, VA 23298
(804) 827-2157; https://research.vcu.edu/human_research/volunteers.htm

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

STATEMENT OF CONSENT AND PARENTAL/LEGAL GUARDIAN PERMISSION

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits to which my child otherwise would be entitled. My signature indicates that I freely consent and give permission for my child to participate in this research study. I will receive a copy of the consent form for my records.

Signature Block for Enrolling Adult Participants

_____
Adult Participant Name (Printed)

_____ _____
Adult Participant's Signature Date

_____
Name of Person Conducting Consent Discussion (Printed)

_____ _____ Signature of
Person Conducting Consent Discussion Date

_____ _____
Principal Investigator Signature (if different from above) Date

Signature Block for Enrolling Child Participants - Parent/Guardian Permission

_____
Name of Child/Youth Participant

_____
Name of First Parent/Legal Guardian (Printed)

_____ _____
Required First Parent/Legal Guardian Signature Date

_____ _____
Optional Second Parent /Legal Guardian's Signature Date

_____
Name of Person Conducting Parental Permission Discussion (Printed)

_____ _____ Signature of
Person Conducting Parental Permission Discussion Date

_____ _____

Principal Investigator Signature (if different from above)	Date

References

Akotia, D. H., Durham, J. T., Arnell, K. M., Petruzelli, D. L., & Katheria, A. C. (2016). Relationship between near-infrared spectroscopy and transabdominal ultrasonography: Noninvasive monitoring of intestinal function in neonates. *Medical Science Monitor*, *22*, 61–68. https://doi.org/10.12659/MSM.895730

Akotia, D. H., Durham, J. T., Arnell, K. M., Petruzzelli, D. L., & Katheria, A. C. (2016). Relationship Between Near-Infrared Spectroscopy and Transabdominal Ultrasonography: Noninvasive Monitoring of Intestinal Function in Neonates. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *22*, 61–68.

Bailey, S. M., Hendricks-Muñoz, K. D., & Mally, P. (2012). Splanchnic-cerebral oxygenation ratio as a marker of preterm infant blood transfusion needs. *Transfusion*, *52*(2), 252–260. https://doi.org/10.1111/J.1537-2995.2011.03263.X

Bailey, S. M., Hendricks-Munoz, K. D., & Mally, P. (2013). Splanchnic-cerebral oxygenation ratio (SCOR) values in healthy term infants as measured by near-infrared spectroscopy (NIRS). *Pediatric Surgery International*, *29*(6), 591–595. https://doi.org/10.1007/s00383-013-3285-9

Bailey, S. M., Hendricks-Munoz, K. D., & Mally, P. v. (2015). Variability in splanchnic tissue oxygenation during preterm red blood cell transfusion given for symptomatic anaemia may reveal a potential mechanism of transfusion-related acute gut injury. *Blood Transfusion = Trasfusione Del Sangue*, *13*(3), 429–434. https://doi.org/10.2450/2015.0212-14

Balegar V, K. K., Jayawardhana, M., Martin, A. J., de Chazal, P., & Nanan, R. K. H. (2020). Association of Bolus Feeding With Splanchnic and Cerebral Oxygen Utilization Efficiency Among Premature Infants With Anemia and After Blood Transfusion. *JAMA Network Open*, *3*(2), e200149. https://doi.org/10.1001/JAMANETWORKOPEN.2020.0149

Baserga, M. C., Gregory, G. A., & Sola, A. (2003). Cerebrovascular response in small preterm infants during routine nursery gavage feedings. *Biology of the Neonate*, *83*(1), 12–18. https://doi.org/10.1159/000067011

Baserga, M., Reich, B., & Braski, K. (2020). Abnormal Splanchnic Regional Saturations in a Preterm Infant That Developed Necrotizing Enterocolitis following a Red Blood Cell Transfusion. *Advances in Neonatal Care*, *20*(5), 401–405. https://doi.org/10.1097/ANC.0000000000000711

