4-7-2016

Exploring the Relationship Between Severity of Illness and Human Milk Volume in Very Low Birth Weight and Extremely Low Birth Weight Infants Over Six Weeks

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Exploring the Relationship Between Severity of Illness and Human Milk Volume in Very Low Birth Weight and Extremely Low Birth Weight Infants Over Six Weeks

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Nursing
with a concentration in Nursing Science
College of Nursing
University of South Florida

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Date of Approval:
April 7, 2016

Keywords: Mother's Own Milk, Donor Human Milk, Score for Neonatal Acute Physiology, Premature Infants, Multilevel Modeling

DEDICATION

One does not complete a doctoral dissertation without the help and support from many individuals. Therefore, I would like to dedicate this work to the many special people that have supported me over many years and made this day possible.

First, I would like to dedicate this accomplishment to my ***family***! Without your love, support, and encouragement, I would not be completing this doctoral journey. Mom, did you realize that you were actually the first person to teach me how to research when you were a graduate student at the University of Alabama? Thank you for teaching me to value education and believing that I could actually achieve this goal! Dad and Mava, thank you for always believing in me and encouraging me to keep striving for the goal! Aleida, my big sister, thank you for proofreading every paper I've ever written and for your daily support handling so many 'life details' so that I had time for schoolwork. Aunt Pearl, thank you for my 'daily dose' of encouragement (via text message) as I pushed hard to finish during the last 2 ½ months of the journey! Hope, thank you for my many encouraging text messages along the journey as well! Eric, thank you for always being just a phone call away when I needed anything and everything! To the Bailey Bunch, thank you for your support! I wish I could name each person here as you each have all played a special part in this day. Please know that I am so grateful for each one of you and that I love you!

I also owe a huge debt of gratitude to my ***friends and colleges*** for their support and encouragement. LiTing, I am so grateful that God saw fit to have our paths cross so that we could travel this educational journey together. I am certain I would not have made it through to completion without your friendship and tutoring! God has given you a special gift when it comes to understanding statistics and I am so grateful for the MANY times that you allowed me to talk and ask questions until the "muddy water" became clear and I had an "ah-ha!" moment! Jessie, my fellow USF breastfeeding advocate, I'm so blessed that we journeyed together through both graduate degrees! I would also like to dedicate this dissertation to my nursing colleagues at Rasmussen College. You are a phenomenal group of nursing educators and I am so blessed to work with you each day! Kim Barnett, I would specifically like to dedicate this work to you as you valued nursing education and continued on your doctoral nursing education journey amidst great obstacles. You helped me to push forward each time the journey became tough! So, I am finishing my degree in your honor. You are dear to my heart and I miss you so! Jennifer Cowherd, you made this day possible in so many ways, I am so blessed that God brought us together as friends and colleagues. I would also like to give a special recognition to Dr. Kelly McCullough, Dean of Nursing at Rasmussen College, New Port Richey. Words cannot adequately express how much I appreciate the many ways that you have supported me over the past four years on this doctoral education journey. I would not be here today without you! I'm so blessed to have you as my Dean of Nursing and my friend! I would also like to dedicate this work to my AWHONN (Association of Women's Health, Obstetric and Neonatal Nurses) colleagues. It is my joy and privilege to work with such a passionate group of nursing leaders at the local, state, and national level that desire to impact the care of women and newborns. I would also like to thank my many friends that have been praying for me throughout

this journey including: Vivian Coates, Carrie Liddell, Gloria Skiles, Tina Valdez, Denise Peterson, Diane Avriett, Jan Bailie, Terry Doyle, USF NP grad friends, and many more from my church family at First Baptist Church of Land O' Lakes! Your prayers and support mean more to me than words can express! Finally, I would like to dedicate this work to the nurses and midwives, from East Pasco Medical Center (now Florida Hospital Zephyrhills) that took me under their wings when I was a brand new graduate nurse. So many nurses influenced me as a new graduate, but I would especially like to thank Madeline Beaumont for believing in me and hiring me as a new graduate nurse! I would also like to thank Rita Watson, Andree Landry, and Lois Bineshtarigh as they served as my preceptors and taught me how to successfully transition from a student nurse to an RN. In addition, I would like to express gratitude to Delrose Brown, Joanie Turner, and Marie McCord, three wonderful midwives who served as mentors to me at the beginning of my nursing journey and beyond. I know I always asked a thousand questions and I thank you for always patiently answering every single one of them! Guess what? I'm still asking questions, and now I am equipped to conduct nursing research that can provide new evidence for the questions that nurses ask each day as we care for our patients.

I would also like to dedicate this work to the ***educators*** that have been influential throughout my nursing career. Dr. Barbara Redding and Dr. Susan McMillan, your passion for nursing education and your genuine interest in your students is inspirational! I want my students to look up to me the way that I have always looked up to each of you! Dr. Frances Rankin, you have been a role model for me since the day you completed my health history and physical to enter nursing school in 1997. I was blessed to be a patient first and subsequently your student! Dr. Cecilia Jevitt, thank you for the many ways that you have influenced my career over the years

including: helping me to get hired for my first nursing job, getting published for the first time as a co-author with you, and especially for planting the seed about this doctoral journey. A wise woman, you, once told me that all nurses that have earned a Ph.D. do not love to write or find the task easy; yet they place enough importance on the task to take the time to pass along knowledge to grow the profession of nursing. Dr. Jason Beckstead, thank for always answering my statistics questions again and again. Dr. Allison Edmonds-Poff, Dr. Denise Passmore, and Dr. Joan Gregory, thank you for watering that seed that Dr. Jevitt planted and encouraging me to continue on this educational journey.

I would also like to dedicate this work to my ***students***. Certainly my career path demonstrates life long learning. My desire is that this personal achievement will help me to be a better nurse educator. I also hope that it inspires some of you to continue your educational pursuits and achieve goals and dreams that you didn't think was possible!

Finally, I would like to dedicate this dissertation to my ***Savior, Jesus Christ***. Ultimately this day belongs to you as you gave me abilities beyond my natural abilities to accomplish the tasks set before me. "…My grace is sufficient for thee: for my strength is made perfect in weakness. Most gladly therefore will I rather glory in my infirmities, that the power of Christ may rest upon me" II Corinthians 12: 9. My prayer is that this educational pursuit can be used for Your Glory! Ultimately, I want my life to count for YOU! You have blessed me with talents as a nurse and it is my greatest desire to use these talents to make a difference in the world.
"And of some have compassion, making a difference:" Jude 1:22

ACKNOWLEDGMENTS

I would like to extend my heartfelt thanks to my doctoral committee: Dr. Maureen Groer, Dr. Melissa Shelton, Dr. Denise Maguire, and Dr. Terri Ashmeade. I am so thankful for how each of you have supported me through candidacy and the dissertation process. Your willingness to provide robust, detailed, and quick feedback along this educational journey has helped me to grow and to finish strong! This day would not be possible without each one of you. Thank you!

I would also like to thank Dr. Eun Sook Kim for sharing your passion and expertise of multilevel modeling. Thank you so much for giving of your time to meet with me and answer so many of my questions as I worked on the data analysis. I would not be here without your guidance.

Finally, I would like to extend a special thanks to Dr. Maureen Groer, my major professor, for mentoring me during my doctoral education journey. I am so grateful for the many opportunities that you afforded me including: working as your research assistant on the NICU MOM study (parent study for this dissertation research), presenting posters with you at the 2014 Experimental Biology conference, and the 2015 International Society of Research on Human Milk and Lactation conference, and ultimately being published twice during my tenure in the doctoral program. I will always be grateful to you!

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ABSTRACT

Very low birth weight and extremely low birth weight neonates have tremendous risk of mortality. This is a grave concern; however, survival alone is not the goal of neonatal intensive care. Survival, along with a reduction or elimination of life long morbidity is the aim of neonatal intensive care.

Human milk is known as the best nutrition for babies and a growing body of evidence supports that human milk is critical in helping these fragile neonates mitigate the overwhelming risks they face. Therefore, the purpose of this study was to examine the relationship between neonatal severity of illness and human milk, specifically mothers own milk (MOM), donor human milk (DHM), and total human milk (THM) intake in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants over the first six weeks of life. Although there is a growing body of evidence that supports the use of human milk in this fragile neonatal population, information is lacking about the relationship between human milk and neonatal illness severity.

The current study was a secondary data analysis from a National Institutes of Health (NIH) funded R21 study in a level three NICU in Florida. Multilevel modeling was used for data analysis to examine relationships between maternal dyad characteristics and severity of illness, operationalized by the Score for Neonatal Acute Physiology-II (SNAP-II), at 12 hours of life and at the end of each week of life for six weeks.

Growth models (linear, quadratic, piecewise) were examined to determine the best model fit for the data, then predictor variables were added and model fit was tested. Birth weight was added to final models as a control as it is seen as a proxy for severity of illness in the literature. Model six demonstrated a significant inverse relationship between MOM(mL) ($\gamma_{MOM(mL)}$) = -.000079, $p < .05$) and SNAP-II scores (Deviance = 287.862, $\Delta\chi^2(df) = 31.38(1)$, $p < .001$, AIC = 303.862, BIC = 336.930). Model 11 demonstrated a significant inverse relationship between THM(mL) ($\gamma_{THM(mL)}$ = -.000127, $p < .001$) and SNAP-II scores (Deviance = 279.280, $\Delta\chi^2(df) = 30.859(1)$, $p < .001$, AIC = 295.280, BIC = 328.347). No relationships were noted between severity of illness and DHM(mL), MOM(%), DHM(%), or THM(%). Therefore the relationships noted between MOM(mL) and THM(mL) and neonatal severity of illness should be interpreted with caution.

CHAPTER ONE

INTRODUCTION

Very low birth weight (VLBW) and extremely low birth weight (ELBW) infants are among the most vulnerable populations cared for in the Neonatal Intensive Care Unit (NICU) (Sehgal, Osborn, & McNamara, 2012). These fragile infants are plagued with increased risk of morbidity and mortality as compared to infants with a normal birth weight. Risk of morbidity associated with decreased birth weight begins when neonates are born weighing less than 2,500 grams, categorized as low birth weight (LBW). Furthermore, risk of morbidity and mortality increases as the birth weight decreases. Therefore the category of LBW has been further subdivided into very low birth weight (less than 1,500 grams) and extremely low birth weight (less than 1,000 grams).