Bashiri, A., Zmora, E., Sheiner, E., Hershkovitz, R., Shoham-Vardi, I., & Mazor, M. (2003). Maternal hypertensive disorders are an independent risk factor for the development of necrotizing enterocolitis in very low birth weight infants. *Fetal Diagnosis and Therapy*, *18*(6), 404–407. https://doi.org/10.1159/000073132

Braski, K., Weaver-Lewis, K., Loertscher, M., Ding, Q., Sheng, X., & Baserga, M. (2017). Splanchnic-Cerebral Oxygenation Ratio Decreases during Enteral Feedings in Anemic Preterm Infants: Observations under Near-Infrared Spectroscopy. *Neonatology*, *113*(1), 75–80. https://doi.org/10.1159/000481396

Brooks, H. J. L., McConnell, M. A., & Broadbent, R. S. (2013). Microbes and the inflammatory response in necrotising enterocolitis. In O. Erez (Ed.), *Preterm Birth*. Open Access: InTech.

Carlson, B. (2014). *Human Embryology and Developmental Biology* (5th ed.). Elsevier.

Cerbo, R. M., Maragliano, R., Pozzi, M., Strocchio, L., Mostert, M., Manzoni, P., & Stronati, M. (2013a). Global perfusion assessment and tissue oxygen saturation in preterm infants: where are we? *Early Human Development*, *89 Suppl 1*, S44-6. https://doi.org/10.1016/S0378-3782(13)70014-8

Cerbo, R. M., Maragliano, R., Pozzi, M., Strocchio, L., Mostert, M., Manzoni, P., & Stronati, M. (2013b). Global perfusion assessment and tissue oxygen saturation in preterm infants: where are we? *Early Human Development*, *89 Suppl 1*, S44-6. https://doi.org/10.1016/S0378-3782(13)70014-8

Clarke-Pounder, J., Howlett, J., Burnsed, J., Donohue, P. K., Gilmore, M. M., & Aucott, S. W. (2015). Withholding feeding during transfusion: Standardization of practice and nutritional outcomes in premature infants. *Journal of Neonatal-Perinatal Medicine*, *8*(3), 199–205. https://doi.org/10.3233/NPM-15814113

Cortez, J., Gupta, M., Amaram, A., Pizzino, J., Sawhney, M., & Sood, B. G. (2011). Noninvasive evaluation of splanchnic tissue oxygenation using near-infrared spectroscopy in preterm neonates. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *24*(4), 574–582. https://doi.org/10.3109/14767058.2010.511335

Corvaglia, L., Martini, S., Battistini, B., Rucci, P., Aceti, A., & Faldella, G. (2014). Bolus vs. continuous feeding: Effects on splanchnic and cerebral tissue oxygenation in healthy preterm infants. *Pediatric Research*, *76*(1), 81–85. https://doi.org/10.1038/PR.2014.52

Corvaglia, L., Martini, S., Battistini, B., Rucci, P., Faldella, G., & Aceti, A. (2017). Splanchnic Oxygenation at First Enteral Feeding in Preterm Infants: Correlation With Feeding Intolerance. *Journal of Pediatric Gastroenterology and Nutrition*, *64*(4), 550–554. https://doi.org/10.1097/MPG.0000000000001308

Dani, C., Coviello, C., Montano, S., Remaschi, G., Petrolini, C., Strozzi, M. C., Maggiora, E., Sabatini, M., & Gazzolo, D. (2021). Effect on splanchnic oxygenation of breast milk, fortified breast milk, and formula milk in preterm infants. *Pediatric Research*, *89*(1), 171–174. https://doi.org/10.1038/s41390-020-0935-1

Dhingra, A., Agrawal, S. K., Kumar, P., & Narang, A. (2009). A randomised controlled trial of two feeding schedules in neonates weighing <or=1750 g. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *22*(3), 198–203. https://doi.org/10.1080/14767050802385749

du Plessis, A. J. (2009). The role of systemic hemodynamic disturbances in prematurity-related brain injury. *Journal of Child Neurology*, *24*(9), 1127–1140. https://doi.org/10.1177/0883073809339361