In 2013 and 2014, very low birth weight (VLBW) newborns accounted for 1.4% of births in the United States. Specifically, 0.73% of neonates were between 1,000 – 1,499 grams and an additional 0.67% of neonates were less than 1,000 grams at birth (ELBW) (Hamilton, Martin, Osterman, Curtin, & Matthews, 2015; Martin, Hamilton, Osterman, Curtin, & Matthews, 2015). In the state of Florida, the 2014 prevalence rate of VLBW newborns was 1.6%, which is a slight increase from the 2013 prevalence rate of 1.54%. Specifically in Hillsborough county, the 2014 VLBW prevalence rate was 1.5% and this was decreased from 1.71% in 2013 (*Florida Community Health Assesment Resource Tool Set*, 2013; *Florida Community Health Assesment Resource Tool Set*, 2014). The healthy People 2020 target is a VLBW prevalence rate of 1.4% or less. Although Florida missed this target in 2013 and 2014, they did achieve this goal in 2000,

2001, 2004, and 2009 (Yu). Overall, the trending of VLBW has remained fairly consistent since 2000 (Yu). Clearly, the literature and use of birth weight in statistical trends supports birth weight as a powerful predictor of infant health or lack thereof (Mathews & MacDorman, 2010, 2012, 2013).

When considering care for these fragile infants, one must consider the cost for the provision of care in the NICU. Intensive care is expensive for any population, and the NICU is no exception. A recent study demonstrated that societal costs for NICU care ranges from $114,000 - $225,000 with a lifetime cumulative cost estimated at $450,000 (Meadow et al., 2012). A better emphasis may be on the efficiency of neonatal intensive care. Doyle (2004b) noted that although NICU care was expensive, it was efficient in the use of monetary resources. Another point of interest is that NICU care has improved the survival rate from 25% in 1979 to 73% in 1997 (Doyle, 2004a).

Infant mortality rate is defined as the number of infants dying during the first year of life per 1,000 live births per year. For example, the total infant mortality rate in the United States (US) was 6.61 in 2008 and 6.39 in 2009. However, the infant mortality rate for VLBW infants for 2008 and 2009 was significantly higher at 237.39 and 231.23 respectively (Mathews & MacDorman, 2012, 2013). This indicates that VLBW infants are more than 100 times more likely to die as compared to infants born at normal weights (Mathews & MacDorman, 2012, 2013). Newborns weighing less than 500 grams are even more fragile. Mathews and MacDorman noted that 85% (2013) – 87% (2012) died within infancy.

VLBW and ELBW infants are also at risk for many serious illnesses. Some of the most common neonatal/infant morbidities in this population include: sepsis, necrotizing enterocolitis (NEC) (Romieu, Werneck, Ruiz Velasco, White, & Hernandez, 2000), intracranial hemorrhage

(IVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP) (Horodynski et al., 2007) (Ambalavanan et al., 2012). Due to the increased risk of morbidity and mortality, these neonates are assessed at birth and frequently throughout their NICU admission for signs and symptoms that alert clinicians to the severity or degree of illness for these neonates. The concept of neonatal illness severity seeks to describe how acutely ill the neonate is at that moment in time as well as to provide some prediction for future morbidity and mortality risk for the neonate. This concept has been operationalized by various instruments including: Score for Neonatal Acute Physiology (SNAP) (Richardson, Gray, McCormick, Workman, & Goldmann, 1991), Score for Neonatal Acute Physiology-II (SNAP-II) (Richardson, Corcoran, Escobar, & Lee, 2001), Score for Neonatal Acute Physiology-Perinatal Extension (SNAP+PE) (Richardson, Phibbs, et al., 1993), Score for Neonatal Acute Physiology- Perinatal Extension – II (SNAP+PE-II) (Richardson et al., 2001), Severity of Illness Scoring System (SISS), Clinical Risk Index for Babies (CRIB), and the Sinkin Score at 12 hours of life (SS_{12}) (Fleisher et al., 1997). Although the various illness severity scores are calculated using data from individual babies, the current literature supports using illness severity scores at the population level versus the individual patient level for outcome predictions. Therefore currently, the greatest utilization of illness severity scores in the literature has been to control for illness severity at birth when comparing mortality rates, morbidity rates, and quality care indicators between and among NICUs. Without controlling for the degree of illness severity upon admission, statistical comparison data may be misleading. However, utilizing illness severity scores may be useful to the clinician at the bedside as well as the researcher. The major advantage to utilizing an illnesses severity tool versus individual physical assessment and clinical judgment is that an instrument will assist the individual in gathering more objective data. This in turn may help to improve the validity and

reliability of the data and therefore yield more useful information for the researcher and clinician.

One area of promising research is focused on the provision of human milk and the potential for neonatal health outcome improvement. Human milk is known as the optimal and natural source of nutrition for all infants (Chung, Raman, Trikalinos, Lau, & Ip, 2008; de Jager, Skouteris, Broadbent, Amir, & Mellor, 2012; Ip, Chung, Raman, Trikalinos, & Lau, 2009). Specifically, the American Academy of Pediatrics (AAP) recommends human milk as the optimal nutrition for high-risk neonates (Eidelman & Schanler, 2012; Gartner et al., 2005). Benefits of human milk for these fragile infants may include: decreased risk of sepsis (Corpeleijn et al., 2012), decreased necrotizing enterocolitis (Corpeleijn et al., 2012; Cristofalo et al., 2013), decreased retinopathy of prematurity (Okamoto et al., 2007), decreased hospital re-admissions (Vohr et al., 2007; Vohr et al., 2006), decreased neurodevelopmental disabilities (Vohr et al., 2007; Vohr et al., 2006), quicker attainment of full enteral feeding (Eidelman & Schanler, 2012; Schanler, 2007, 2011; Vohr et al., 2007) and earlier hospital discharge (Vohr et al., 2007).

Statement of the Problem

Human milk is known to provide benefits to very low birth weight and extremely low birth weight infants; however, there is still a high rate of mortality and morbidity among these vulnerable populations. Information is lacking in understanding the dose dependent relationship that human milk has on mitigating illness severity in this vulnerable population. The purpose of this study is to examine the relationship between the severity of illness and human milk (mother's own milk and donor human milk) volume intake in very low birth weight and extremely low birth weight infants over the first six weeks of life.

Research Questions

This study addressed the following questions:

1. What is the relationship between mothers own milk (MOM) intake and neonatal severity of illness for very low birth weight and extremely low birth weight infants over the first six weeks of life?
2. What is the relationship between donor human milk (DHM) intake and neonatal severity of illness for very low birth weight and extremely low birth weight infants over the first six weeks of life?
3. What is the relationship between total human milk intake (THM) (combined total of MOM and DHM) and neonatal severity of illness for very low birth weight and extremely low birth weight infants over the first six weeks of life?

Definition of Relevant Terms

For the purpose of this study, the following terms are defined:

Very low birth weight – Newborns weighing less than 1500 grams at birth.

Extremely low birth weight – Newborns weighing less than 1000 grams at birth.

Infancy – The first year of life.

Infant mortality rate - The number of infants dying during the first year of life per 1,000 live births per year in the United States.

Lactogenesis Stage II - The onset of mature milk production.

Preterm Human Milk – Human milk produced by a mother that delivered her baby prior to 37 completed weeks of gestation.

Preterm Neonate – A baby that is born prior to 37 completed weeks of gestation.

Total Human Milk Volume – The combined volume of mother's own milk and donor human milk reported in milliliters (mL).

Significance to Nursing

Human milk is known to provide the most optimal nutrition for VLBW and ELBW infants (Eidelman & Schanler, 2012). However, nurse scientists are still seeking to understand more about the volume of human milk intake required to produce statistically significant differences in severity of illness for VLBW and ELBW infants. This study seeks to gain additional supporting data to help nurse scientists to understand the relationship between human milk volume intake and severity of illness. Known thresholds will help nurses to encourage mothers to reach at least these minimal goals. The impact of this study will benefit the infant as well as the entire family. A NICU admission is an extremely stressful event for a new mother. The knowledge that a mother's milk may potentially achieve better health outcomes for her baby can be encouraging during this most distressing time.

CHAPTER TWO

REVIEW OF LITERATURE

Chapter two begins with a discussion of the conceptual framework utilized to construct the proposed secondary data analysis. This is followed by an extensive literature review that was conducted using search engines including: PubMed, Web of Knowledge, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Database. Search terms in the literature review included: very low birth weight infants, extremely low birth weight infants, extreme prematurity, gestational age, human milk, donor human milk, maternal infection, antenatal steroids, severity of illness, score for neonatal acute physiology, mean blood pressure, temperature instability, partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO_2/FIO_2), oxygenation, respiratory instability, hemodynamic instability, serum pH, acid-base balance, seizures, urine output, and renal injury/failure.

Conceptual Framework

Very low birth weight and extremely low birth weight neonates are some of the most fragile patients among the NICU population (Blencowe et al., 2012). Nutritional support for this fragile patient population is a major focus of care in the NICU. Human milk is known to be the best source of nutrition for infants and is particularly beneficial for acutely ill neonates (Bhatia, 2013; Chung et al., 2008; de Jager et al., 2012; Eidelman & Schanler, 2012; Gartner et al., 2005; Ip et al., 2009). In addition to the macro nutrient and micro nutrient content, human milk is a unique food that contains bioactive components which help to strengthen the neonate's immune system (Bhatia, 2013). Furthermore, the nutritional content of human milk produced from a

mother of a premature neonate may differ from milk produced from a mother of a term neonate in order to meet the increased nutritional needs of her premature baby (Bauer & Gerss, 2011). Current literature supports that human milk has a positive effect on health outcomes for infants including reduction of risk for common ailments for these premature infants such as necrotizing enterocolitis (Cristofalo et al., 2013; Parker, 2013) and sepsis (Bhatia, 2013; Schanler, 2011). It is likely that human milk may help to reduce illness severity over time. Specifically, a dose dependent relationship may exist between the amount of human milk ingested and the change in the neonatal illness severity over time. To date, no other known study has evaluated the relationship between human milk volume intake and neonatal illness severity over time.

When considering the relationship between human milk volume intake and neonatal severity of illness, one must consider other maternal or infant characteristics that may contribute to the infant's severity of illness risk. These maternal/infant dyad characteristics must be controlled for including: antenatal steroid injections (Henderson, Hartmann, Newnham, & Simmer, 2008; Morken, 2012), antenatal infection (Chiesa et al., 2003), gestational age, and birth weight (Chiesa et al., 2003).

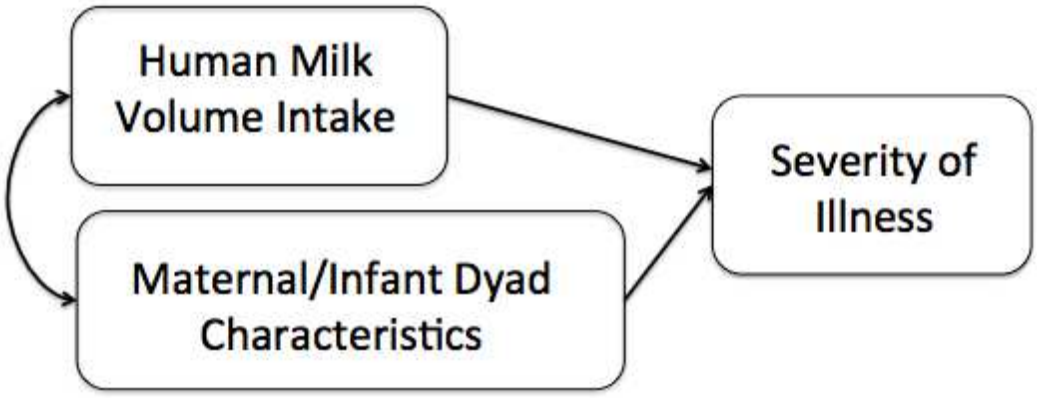

Figure 1. *Conceptual Framework*.

Human Milk

Human milk is recognized as the best source of nutrition for infants; and it is especially important for vulnerable NICU populations such as VLBW and ELBW infants. Although critically important, provision of human milk is not met without significant challenges including: separation of the mother/infant dyad (Lee, Lee, & Kuo, 2009), delay and/or infrequent pumping (Henderson et al., 2008; Smith, 2013), low milk volume (Henderson et al., 2008), physical breast discomfort (Lee et al., 2009), maternal stress (Lee et al., 2009), and lack of adequate support (Smith, 2013). It is important to recognize that these infants are some of the most critically ill patients; and they are in need of the best nutrition available, mother's own milk that has been appropriately fortified. The breastfeeding challenges that VLBW and ELBW mother/infant dyads face demands the attention of the healthcare team to increase lactation support so that this vulnerable population has the best chance of receiving an exclusive human milk diet (Pineda, 2011; Vohr et al., 2007).

Benefits of human milk. The body of evidence regarding the benefits of human milk for VLBW and ELBW babies is growing rapidly. The literature supports that the risk for many common neonatal morbidities can be decreased with the provision of human milk including: NEC (Contreras-Lemus et al., 1992; Cristofalo et al., 2013), urinary tract infection (Contreras-Lemus et al., 1992; Corpeleijn et al., 2012), infectious diarrhea (Contreras-Lemus et al., 1992), sepsis (Corpeleijn et al., 2012), respiratory illnesses (Vohr et al., 2007), and even death (Corpeleijn et al., 2012). Human milk may also decrease the need for common interventions such as antibiotic administration and blood transfusions (Contreras-Lemus et al., 1992). Finally, human milk has been shown to help neonates achieve milestones sooner including the attainment of full enteral feeds and earlier discharge from the NICU (Vohr et al., 2007).

Prevalence of the use of human milk. While human milk is known to have positive health affects for VLBW and ELBW infants, in the absence of any medical contraindications, it is ultimately the mothers' choice whether she will provide human milk for her baby (Smith, 2013; Vohr et al., 2006). Mothers of VLBW and ELBW infants are encouraged to express human milk for their babies. If the mother has an inadequate milk supply or does not wish to express human milk for her baby, many NICUs are now providing the option of donor human milk for these fragile infants. However, it is still ultimately the mothers' decision if she will express her milk or provide consent for donor human milk.

Breastfeeding initiation rates for these fragile infants range from 39.1% – 90% (Meier, Engstrom, Mingolelli, Miracle, & Kiesling, 2004; Pineda, 2011; Smith, 2013; Vohr et al., 2006). This is a very wide range and perhaps indicates that the health care providers and the culture of the organization may affect the success of human milk provision for this population. Perrine and Scanlon (2013) conducted a study with data accounting for 80% of the births in the US and found that human milk provision in US NICUs is on the rise. In 2011, 30.8% of NICUs provided human milk for the majority (>90%) of their patients and this is an upward trend from 2009 (26.7%) and 2007 (21.1%) (Perrine & Scanlon, 2013). They also found an increasing trend (11.5% in 2007 to 22% in 2011) in U.S. NICUs utilizing donor milk. An international survey of 124 hospitals across Australia, New Zealand, Canada, Scandinavia, United Kingdom, and Ireland reported that 48% of NICUs had access to donor human milk (Klingenberg, Embleton, Jacobs, O'Connell, & Kuschel, 2012). Furthermore, it is interesting to note that 100% of the NICUs surveyed in Scandinavia had access to donor milk (Klingenberg et al., 2012). Clearly, feeding practices for preterm neonates vary greatly across the globe.

Human milk changes. Human lactation is a dynamic process and therefore the nutritional content of human milk is continually changing (Agostoni et al., 2010). Human milk changes from the beginning to the end of each feeding/pumping session (Bishara, Dunn, Merko, & Darling, 2008). Human milk also changes across the stages of lactation: colostrum, transitional milk and mature milk (Bauer & Gerss, 2011).

Recently, additional evidence has been provided of changes in preterm milk over time by He, Sun, Quan, and Wang (2014); however, this article was only available in Chinese and therefore only the abstract could be reviewed. It is also critical to consider the potential differences between human milk produced by mothers that delivered preterm infants and human milk produced by mothers of term infants. While some studies have demonstrated that preterm milk is different than term milk (Bauer & Gerss, 2011; Dempsey & Miletin, 2010), a recent study did not produce similar results (Hsu et al., 2014).

Donor human milk. Donor human milk is recommended by the AAP as the alternative when mother's own milk is not available or it is medically contraindicated (Eidelman & Schanler, 2012). Donor human milk is a commodity that is donated by mothers and is then processed by human milk banks to ensure the safety of the donor milk that is provided for the recipient infants (Carroll, 2014). Although freezing and Holder pasteurization are important for milk safety, it may affect the non-nutritive/ bioactive components in the milk. However, a recent study provided reassuring evidence that not all bioactive components are eliminated in donor human milk (Groer et al., 2014). This is critically important as these non-nutritive, bioactive components are only found in human milk.

One concern that has been raised with donor human milk provision is the decreased growth patterns as compared to formula fed infants (Quigley & McGuire, 2014). One strategy to

improve growth patterns with donor human milk is to utilize preterm donor human milk versus term donor human milk due to the potential variation in the milk biology. The first challenge with this strategy is that many milk banks do not supply preterm human milk. Of the milk banks that do provide this service, the volume of preterm donor milk is very limited (Dempsey & Miletin, 2010). These challenges also impact research that seeks to compare outcomes for VLBW infants provided either term or preterm donor human milk. In 2010 (Dempsey & Miletin), a Cochrane review indicated that no studies met inclusion criteria to provide evidence comparing neonatal outcomes with regards to term and preterm donor human milk. Despite the concern with decreased short-term growth patterns, the evidence still supports the use of donor human milk because of the decreased risk of NEC as compared to formula fed groups (Quigley & McGuire, 2014).

Dose dependent relationship. The literature has demonstrated a dose dependent relationship between the amount of human milk ingested and positive health outcomes for infants (Corpeleijn et al., 2012; Vohr et al., 2007; Vohr et al., 2006). Specifically, Vohr et al. (2006) and Vohr et al. (2007) demonstrated that for every 10mL/kg per day of breastmilk, corresponding health effects would be noted. Corpeleijn et.al. (2012) noted positive health effects with any amount of human milk intake during the first 5 days of life; however during the days of life, six through ten, at least 50% of the infant's diet needed to consist of their mothers own milk (MOM) to demonstrate positive health outcomes (HR=0.37, 95% CI 0.22, 0.65). Additional research is needed in this area to determine exact thresholds where breastfeeding exerts maximal benefit for the infant.

Maternal/Infant Characteristics

The main focus of this study is to examine the relationship between human milk volume intake and neonatal severity of illness. It is important to consider variables that may also affect this relationship. The following section reviews variables that may influence neonatal illness severity, human milk volume intake, or both.

Antenatal steroids. Antenatal steroids are frequently administered to obstetrical patients when preterm delivery is anticipated in order to promote fetal lung maturity. The more mature the fetal lungs are, the less severity of illness one would anticipate. Antenatal steroid administration has been shown to reduce the risk of respiratory morbidities in neonates (Bartels, Kreienbrock, Dammann, Wenzlaff, & Poets, 2005; Corchia et al., 2013) and hypotension requiring medical intervention (Fanaroff & Fanaroff, 2006). It is interesting to note that steroids may also be administered to a small number of infants in the postnatal period as a treatment for hypotension (Fanaroff & Fanaroff, 2006) as well as the prevention or treatment of chronic lung disease (Doyle, Ehrenkranz, & Halliday, 2014a, 2014b). A final consideration of antenatal steroids is their potential effect of delaying lactogenesis stage II (full milk production) and therefore decreasing the mothers' milk volume that is available for her fragile infant (Henderson et al., 2008).

Maternal infection. Maternal infections are often accompanied by an increase in neonatal morbidities and increase in severity of illness in infants (Alexander, Gilstrap, Cox, McIntire, & Leveno, 1998). Risk factors for infection include: administration of antenatal antibiotics, maternal fever, uterine tenderness, foul odor at delivery, fetal/maternal tachycardia, premature rupture of membranes, and diagnosis of chorioamnionitis. Neonatal morbidities

associated with maternal infection include: lower gestational age at birth, low five minute Apgar score, and sepsis (Alexander et al., 1998; Hornik et al., 2012).