Elsayed, Y. N., & Fraser, D. (2017). Patent Ductus Arteriosus in Preterm Infants, Part 1: Understanding the Pathophysiologic Link Between the Patent Ductus Arteriosus and Clinical Complications. *Neonatal Network : NN*, *36*(5), 265–272. https://doi.org/10.1891/0730-0832.36.5.265

Fanaro, S. (2013). Feeding intolerance in the preterm infant. *Early Human Development*, *89 Suppl 2*, S13-20. https://doi.org/10.1016/j.earlhumdev.2013.07.013

Fortune, P. M., Wagstaff, M., & Petros, A. J. (2001). Cerebro-splanchnic oxygenation ratio (CSOR) using near infrared spectroscopy may be able to predict splanchnic ischaemia in neonates. *Intensive Care Medicine*, *27*(8), 1401–1407.

Fox, J. R., Thacker, L. R., & Hendricks-Munoz, K. D. (2015). Early Detection Tool of Intestinal Dysfunction: Impact on Necrotizing Enterocolitis Severity. *American Journal of Perinatology*, *32*(10), 927–932. https://doi.org/10.1055/s-0034-1543984

Freeman-Ladd, M., Cohen, J. B., Carver, J. D., & Huhta, J. C. (2005). The hemodynamic effects of neonatal patent ductus arteriosus shunting on superior mesenteric artery blood flow. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *25*(7), 459–462. https://doi.org/10.1038/sj.jp.7211294

Fullerton, B. S., Hong, C. R., Velazco, C. S., Mercier, C. E., Morrow, K. A., Edwards, E. M., Ferrelli, K. R., Soll, R. F., Modi, B. P., Horbar, J. D., & Jaksic, T. (2017). Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: A prospective cohort study. *Journal of Pediatric Surgery*. https://doi.org/10.1016/j.jpedsurg.2017.10.029

Ganapathy, V., Hay, J. W., & Kim, J. H. (2012). Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. *Breastfeeding Medicine : The Official Journal of the Academy of Breastfeeding Medicine*, *7*(1), 29–37. https://doi.org/10.1089/bfm.2011.0002

Gardner, S. L., Carter, B. S., Enzman-Hines, M. I., & Hernandez, J. A. (2015). *Merenstein & Gardner's Handbook of Neonatal Intensive Care*.

Gephart, S. M., McGrath, J. M., Effken, J. A., & Halpern, M. D. (2012). Necrotizing enterocolitis risk: state of the science. *Advances in Neonatal Care : Official Journal of the National Association of Neonatal Nurses*, *12*(2), 77–79. https://doi.org/10.1097/ANC.0b013e31824cee94

Gephart, S. M., Spitzer, A. R., Effken, J. A., Dodd, E., Halpern, M., & McGrath, J. M. (2014). Discrimination of GutCheck(NEC): a clinical risk index for necrotizing enterocolitis. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *34*(6), 468–475. https://doi.org/10.1038/jp.2014.37

Gephart, S. M., Wetzel, C., & Krisman, B. (2014). Prevention and early recognition of necrotizing enterocolitis: a tale of 2 tools--eNEC and GutCheckNEC. *Advances in Neonatal Care : Official Journal of the National Association of Neonatal Nurses*, *14*(3), 201–202. https://doi.org/10.1097/ANC.0000000000000063

Ghidini, A., Espada, R. A., & Spong, C. Y. (2001). Does exposure to magnesium sulfate in utero decrease the risk of necrotizing enterocolitis in premature infants? *Acta Obstetricia et Gynecologica Scandinavica*, *80*(2), 126–129.