Birth weight and gestational age. Birth weight and gestational age are both important to consider when assessing for the risk of severity of illness. Clearly the smallest and most immature babies have some of the highest risks of morbidity and mortality among the infant population (Ambalavanan et al., 2012).

Birth weight has been used as a proxy for severity of illness as it explains some of the risks attributable to these infants (Richardson, Gray, McCormick, Workman, & Goldmann, 1993; Richardson, Phibbs, et al., 1993). The relationship between birth weight and illness severity/mortality is inverse. As birth weight decreases, risk for morbidity and mortality increases. Mortality is almost certain when birth weight is below 500 grams (Richardson, Phibbs, et al., 1993). Lower birth weight and lower gestational age has been associated with increased risk of mortality (Davis et al., 2010; Richardson, Phibbs, et al., 1993; Subhedar, Tan, Sweeney, & Shaw, 2000). Furthermore, if the infant is small for gestational age, the mortality risk increases 2.5 fold (Bartels et al., 2005). Lower birth weight and lower gestational age has also been associated with increased morbidity including: neurodevelopmental impairment (Davis et al., 2010), symptomatic hypotension (Fanaroff & Fanaroff, 2006), retinopathy of prematurity (Hauspurg et al., 2011), and seizures (Davis et al., 2010). In contrast, higher birth weight has been associated with improved outcomes (Meyn, Ness, Ambalavanan, & Carlo, 2010).

Neonatal Severity of Illness

Severity of illness is a concept used to describe how acutely ill and physiologically unstable an infant is currently, as well as to create a prediction of future morbidity and mortality risk (Richardson et al., 2001). Very low birth weight and extremely low birth weight infants are

at tremendous risk for physiologic instability and mortality (Ambalavanan et al., 2012). Mean blood pressure, temperature instability, PaO_2/FiO_2 ratio, serum pH, presence of multiple seizures and urine output all may be signs of severity of illness. Research instruments have been used extensively in NICUs to measure the concept of neonatal severity of illness including the revised Score for Neonatal Acute Physiology (SNAP-II).

History of the development of the SNAP-II instrument. The original score for neonatal acute physiology (SNAP) and score for neonatal acute physiology perinatal extension (SNAP-PE) was published in 1993; however, it was a lengthy and time-consuming instrument. Therefore in 2001, Richardson et al. created a more parsimonious tool with the second versions of SNAP-II and SNAPPE-II. The Score for Neonatal Acute Physiology (SNAP-II) is an instrument designed to measure illness severity and predict mortality in the neonatal population. It was initially developed as a measurement tool for the day of admission; however, some studies have used it sequentially during the NICU stay (Lim & Rozycki, 2008). The SNAPPE-II instrument is a further development of the SNAP-II score including invariant measures such as: APGAR, birth weight, and small for gestational age. The SNAPPE-II was measured for the parent study, but it cannot be used as a sequential measure, therefore it was not used for this proposed secondary data analysis.

Utilization of SNAP-II. The SNAP-II instrument has been used in research studies to operationalize neonatal illness severity across four continents including: North America (Brindle, Ma, & Skarsgard, 2010; Chien et al., 2001; Chien et al., 2002; Coleman et al., 2013; Dammann et al., 2010; Dammann et al., 2009; Lam, Claydon, Mitton, & Skarsgard, 2006; Lee et al., 2003; Lim & Rozycki, 2008; Madan, Fiascone, Balasubramanian, Griffith, & Hagadorn, 2008; Mills, Lin, Macnab, & Skarsgard, 2010; Nasr & Langer, 2011; Richardson et al., 2001; Skarsgard,

MacNab, Qiu, Little, & Lee, 2005; Soraisham, Singhal, McMillan, Sauve, & Lee, 2009; Stanger, Mohajerani, & Skarsgard, 2014; Wilson et al., 2013; Wong et al., 2013; Zupancic et al., 2007; Zwicker et al., 2013), South America (Lucas da Silva, Euzebio de Aguiar, & Reis, 2012; Zardo & Procianoy, 2003), Asia (Kadivar, Sagheb, Bavafa, Moghadam, & Eshrati, 2007; Ma et al., 2010; Mathur & Arora, 2007; Nakwan, Nakwan, & Wannaro, 2011; Sundaram, Dutta, Ahluwalia, & Narang, 2009), and Europe (Capasso et al., 2013; De Felice et al., 2005; Figueras-Aloy et al., 2003; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2007; Iacobelli et al., 2013; Miletin, Pichova, Doyle, & Dempsey, 2010; ter Horst, Jongbloed-Pereboom, van Eykern, & Bos, 2011). The SNAP-II has commonly been used to assess baseline neonatal severity of illness and establish morbidity/mortality risk by using physiologic data from the first 12 hours of life. However, some studies have expanded this assessment window to the first 24 hours of life (Coleman et al., 2013; ter Horst et al., 2011; Zwicker et al., 2013). Although less frequently, this instrument has also been used to measure neonatal illness severity at other time points including: after neonatal transport (Lucas da Silva et al., 2012; Mathur & Arora, 2007), sepsis (Sundaram et al., 2009), and finally assessing the SNAP-II score during at the highest time of clinical illness (Figueras-Aloy et al., 2003; Figueras-Aloy et al., 2004; Figueras-Aloy et al., 2007).

The vast majority of studies have used the SNAP-II score as a single measure, usually establishing the neonates' baseline risk at birth; however, the concept of physiologic instability has the ability to change continually. Therefore conceptually, this concept could be measured at birth, at later time points, as well as sequentially during a hospitalization. To date, only two studies have used the SNAP-II instrument to measure neonatal illness severity over time (Lim & Rozycki, 2008; Madan et al., 2008). One study measured initial illness severity at birth and then again with the timing of a medication treatment (Madan et al., 2008); while the other study

measured daily SNAP-II scores over the course of the NICU length of stay (Lim & Rozycki, 2008). The authors did not find relationships between severity of illness scores and morbidity as expected and therefore advised caution when utilizing the SNAP-II instrument sequentially.

While the validity of the SNAP-II instrument has been supported in many studies as a measurement of baseline risk, little is known about this instrument's ability to be used as a sequential measure. Although the two studies that used the SNAP-II instrument sequentially advised caution when using this instrument sequentially; these data are limited and warrant further investigation.

Mean blood pressure. Mean arterial blood pressure (MAP) is a routine vital sign used to assess perfusion in all NICU populations including VLBW and ELBW infants. These infants are especially prone to hypotension as compared to their more mature counterparts (Fanaroff & Fanaroff, 2006; Laughon et al., 2007; Martens et al., 2003; Sehgal et al., 2012). The treatment rates for hypotension range from 29% - 93% (Fanaroff & Fanaroff, 2006; Laughon et al., 2007), and the incidence of hypotension decreases as their gestational age increases (Laughon et al., 2007). Although this measurement is utilized on a routine basis to asses illness severity, there is no standard definition for hypotension in these small, fragile infants (Fanaroff & Fanaroff, 2006; Laughon et al., 2007; Logan, O'Shea, Allred, Laughon, Bose, Dammann, Batton, Engelke, et al., 2011; Sehgal et al., 2012). Therefore clinicians and researchers have defined it in various ways including: initiation of hypotensive treatments by providers (Fanaroff & Fanaroff, 2006), MAP less than 30 mmHg (Martens et al., 2003), and a three part definition (lowest MAP in the lowest quartile for the corresponding gestational age, treatment with vasopressor, blood pressure lability) (Logan, O'Shea, Allred, Laughon, Bose, Dammann, Batton, Engelke, et al., 2011; Logan, O'Shea, Allred, Laughon, Bose, Dammann, Batton, Kuban, et al., 2011). Hypotension is

an important severity of illness sign as it has been associated with increased risk of mortality (Fanaroff & Fanaroff, 2006; Martens et al., 2003) and may be associated with neurological morbidity (Martens et al., 2003); however some studies have failed to demonstrate this (Logan, O'Shea, Allred, Laughon, Bose, Dammann, Batton, Engelke, et al., 2011; Logan, O'Shea, Allred, Laughon, Bose, Dammann, Batton, Kuban, et al., 2011).

Temperature instability. Temperature is another physiologic indicator that can provide information on the severity of the infant's condition. Very low birth weight and extremely low birth weight infants are especially at risk for temperature instability due to their large body surface area, thin epidermal layers, limited amount of insulating fat, and increased peripheral blood flow (Mok, Bass, Ducker, & McIntosh, 1991). Interventions used to mitigate this risk include the use of pre-warmed blankets, radiant heat, and utilization of a plastic bag with a hole cut for the head and covering the infant's body to prevent evaporative heat loss for the tiniest babies that cannot be dried at birth without skin damage (Fuchs et al., 2012).

Research has demonstrated that hypothermia is associated with an increased risk of mortality in these fragile infants (Bartels et al., 2005; Garcia-Munoz Rodrigo, Rivero Rodriguez, & Siles Quesada, 2013). Specifically, Bartels, Kreinenbrock, Dammann, Wenzlaff and Poets (2005) found this association at a temperature of less than 35.5°C, while Garcia-Munoz Rodrigo et al. (2013) demonstrated this risk at a temperature of less than 36°C. Hypothermia and temperature instability has also been associated with several other common neonatal morbidities including: intraventricular hemorrhage (Bartels et al., 2005; Garcia-Munoz Rodrigo et al., 2013), respiratory distress syndrome (Bartels et al., 2005; Mok et al., 1991), and sepsis (Tamim, Alesseh, & Aziz, 2003).

Partial pressure of arterial oxygen (PaO_2) /Fraction of inspired oxygen (FiO_2) ratio.

Oxygenation is the most basic need for every human being and VLBW/ELBW infants are especially at risk for respiratory decompensation (Clark et al., 2013). If adequate gas exchange fails to occur, the infant's severity of illness increases rapidly and will lead to morbidity and eventually mortality without prompt intervention (Clark et al., 2013). The greatest initial risk for respiratory severity of illness in this premature population has been linked to the lack of adequate surfactant in premature lungs at birth (Avery & Mead, 1959; Fujiwara et al., 1980).

Although the most frequently used, non-invasive, clinical measure of oxygenation status is oxygen saturation (SpO_2) (Iyer & Mhanna, 2013), a more precise measurement is needed to determine severity of illness (Fuchs et al., 2012; Iyer & Mhanna, 2013). The oxygenation ratio (PaO_2/FiO2) has been used in several studies as an indicator of severity of illness (Ammari et al., 2005; Halbertsma, Vaneker, Pickkers, & Hoeven, 2009).

The oxygenation ratio (OR) is a mathematical calculation from two values: the partial pressure of arterial oxygen (PaO_2) and the fraction of inspired oxygen (FiO_2). The PaO_2 is a value obtained from an arterial blood gas (ABG), which is an invasive measure yet the ABG remains the gold standard to obtain information on oxygenation status and severity of illness (Fuchs et al., 2012; Iyer & Mhanna, 2013). Although this measure is more precise, the disadvantage is that arterial blood gases are invasive and multiple lab draws put these tiny infants at risk for iatrogenic anemia (Kirpalani et al., 2006). FiO_2 is the concentration or percentage of oxygen being delivered to the infant. FiO_2 is titrated from 21% (room air) up to 100% to meet the infant's respiratory needs (Fuchs et al., 2012). Nurses play an important role in the oxygen titration process, which is critical in order to avoid periods of hypoxia and hyperoxia (Fuchs et al., 2012; Sink, Hope, & Hagadorn, 2011), which potentially may lead to iatrogenic injuries such

as retinopathy of prematurity (Chen et al., 2011; Hauspurg et al., 2011). The higher the concentration of oxygen needed to maintain adequate oxygenation, the greater the severity of illness (Ammari et al., 2005).

As nurses and providers work to mitigate the increasing risks that accompany increasing severity of illness, consequences and risks of treatments must be acknowledged. For example, mechanical ventilation is needed for many of these infants; however, it is not without risk (Aly, Hammad, Essers, & Wung, 2012). Newer, less invasive options such as continuous positive airway pressure (CPAP) are being utilized (Ammari et al., 2005) and may decrease some of these risks.

Serum pH. Serum pH indicates the presence of acidosis, alkalosis, or a pH within the normal range. One measure of intrapartum risk for the neonate utilizes arterial pH from a cord blood sample obtained at birth (Malin, Morris, & Khan, 2010). This laboratory measure is often taken only for neonates that are considered at high risk for neonatal asphyxia at birth; however, Malin, Morris and Khan (2010) are advocates that cord blood samples be assessed more routinely and be used as an outcome measure for the intrapartum period and beyond as research has demonstrated an increased risk of morbidity for those neonates born with a low cord pH. Subsequent neonatal arterial blood gasses are routinely used in the NICU to assess ongoing acid base balance. These values also determine oxygenation status and are utilized to adjust ventilator settings in order to keep the pH normal.

As mentioned above, research has also indicated an abnormal pH being associated with increased morbidity risk for infants. For example, a common morbidity of ELBW and VLBW infants is retinopathy of prematurity Horodynski et al. (2007). It is well known that ROP is associated with high PaO_2 levels; however, Hauspurg et al. (2011) showed that there is also an

association between ROP and a low pH and high PCO_2. Another concern of interest is that a combination of hyperoxia and acidemia upon admission to the NICU may increase the risk of hypoxic ischemic encephalopathy (Kapadia et al., 2013). Clearly, infants that are unable to maintain homeostasis are more ill. Interventions targeting acid base balance are critical for this population.

Presence of multiple seizures. Neonatal seizures, especially repetitive seizures are of concern and have been associated with an increase in illness severity, neurodevelopmental impairment, as well as mortality risk in premature infants (Davis et al., 2010). Due to the immature neurological system of these infants, seizure activity is often subtle and therefore may go undetected by clinicians without the use of an electroencephalogram (EEG) (Murray et al., 2008).

A common cause of neonatal seizures is birth asphyxia. Some clinicians may routinely order prophylactic anticonvulsants for these infants to prevent seizures; however, Evans, Levene, and Tsakmakis (2007) warn that there is not enough information at this time to routinely advise this practice. A more recent treatment that has emerged for neonatal seizures is therapeutic hypothermia. This whole body cooling treatment has been associated with a reduction in neonatal seizures (Bonifacio et al., 2011; Meyn et al., 2010; Srinivasakumar et al., 2013). Specifically, Srinivasakumar et al. (2013) noted a reduction in seizures only for those infants with moderate hypoxic ischemic encephalopathy (HIE); whereas, Bonifacio et al. (2011) noted a reduction for moderate as well as severe HIE.

Urine output. Urine output, or specifically a decrease in urine output indicates a decrease in renal function usually due to acute kidney injury (AKI). A common cause of AKI in neonates is end organ damage caused by perinatal/birth asphyxia (Bezerra, Vaz Cunha, &

Liborio, 2013; Karlowicz & Adelman, 1995; Kaur et al., 2011). Other causes of AKI in this population may include hypotension (Ikegami et al., 2010; Viswanathan, Manyam, Azhibekov, & Mhanna, 2012) and incomplete maturation of the premature kidney (Cataldi et al., 2005).

Urine output is utilized routinely as a measure of illness severity in NICU care as it has been associated with an increased risk of mortality (Bezerra et al., 2013; Viswanathan et al., 2012). Although urine output is easily measured with or without an indwelling catheter, it is fraught with potential error from chart review calculations and/or missing data entries (Richardson et al., 2001; Sutton et al., 2002).

The greatest challenge with this measure is the lack of a consistent definition and the limited amount of evidence informing the operational definition of AKI in the VLBW and ELBW infant population (Akcan-Arikan et al., 2007; Cataldi et al., 2005; Viswanathan et al., 2012). Most definitions for AKI include parameters for urine output as well as serum creatinine. Various studies have used urine outputs ranging from 0.5 mL/kg/h to less than 1.5 mL/kg/h as an indication of AKI (Bezerra et al., 2013; Karlowicz & Adelman, 1995; Viswanathan et al., 2012). It is also critical to note that although decreased urine output indicates renal compromise, many neonates have AKI without oliguria (Bezerra et al., 2013; Karlowicz & Adelman, 1995; Viswanathan et al., 2012). Current research is focused on defining classification systems for AKI in neonatal populations so that the language used is universal and data from various studies can be compared (Bezerra et al., 2013).

Summary

Clearly, the needs of VLBW and ELBW neonates have been an important focus in recent nursing and medical research. The literature undeniably supports that these newborns are fragile and that they are at greater risk for morbidity and mortality as compared to infants born at a

normal birth weight. These babies are acutely ill and require extended intensive care due to their ongoing severity of illness over the weeks and months following their birth.

The literature is also clear that human milk, including mother's own milk and donor human milk contains bioactive components that are helpful in strengthening the immune system of these fragile infants. This is believed to be the reason that human milk helps to mitigate some of the risks for mortality and common morbidities that this population faces.

Although a plethora of research has focused on this population, there are still gaps in the literature. More knowledge is needed in the area of dose specific amounts of mother's own milk, donor human milk, or the combination of these enteral foods that are needed to impact neonatal illness severity. Specifically, more knowledge is needed to understand the relationships between neonatal severity of illness and the volume of human milk intake by VLBW and ELBW infants. This study seeks to provide evidence on the relationship between specific amounts of human milk and the ongoing weekly affect on the neonatal severity of illness for VLBW and ELBW babies over the first six weeks of life in the neonatal intensive care unit.

CHAPTER THREE

METHOD

This chapter provides details regarding the study design, the study setting, as well as describes the population of interest and the recruitment procedures for the study sample. All study variables are operationalized and the SNAP-II instrument is discussed in detail. Procedures are outlined including the process for institutional approvals, recruitment of participants, and data collection. Finally, the plan for the data analysis specific to each aim of the study concludes this chapter.

Research Design

This research study was a secondary data analysis that used longitudinal data from an NIH funded (2012-2015), R21 exploratory study. The parent study sought to investigate the quantitative amounts of immunobiological components ingested via human milk, and the possible associations with enteral health, skin immunity, and clinical outcomes for VLBW and ELBW infants. The principal investigator of the primary study, Dr. Maureen Groer, provided initial approval for this secondary data analysis. An IRB application was submitted, however the University of South Florida IRB determined this secondary data analysis did not meet the definition of human subject research and provided a letter of determination indicating that IRB approval was not needed for this secondary data analysis (See Appendix A).

The purpose of this study was to explore the relationship between human milk volume intake and severity of illness in very low birth weight and extremely low birth weight infants. Because human milk has been linked to improvement of infant health outcomes, this study

sought to explore the possible impact of human milk on the severity of illness over the first six weeks of life for this vulnerable population. Although the parent study collected severity of illness scores each week for the first six weeks, the parent study is only utilizing the initial severity of illness measure (SNAP-II) in their analysis; however, this secondary data analysis explored the weekly changes in severity of illness (SNAP-II) for the six-week duration of the parent study.

Setting

The parent study took place in a tertiary care medical center that is affiliated with the University of South Florida. Specifically, the study site was an 82 bed, level three, neonatal intensive care unit.

Population and Sample

The target population for the parent study included mother/infant dyads admitted to the NICU with a birth weight between 750 and 1500 grams with mothers who intended to provide human milk as a nutritional source for the infant. Research participants were recruited by one of two-nurse research coordinators employed by the affiliated hospital. NIH funding for the parent study provided partial salary compensation for the research coordinators. Mother/infant dyads were screened upon admission to the NICU by the research coordinators. They approached dyads meeting study inclusion/exclusion criteria and provided information about the study. Inclusion criteria for the parent study included: infants of all ethnicities and genders that were admitted to the NICU with a birth weight between 750 – 1500 grams. Exclusion criteria for mothers included: HIV infections, autoimmune disease, long-term steroid use, and immunosuppressive medication use. Exclusion criteria for infants included: significant congenital anomalies, hereditary disease, requiring immediate surgery and moribund infants.