Goldstein, G. P., Rao, A., Ling, A. Y., Ding, V. Y., Chang, I. J., & Chock, V. Y. (2020). Influence of enteral feeding and anemia on tissue oxygen extraction after red blood cell transfusion in preterm infants. *Transfusion*, *60*(3), 466–472. https://doi.org/10.1111/TRF.15680

Greisen, G. (2005). Autoregulation of cerebral blood flow in newborn babies. *Early Human Development*, *81*(5), 423–428. https://doi.org/10.1016/j.earlhumdev.2005.03.005

Hashem, R. H., Mansi, Y. A., Almasah, N. S., & Abdelghaffar, S. (2017). Doppler ultrasound assessment of the splanchnic circulation in preterms with neonatal sepsis at risk for

necrotizing enterocolitis. *Journal of Ultrasound*, *20*(1), 59–67. https://doi.org/10.1007/s40477-016-0228-z

Ilhan, O., & Bor, M. (2021). Effects of Caffeine on Splanchnic Oxygenation in Preterm Infants. *American Journal of Perinatology*, *38*(10), 1062–1069. https://doi.org/10.1055/S-0040-1701610

Kalteren, W. S., Kuik, S. J., van Braeckel, K. N. J. A., Hulscher, J. B. F., Bos, A. F., Kooi, E. M. W., & van der Laan, M. E. (2018). Red Blood Cell Transfusions Affect Intestinal and Cerebral Oxygenation Differently in Preterm Infants with and without Subsequent Necrotizing Enterocolitis. *American Journal of Perinatology*, *35*(11), 1031–1037. https://doi.org/10.1055/S-0038-1636532

Killion, E. (2021). Feeding practices and effects on transfusion-associated necrotizing enterocolitis in premature neonates. *Advances in Neonatal Care*, *21*(5), 356–364. https://doi.org/10.1097/ANC.0000000000000872

Krishnamurthy, S., Gupta, P., Debnath, S., & Gomber, S. (2010). Slow versus rapid enteral feeding advancement in preterm newborn infants 1000-1499 g: a randomized controlled trial. *Acta Paediatrica (Oslo, Norway : 1992)*, *99*(1), 42–46. https://doi.org/10.1111/j.1651-2227.2009.01519.x

Kuik, S. J., Kalteren, W. S., Mebius, M. J., Bos, A. F., Hulscher, J. B. F., & Kooi, E. M. W. (2020). Predicting intestinal recovery after necrotizing enterocolitis in preterm infants. *Pediatric Research*, *87*(5), 903–909. https://doi.org/10.1038/S41390-019-0634-Y

Kuik, S. J., van Zoonen, A. G. J. F., Bos, A. F., van Braeckel, K. N. J. A., Hulscher, J. B. F., & Kooi, E. M. W. (2019). The effect of enteral bolus feeding on regional intestinal oxygen saturation

in preterm infants is age-dependent: A longitudinal observational study. *BMC Pediatrics*, *19*(1). https://doi.org/10.1186/S12887-019-1805-Z

le Bouhellec, J., Prodhomme, O., Mura, T., Jacquot, A., Combes, C., Gamon, L., Durand, S., Filleron, A., & Cambonie, G. (2021). Near-Infrared Spectroscopy: A Tool for Diagnosing Necrotizing Enterocolitis at Onset of Symptoms in Preterm Neonates with Acute Gastrointestinal Symptoms? *American Journal of Perinatology*, *38*, E299–E308. https://doi.org/10.1055/S-0040-1710033

Ledo, A., Aguar, M., Núñez-Ramiro, A., Saénz, P., & Vento, M. (2017). Abdominal Near-Infrared Spectroscopy Detects Low Mesenteric Perfusion Early in Preterm Infants with Hemodynamic Significant Ductus Arteriosus. *Neonatology*, *112*(3), 238–245. https://doi.org/10.1159/000475933

Longin, E., Gerstner, T., Schaible, T., Lenz, T., & Konig, S. (2006). Maturation of the autonomic nervous system: differences in heart rate variability in premature vs. term infants. *Journal of Perinatal Medicine*, *34*(4), 303–308. https://doi.org/10.1515/JPM.2006.058

Lucchini, R., Bizzarri, B., Giampietro, S., & de Curtis, M. (2011). Feeding intolerance in preterm infants. How to understand the warning signs. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *24 Suppl 1*, 72–74. https://doi.org/10.3109/14767058.2011.607663

Marin, T., Moore, J., Kosmetatos, N., Roback, J. D., Weiss, P., Higgins, M., McCauley, L., Strickland, O. L., & Josephson, C. D. (2013). Red blood cell transfusion-related necrotizing

enterocolitis in very-low-birthweight infants: a near-infrared spectroscopy investigation. *Transfusion*, *53*(11), 2650–2658. https://doi.org/10.1111/trf.12158

Marin, T., & Strickland, O. L. (2013). Transfusion-related necrotizing enterocolitis: a conceptual framework. *Advances in Neonatal Care : Official Journal of the National Association of Neonatal Nurses*, *13*(3), 166–174. https://doi.org/10.1097/ANC.0b013e318285f901

Martini, S., Aceti, A., Beghetti, I., Faldella, G., & Corvaglia, L. (2018). Feed-related Splanchnic Oxygenation in Preterm Infants with Abnormal Antenatal Doppler Developing Gut Complications. *Journal of Pediatric Gastroenterology and Nutrition*, *66*(5), 755–759. https://doi.org/10.1097/MPG.0000000000001804

Martini, S., & Corvaglia, L. (2018). Splanchnic NIRS monitoring in neonatal care: Rationale, current applications and future perspectives. *Journal of Perinatology*, *38*(5), 431–443. https://doi.org/10.1038/S41372-018-0075-1

Martini, S., Corvaglia, L., Aceti, A., Vitali, F., Faldella, G., & Galletti, S. (2019). Effect of Patent Ductus Arteriosus on Splanchnic Oxygenation at Enteral Feeding Introduction in Very Preterm Infants. *Journal of Pediatric Gastroenterology and Nutrition*, *69*(4), 493–497. https://doi.org/10.1097/MPG.0000000000002420

Martini, S., Spada, C., Aceti, A., Rucci, P., Gibertoni, D., Battistini, B., Arcuri, S., Faldella, G., & Corvaglia, L. (2020). Red blood cell transfusions alter splanchnic oxygenation response to enteral feeding in preterm infants: an observational pilot study. *Transfusion*, *60*(8), 1669–1675. https://doi.org/10.1111/TRF.15821

Massa-Buck, B., Amendola, V., McCloskey, R., & Rais-Bahrami, K. (2017). Significant Correlation between Regional Tissue Oxygen Saturation and Vital Signs of Critically Ill Infants. *Frontiers in Pediatrics*, *5*, 276. https://doi.org/10.3389/fped.2017.00276

Mefford, L. C. (2004). A theory of health promotion for preterm infants based on Levine's Conservation Model of Nursing. *Nursing Science Quarterly*, *17*(3), 260–266. https://doi.org/10.1177/0894318404266327

Mintzer, J. P., Parvez, B., & la Gamma, E. F. (2018). Regional Tissue Oxygen Extraction and Severity of Anemia in Very Low Birth Weight Neonates: A Pilot NIRS Analysis. *American Journal of Perinatology*, *35*(14), 1411–1418. https://doi.org/10.1055/S-0038-1660458

Moore, J. E. (2013). Newer monitoring techniques to determine the risk of necrotizing enterocolitis. *Clinics in Perinatology*, *40*(1), 125–134. https://doi.org/10.1016/j.clp.2012.12.004

Moore, T. A., & Pickler, R. H. (2017). Feeding intolerance, inflammation, and neurobehaviors in preterm infants. *Journal of Neonatal Nursing*, *23*(3), 134–141. https://doi.org/10.1016/j.jnn.2016.09.009

Moore, T. A., & Wilson, M. E. (2011). Feeding intolerance: a concept analysis. *Advances in Neonatal Care : Official Journal of the National Association of Neonatal Nurses*, *11*(3), 149–154. https://doi.org/10.1097/ANC.0b013e31821ba28e

Mowitz, M. E., Dukhovny, D., & Zupancic, J. A. F. (2018). The cost of necrotizing enterocolitis in premature infants. *Seminars in Fetal & Neonatal Medicine*, *23*(6), 416–419. https://doi.org/10.1016/J.SINY.2018.08.004

Muller, M. J., Paul, T., & Seeliger, S. (2016). Necrotizing enterocolitis in premature infants and newborns. *Journal of Neonatal-Perinatal Medicine*, *9*(3), 233–242. https://doi.org/10.3233/NPM-16915130

Munshi, U. K., & Clark, D. A. (2017). Development of the Gastrointestinal Circulation of the Fetus and the Newborn. In *Fetal and Neonatal Physiology* (5th ed., pp. 555–559). Elsevier.