After eligibility was determined, the research coordinator met with the mother and provided information about the study to obtain informed consent. Mothers were provided with a $50 gift card honorarium for participating in the study. Power analytic strategies indicated that a goal of 75 participants was adequate for the parent study. Therefore, the final recruitment goal was 100 participants to allow for possible study attrition.

Measures (Instruments)

The dependent variable of interest in this secondary analysis was neonatal severity of illness. Neonatal severity of illness was operationalized via the score for neonatal acute physiology, version two (SNAP-II). Each of the independent variables was obtained via a prospective chart review during the parent study.

SNAP-II. The SNAP-II score was calculated using six variables including: mean blood pressure, lowest temperature, PaO_2 (mmHg) / FIO_2 (%), lowest serum pH, presence of multiple seizures, and urine output (mL/kg.h) (Richardson et al., 2001) (See Appendix B).

The SNAP-II is a summative rating scale measurement instrument that provides a continuous level of measurement total score that ranges from 0-115. A higher score indicates an infant that is more acutely ill. This instrument includes six sub scales that provide an ordinal level of measurement including: mean blood pressure (0-19 points), lowest temperature (0-15 points), PO_2/FIO_2 (0-28 points), serum pH (0-16), presence of multiple seizures (0-19 points), and urine output (0-18 points) (Richardson et al., 2001) (See Appendix B). The SNAP-II scores were collected within 12 hours of birth and then weekly for six weeks.

Criterion validity was demonstrated by a Pearson correlation for all birth weights (r=0.91) and (r =0.90) for < 1500 grams between the SNAP-PE and the SNAPPE-II. Discrimination of the SNAPPE-II was assessed using the area under the receiver operator curve

(AUC) for all birth weights (0.91 ± 0.01) and for birth weights <1500 grams (0.85 ± 0.01). This demonstrated good discrimination as 1.0 equals a perfect score and 0.5 means that it is completely random. The Hosmer-Lemeshow goodness of fit test for the SNAPPE-II was 0.9 for all birth weights and 0.86 for < 1500 grams (Richardson et al., 2001). In 2007, Zupancic et al. provided further validity data specifically for the SNAP-II including: AUC 0.86 ± 0.01 for all births and 0.82 ± 0.01 for infants < 1500 grams and Hosmer-Lemeshow goodness of fit 0.336 for all birth weights and 0.768 for < 1500 grams. No reliability data were reported with either study.

Human milk volume. Human milk volume was the major independent variable of interest. Exact milk intake, in milliliters (mL), was routinely documented in the healthcare record for every feeding in the NICU. A research assistant calculated weekly totals of human milk volume intake via chart review. Human milk was calculated for four categories including: expressed breast milk (EBM), expressed breast milk with human milk fortifier (EBM-HMF), donor human milk (DHM), and donor human milk with human milk fortifier (DHM-HMF).

Aliquots of milk samples (0.5 mL) were obtained by the nurse from each batch of the mother's own milk and separately from each batch of donor human milk for the study period of six weeks or upon discharge. The human milk samples were collected using one mL needleless syringes, labeled, and frozen at -20°C. One to two times per week, specimens were transported on ice to the USF biobehavioral lab where they were stored at -80°C until processing. Processing milk samples included thawing of the aliquots and combining milk samples to create weekly-pooled milk specimens for laboratory testing for the parent study.

All donor human milk used in this study was purchased by the study NICU from two non-profit milk banks in northern Texas. Therefore the DHM went through the standard human milk bank processing procedures to ensure the safety of the human donor milk including: donor

screening, holder pasteurization, and quality control testing. While many human milk banks only accept term human milk donations, one of the milk bank suppliers for study NICU accepted preterm milk donations as well. Finally, pooled milk samples from multiple donors were shipped frozen to the NICU. Milk was then thawed and distributed to the recipient infants.

Demographic data form. Finally, a demographic data form was completed for each participant in the parent study. Information utilized for the secondary data analysis included race, ethnicity, maternal age, socioeconomic status, and educational level. Mothers expected to deliver prematurely should have received two doses of antenatal steroids for fetal lung maturity. Depending on the amount of time prior to the premature delivery of the infant, the mother may have received one or more doses prior to delivery. The parent data set included if any steroids were provided to the mother, therefore this was a dichotomous independent variable. Maternal infection data were also collected. Specifically, the infection of concern was a maternal diagnosis of chorioamnionitis at the time of her hospitalization and premature delivery. This was also a dichotomous independent variable. Both of these maternal factors were independent variables collected via chart review and recorded on the demographic data form. Finally, infant birth weight and gestational age were both important infant factors to consider. However, due to the expected high collinearity between these two variables, only birth weight was included as a control variable. Birth weight was a continuous, independent variable collected via prospective chart review during the parent study.

Procedures

Dr. Maureen Groer, principal investigator (PI), granted the initial approval for this secondary data analysis. The Tampa General Hospital (TGH) and University of South Florida (USF) IRBs approved the parent study. An IRB application was submitted, however the

University of South Florida IRB determined this secondary data analysis did not meet the definition of human subject research and provided a letter of determination indicating that IRB approval was not needed for this secondary data analysis (See Appendix A). The parent study included funded and non-funded research team members including: three neonatologists, two statisticians, three TGH research nurse coordinators, and three research assistants. Upon initiation of the parent study, the parent study PI met with all study personal to ensure each person understood his/her role. The parent study PI also met with the NICU staff nurses to explain the study and provide an opportunity for questions to be addressed.

Recruitment for the parent study was completed by the TGH NICU research nurse coordinators. The research nurse coordinators screened maternal/infant dyads each weekday for study eligibility upon admission to the NICU for the duration of the three year recruitment period. TGH research nurse coordinators spent time with each eligible dyad to discuss the research study and complete the informed consent process.

Data collection started with the mother completing a demographic data form. The TGH research nurse coordinators collected the forms and ensured that the demographic data form was complete. The completed demographic data forms were picked up by a research assistant one to two times per week. Data were entered into SPSS and kept on a secure USF network. The identifying information was kept on an Excel spreadsheet in a paper and electronic format that is in a locked cabinet in a locked office. Research assistants retrieved additional data via chart review. Exact volumes of human milk intake per feeding were charted routinely by NICU nurses. Research assistants totaled weekly milk volumes consumed by the infants. Research assistants also collected data from the chart to assign the initial SNAP-II score within 12 hours of

birth as well as sequential SNAP-II scores each week for the six weeks of the study. All data points were entered into SPSS for data analysis.

Data Analysis

Data analysis began by performing descriptive statistics (means, standard deviations, frequencies, and percentages) of the demographic data. Data were examined for outliers, missing data, and normal distribution. If skewness or kurtosis was present, then data were transformed based on the distribution of the data. Next, level one data were aggregated and means for infants were used to calculate Pearson's product moment correlations between milk volume, SNAP-II scores, and maternal/infant characteristics. The initial correlations provided information for multilevel models.

Multilevel modeling was used to compare growth models for the best fitting model including linear, quadratic, cubic, and piecewise trends. Model fit was evaluated using chi-square (χ^2) and goodness of fit testing including Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). A smaller AIC and BIC were desirable to demonstrate the best fitting model. For the model comparison between two nested models using chi-square difference tests, a statistically significant chi-square difference indicated a better fit of a more complex model with less degrees of freedom. The piecewise model demonstrated the best fit and was used as a base model to systematically add level one and level two independent variables to the model. Finally, birth weight, a proxy for illness severity in the literature, was added as a control to the models that demonstrated a statistically significant relationship between severity of illness and human milk. Ultimately, the goal was to have a model that explained the greatest amount of variance while still maintaining a parsimonious model. SPSS statistical software (IBM SPSS Statistics 22) was used for all statistical data analysis.

The current study used multilevel modeling to explore the relationship between total human milk volume, maternal/infant dyad characteristics, and severity of illness in VLBW and ELBW infants during the first six weeks of life. Multilevel modeling was optimal because it allowed for repeated measures that took place weekly for six weeks. Multilevel modeling also allowed for some missing data points which often occurs with repeated measure studies (Tabachnick & Fidell, 2013).

The multilevel model study design is illustrated in Figure 2. This figure defines each of the independent variables including specific maternal/infant dyad characteristics that were controlled for in this model. The weekly time points and weekly cumulative mother's own milk (MOM), donor human milk (DHM), and total human milk (THM) volume were all level one independent variables because they changed weekly. Birth weight, antenatal steroids, and maternal infection were level two independent variables as they remained constant throughout the six-week study period.

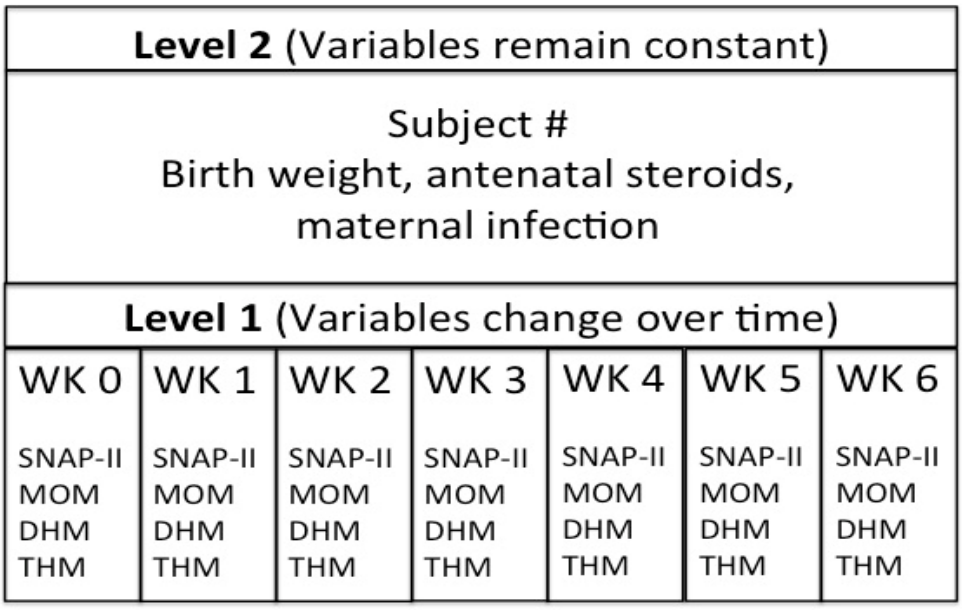

Figure 2. *Study Design.* MOM = Mother's Own Milk; DHM = Donor Human Milk; THM = Total Human Milk.