Nankervis, C. A., Giannone, P. J., & Reber, K. M. (2008). The neonatal intestinal vasculature: contributing factors to necrotizing enterocolitis. *Seminars in Perinatology*, *32*(2), 83–91. https://doi.org/10.1053/j.semperi.2008.01.003

Necrotizing enterocolitis | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. (n.d.). Retrieved February 27, 2022, from https://rarediseases.info.nih.gov/diseases/9767/disease

Neu, J. (2007). Gastrointestinal development and meeting the nutritional needs of premature infants. *The American Journal of Clinical Nutrition*, *85*(2), 629S-634S. https://doi.org/10.1093/ajcn/85.2.629S

Neu, J., & Walker, W. A. (2011). Necrotizing enterocolitis. *The New England Journal of Medicine*, *364*(3), 255–264. https://doi.org/10.1056/NEJMra1005408

Ogunyemi, D., Murillo, M., Jackson, U., Hunter, N., & Alperson, B. (2003). The relationship between placental histopathology findings and perinatal outcome in preterm infants. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *13*(2), 102–109. https://doi.org/10.1080/jmf.13.2.102.109

Osterman, M. J. K., Hamilton, B. E., Martin, J. A., Driscoll, A. K., & Valenzuela, C. P. (2022). Births: Final Data for 2020 Figure 1. Live births and general fertility rates: United States. *National Vital Statistics Reports*, *70*(17). https://www.cdc.gov/nchs/products/index.htm.

Özkan, H., Çetinkaya, M., Dorum, B. A., & Köksal, N. (2021). Mesenteric tissue oxygenation status on the development of necrotizing enterocolitis. *Turkish Journal of Pediatrics*, *63*(5), 811–817. https://doi.org/10.24953/TURKJPED.2021.05.009

Palleri, E., Wackernagel, D., Wester, T., & Bartocci, M. (2020). Low Splanchnic Oxygenation and Risk for Necrotizing Enterocolitis in Extremely Preterm Newborns. *Journal of Pediatric Gastroenterology and Nutrition*, *71*(3), 401–406. https://doi.org/10.1097/MPG.0000000000002761

Parker, L., Torrazza, R. M., Li, Y., Talaga, E., Shuster, J., & Neu, J. (2015). Aspiration and evaluation of gastric residuals in the neonatal intensive care unit: state of the science. *The Journal of Perinatal & Neonatal Nursing*, *29*(1), 51–59; quiz E2. https://doi.org/10.1097/JPN.0000000000000080

Patel, A. K., Lazar, D. A., Burrin, D. G., Smith, E. O., Magliaro, T. J., Stark, A. R., Brandt, M. L., Zamora, I. J., Sheikh, F., Akinkuotu, A. C., & Olutoye, O. O. (2014). Abdominal near-infrared spectroscopy measurements are lower in preterm infants at risk for necrotizing enterocolitis. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, *15*(8), 735–741. https://doi.org/10.1097/PCC.0000000000000211

Riskin, A., Cohen, K., Kugelman, A., Toropine, A., Said, W., & Bader, D. (2017). The Impact of Routine Evaluation of Gastric Residual Volumes on the Time to Achieve Full Enteral

Feeding in Preterm Infants. *The Journal of Pediatrics*, *189*, 128–134. https://doi.org/10.1016/j.jpeds.2017.05.054

Romejko-Wolniewicz, E., Oleszczuk, L., Zareba-Szczudlik, J., & Czajkowski, K. (2013). Dosage regimen of antenatal steroids prior to preterm delivery and effects on maternal and neonatal outcomes. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *26*(3), 237–241. https://doi.org/10.3109/14767058.2012.733758