CHAPTER FOUR

RESULTS

Preliminary Analyses

Outliers, missing data and normality. The parent study recruited a total of 95 participants that included 73 singletons and 22 multiples. Since twins and triplets shared the same gestation and mother, they would not provide a source of independent data; therefore random selection was used to include only one neonate from each multiple gestation pregnancy. This reduced the sample size to 85. Initial analysis revealed six neonates had partial missing data including: eight SNAP-II scores and corresponding weekly milk intake volumes (two at birth, two at week five of life and four at week six of life). However, by using the multilevel modeling techniques, inclusion of all collected data was possible for these cases. One additional neonate was removed from the study because although initial demographic data were collected, no other data for the six weeks of the study were collected for this infant.

Although the study sample included neonates at risk for illness due to their very low birth weight and admission to the neonatal intensive care unit, initial analysis revealed that the dependent variable of interest, severity of illness, was not demonstrated as evidenced by a SNAP-II score of zero at every time point in the study. This may be partially due to the advances in perinatal care over the past few decades; however, including neonates that did not demonstrate evidence of illness severity would blunt the effects of the remaining study sample that did demonstrate illness severity via the SNAP-II instrument. Therefore neonates that earned

a SNAP-II score of zero for all time points (n=17) were removed from the analysis providing a final sample size of 67 neonates in this secondary data analysis.

Description of the sample. All of the research participants were premature neonates with gestational ages ranging from 24 to 32 weeks and six days (*M*= 27.86, *SD* =1.89) gestation. According to the inclusion criteria all neonates were less than 1,500 grams and the study sample ranged from 600 grams to 1,485 grams (*M*= 1064, *SD* =217.37). The majority of the neonates (58.2%, n=39) were very low birth weight and 41.8% (n=28) were extremely low birth weight.

The study sample was racially and ethnically diverse. Equal numbers of Caucasian (32.8%, n=22) and African American (32.8%, n=22) mothers were represented. Fathers were similar, but there were a few more African Americans (37.3%, n=25). Hispanic ethnicity was also represented in this sample with 22.4% (n=15) self-identifying as Hispanic White and 1.5% (n=1) as Hispanic Black. The remaining sample consisted of various races including: Asian/Pacific Islander, Native American, or other. See Table 1 below for parental self-reported race/ethnicity data.

The maternal age ranged from 15 to 46 years with a mean of 28 years. More than half of the mothers completed high school (55.2%, n=37) and an additional 28.4% (n=19) of the mothers completed a college or post-graduate degree. The remaining 11 mothers indicated that they completed middle school (10.4%, n=7) or grammar school (6%, n=4).

Self-reported income amounts were diverse and ranged from under $4,999 and up to $70,000 and beyond. However, almost three-quarters of the sample (71.6%, n=48) indicated that they made $39,999 or less. Two mothers (3%) indicated that they earned between $40,000 - $69,999 and eight mothers indicated an income at $70,000 and beyond. It was also noted that nine participants (13.4%) chose not to disclose their income level.

Table 1

Race/Ethnicity

	Maternal *n / %*	*Paternal* *n / %*
Caucasian	22 (32.8%)	17 (25.4%)
African American	22 (32.8%)	25 (37.3%)
Hispanic White	15 (22.4%)	18 (26.9%)
Other	5 (7.5%)	4 (6.0%)
Asian/Pacific Islander	2 (3.0%)	0 (0%)
Hispanic Black	1 (1.5%)	1 (1.5%)
Native American	0 (0%)	1 (1.5%)
Not Reported	0 (0%)	1 (1.5%)

Note. $N = 67$

Level 1 Variables Descriptive Statistics

The level one dependent variable of interest was severity of illness operationalized via the SNAP-II instrument. SNAP-II scores were collected on the first day of life and at the end of each week of life for a total of six weeks of life, thus seven data points. The minimum SNAP-II score across all time points was zero and the maximum score was 66 at the end of week one of life, closely followed by a score of 54 on the first day of life. When evaluating the means for SNAP-II scores at each week of life, the highest mean is at the end of week 1 of life (M = 14.478, SD=11.45), closely followed by the mean at birth (M = 12.708, SD = 9.65) and then a decreasing trend over time. See Figure 3 that shows a scatterplot of SNAP-II scores at each time point and Figure 4 demonstrating a graph of the means for SNAP-II scores at each of the seven time points in the study.

Descriptive statistics and histograms were performed to evaluate the SNAP-II value at each time point. See Table 2 for descriptive statistics for the SNAP-II instrument at each of the seven time points. All SNAP-II scores demonstrated positive skewness (1.731 -5.043) and positive kurtosis (3.495 – 29.926).

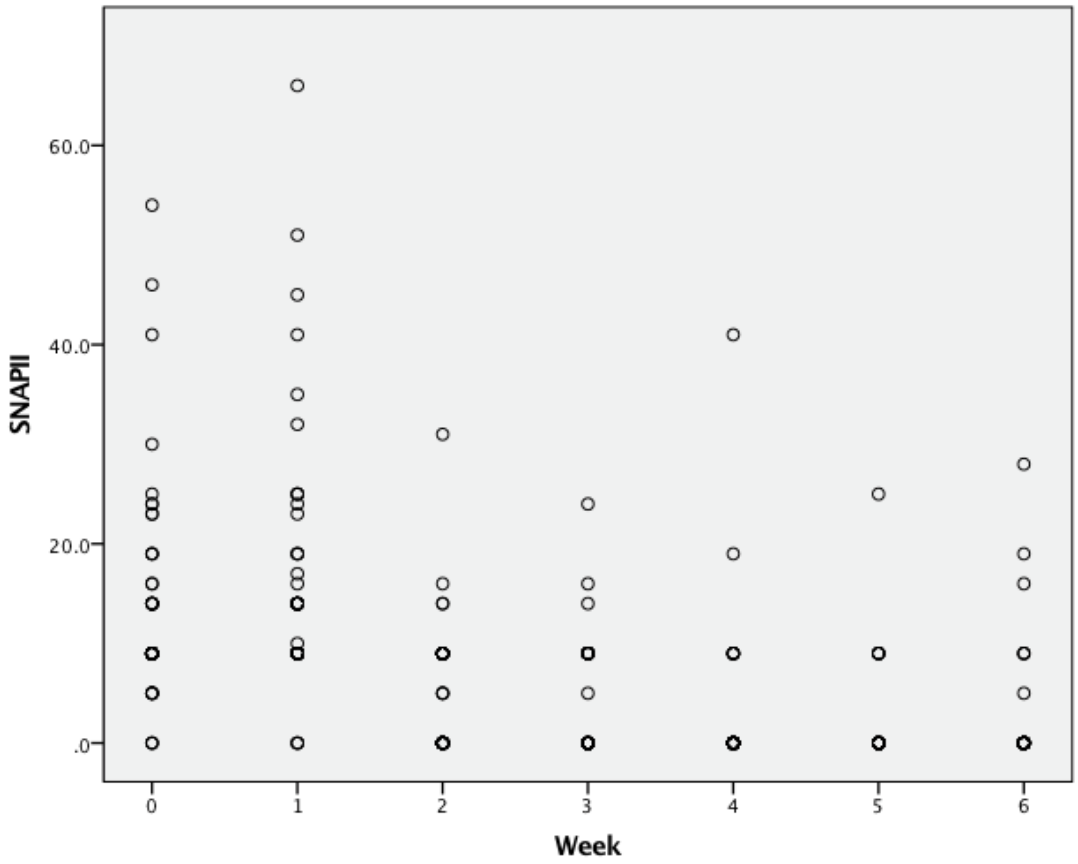

Figure 3. *Scatterplot of SNAP-II Scores by Week*

Skewness indicates that the data are not symmetrical, specifically positive skewness means that more cases accumulate on the left side of the graph and there is a long right tail. Positive kurtosis indicates that the values are too peaked and have short and thick tails (Tabachnick & Fidell, 2013). Log10 transformation was used to correct for the non-normality data structure. Since SNAP-II scores did contain zero values, one was added to each SNAP-II score prior to the log transformation procedure (Tabachnick & Fidell, 2013).

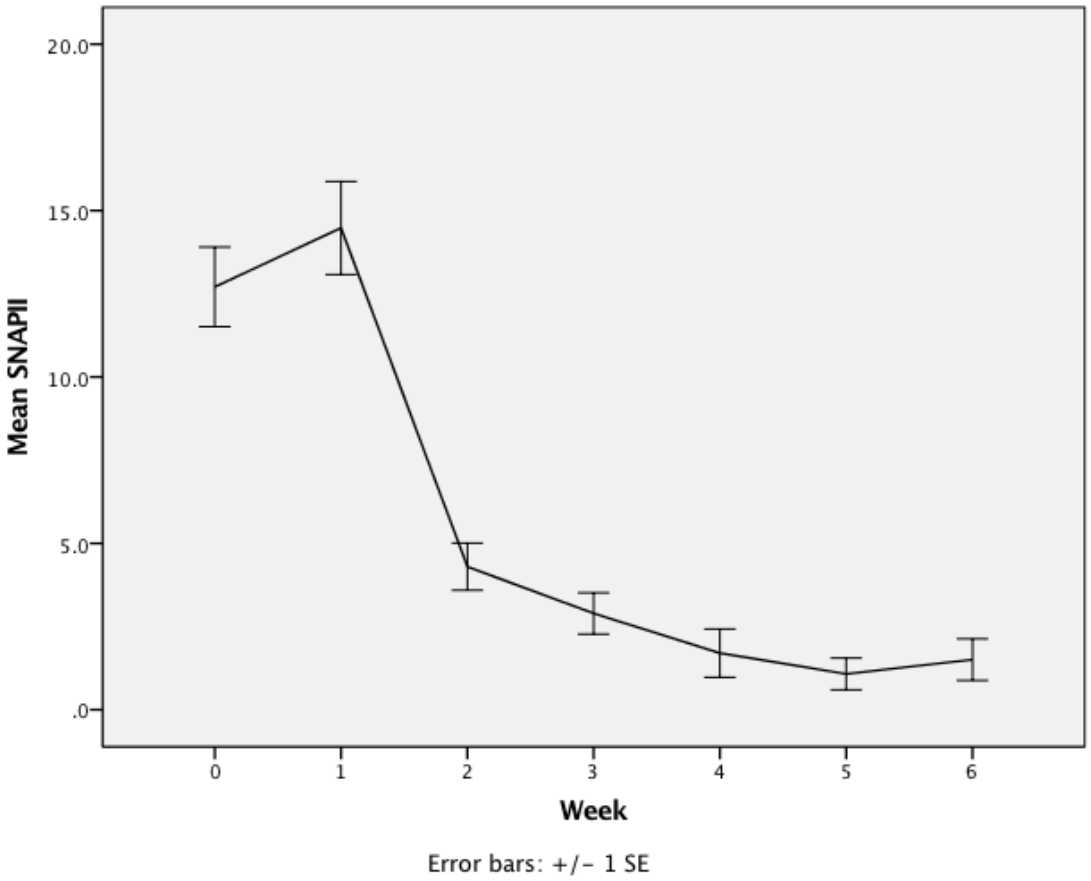

Figure 4. *Graph of Means of SNAP-II Scores from Birth through each Week of Life*