Sahin, S., Gozde Kanmaz Kutman, H., Bozkurt, O., Yavanoglu Atay, F., Emre Canpolat, F., Uras, N., Suna Oguz, S., & Underwood, M. A. (2020). Effect of withholding feeds on transfusion-related acute gut injury in preterm infants: a pilot randomized controlled trial. *Journal of Maternal-Fetal and Neonatal Medicine*, *33*(24), 4139–4144. https://doi.org/10.1080/14767058.2019.1597844

Schat, T. E., van Zoonen, A. G. J. F., van der Laan, M. E., Mebius, M. J., Bos, A. F., Hulzebos, C. v., Boezen, H. M., Hulscher, J. B. F., & Kooi, E. M. W. (2019). Early cerebral and intestinal oxygenation in the risk assessment of necrotizing enterocolitis in preterm infants. *Early Human Development*, *131*, 75–80. https://doi.org/10.1016/J.EARLHUMDEV.2019.03.001

Sharma, R., & Hudak, M. L. (2013). A clinical perspective of necrotizing enterocolitis: past, present, and future. *Clinics in Perinatology*, *40*(1), 27–51. https://doi.org/10.1016/j.clp.2012.12.012

Sherman, M. P. (2010). New concepts of microbial translocation in the neonatal intestine: mechanisms and prevention. *Clinics in Perinatology*, *37*(3), 565–579. https://doi.org/10.1016/j.clp.2010.05.006

Shimada, S., Kasai, T., Hoshi, A., Murata, A., & Chida, S. (2003). Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. *Pediatrics International : Official Journal of the Japan Pediatric Society*, *45*(3), 255–262.

Smith, A., Armstrong, S., Dempsey, E., & EL-Khuffash, A. (2022). The impact of a PDA on tissue oxygenation and haemodynamics following a blood transfusion in preterm infants. *Pediatric Research*. https://doi.org/10.1038/S41390-022-01967-3

Smith, L. M., Qureshi, N., & Chao, C. R. (2000). Effects of single and multiple courses of antenatal glucocorticoids in preterm newborns less than 30 weeks' gestation. *The Journal of Maternal-Fetal Medicine*, *9*(2), 131–135. https://doi.org/10.1002/(SICI)1520-6661(200003/04)9:2<131::AID-MFM9>3.0.CO;2-M

Torrazza, R. M., Parker, L. A., Li, Y., Talaga, E., Shuster, J., & Neu, J. (2015). The value of routine evaluation of gastric residuals in very low birth weight infants. *Journal of Perinatology : Official Journal of the California Perinatal Association*, *35*(1), 57–60. https://doi.org/10.1038/jp.2014.147

van der Heide, M., Hulscher, J. B. F., Bos, A. F., & Kooi, E. M. W. (2021). Near-infrared spectroscopy as a diagnostic tool for necrotizing enterocolitis in preterm infants. *Pediatric Research*, *90*(1), 148–155. https://doi.org/10.1038/S41390-020-01186-8

Vesoulis, Z. A., & Mathur, A. M. (2017). Cerebral Autoregulation, Brain Injury, and the Transitioning Premature Infant. *Frontiers in Pediatrics*, *5*, 64. https://doi.org/10.3389/fped.2017.00064

Weaver, B., Guerreso, K., Conner, E. A., Russell, K., Vogel, R., & Rodriguez, M. (2018). Hemodynamics and perfusion in premature infants during transfusion. *AACN Advanced Critical Care*, *29*(2), 126–137. https://doi.org/10.4037/AACNACC2018402

Wynn, J. L., & Wong, H. R. (2010). Pathophysiology and treatment of septic shock in neonates. *Clinics in Perinatology*, *37*(2), 439–479. https://doi.org/10.1016/j.clp.2010.04.002

Zhong, J., Lui, K., & Schindler, T. (2019). The Effect of Continuous Positive Airway Pressure on Cerebral and Splanchnic Oxygenation in Preterm Infants. *Neonatology*, *116*(4), 363–368. https://doi.org/10.1159/000501936