Table 2

SNAP-II Scores - Descriptive Statistics

	n	Minimum	Maximum	*M*	*SD*	Skewness	Kurtosis
SNAP0	65	0	54	12.708	9.650	2.379	6.852
SNAP1	67	0	66	14.478	11.447	2.465	7.176
SNAP2	67	0	31	4.299	5.810	1.731	5.137
SNAP3	67	0	24	2.896	5.085	1.815	3.495
SNAP4	67	0	41	1.701	5.947	5.043	29.926
SNAP5	66	0	25	1.061	3.835	4.544	24.044
SNAP6	66	0	28	1.439	4.855	3.938	16.530

Note. SNAP = Score for Neonatal Acute Physiology

The independent variables of interest at level one included weekly intake amounts of milk volumes in milliliters as well as calculated percentages of intake for mother's own milk

(MOM), donor human milk (DHM), and total human milk (THM) as noted above. MOM, DHM, and THM ranged from zero to 100% of the neonates diet. The average weekly diet for neonates in this study was made up of 62.2% of mother's milk, 10.2% of donor milk, for a combined total of 72.4% of human milk. The data demonstrated as expected that the amount of milk intake increases over time. See Figure 5 that includes a scatterplot of individual intake of MOM, DHM, and THM across the seven time points. Descriptive statistics for MOM and THM demonstrated normality, however, donor human milk volume and the percentage of donor human milk volume showed skewness and kurtosis (See Table 3). Log10 transformation was used to correct the non-normality distribution for both donor human milk variables. Since some values were zero for milk intake, a one was added to each DHM value prior to the log transformation procedure (Tabachnick & Fidell, 2013). See Table 3 for the full descriptive statistics for milk variables.

Table 3

Milk Intake Volumes - Descriptive Statistics

	N	*Minimum*	*Maximum*	*Mean*	*SD*	*Skewness*	*Kurtosis*
MOM(mL)	463	0	2768	596.897	668.94	.846	-.514
DHM(mL)	463	0	1891	122.514	354.36	3.071	8.450
THM(mL)	463	0	2768	719.411	699.92	.474	-1.127
MOM(%)	463	0	1	.622	.445	-.492	-1.624
DHM(%)	463	0	1	.102	.259	2.525	4.981
THM(%)	463	0	1	.724	.427	-1.000	-.919

Note. MOM(mL) = Mother's own milk volume intake measured in milliliters; DHM(mL) = Donor human milk volume intake measured in milliliters; THM(mL) = Total human milk volume intake measured in milliliters; MOM(%) = Percentage of mother's own milk intake; DHM(%) = Percentage of donor human milk intake; THM(%) = Percentage of total human milk intake; Measured for 67 babies over time.

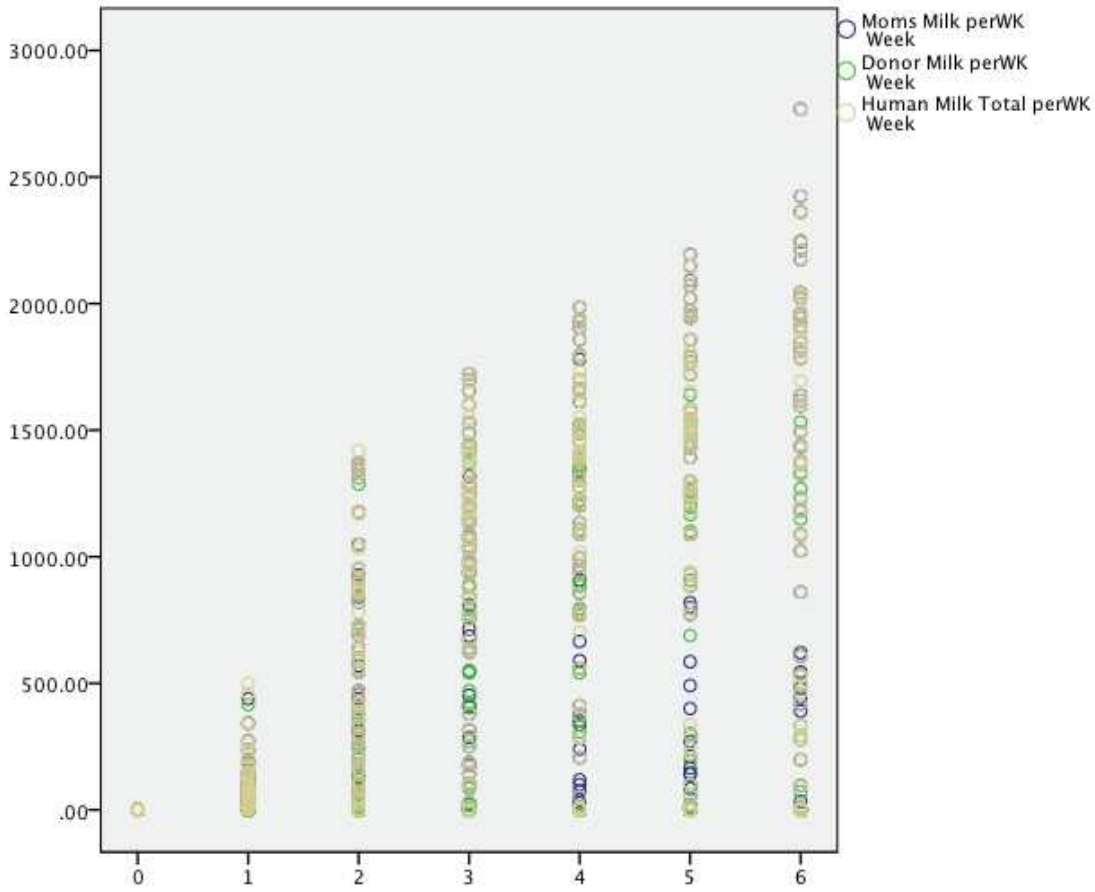

Figure 5. Scatterplot of MOM, DHM, and THM Intake for Each Week of Life.

Level 2 Variables Descriptive Statistics

Level two variables were time invariant and included subject level data for each dyad including: infant birth weight, maternal history of antenatal steroid administration, and maternal diagnosis of chorioamnionitis. Neonatal birth weight ranged from 600 grams to 1,485 grams (M = 1064, SD = 217.37) with a normal distribution. See Table 4 for full descriptive statistics for infant birth weight. A total of six mothers (9%) were diagnosed with chorioamnionitis. A total of 47 mothers (70.1%) received at least one antenatal steroid injection prior to delivery.

Correlations

Prior to constructing multilevel models for comparison, correlations were used to

Table 4

Birth Weight - Descriptive Statistics

	N	*Minimum*	*Maximum*	*Mean*	*SD*	*Skewness*	*Kurtosis*
Birth Weight/g	67	600	1485	1064	217.37	.036	-.705

examine the relationships among the study variables. See Table 5 for correlations of aggregated key variables. Due to the multilevel nature of the dataset, level one data were aggregated for infants prior to running correlations among the study variables. Statically significant negative correlations were noted between SNAP-II scores and mother's own milk volume (r = -.398, p = .001), total human milk volume (r = -.479, p < .001), and infant birth weight (r =-.579, p < .001). These relationships remained after log10 transformation of the SNAP-II score (r = .384, p = .001; r = -.472, p < .001; r = -.629, p < .001). However, when evaluating relationships between the SNAP-II score and percentage of MOM (r = -.035, p > .05) and percentage of THM (r = -.044, p > .05), the statically significant correlations did not remain. Correlations were not significant for donor human milk volume (r = -.076, p > .05), percentage of DHM (r =.000, p > .05), log10 transformed donor human milk volume (r =-.049, p > .05), and log10 transformed percentage of DHM (r =-.001, p > .05). Statistically significant correlations were not demonstrated between SNAP-II scores and antenatal steroid administration (r =.108, p > .05), or SNAP-II scores and maternal diagnosis of chorioamnionitis (r = -.011, p > .05). Therefore, antenatal steroids and chorioamnionitis were not included in the final model. As expected, SNAP-II scores demonstrated statically significant negative correlations to infant birth weight (r = -.579, p < .001), and was used as a control variable in the model.

Multilevel Modeling Approach

The study design included repeated measures that were nested within individual babies. The intraclass correlation coefficient (ICC) was calculated from the unidentified model with the original SNAP-II scores to determine the amount of influence of the individual babies. The ICC of 0.2 indicated that the individual baby could explain 20 percent of the variance noted in the data. Since data dependency was present, a multilevel modeling approach was appropriate for this study. Therefore level two variables represented the data for the individual mother/baby dyad that was time invariant. These time invariant variables include the infants' birth weight, maternal history of receiving antenatal steroid injections, and a perinatal diagnosis of chorioamnionitis during the current antepartum and intrapartum period. Level one variables were time variant as they were measured on the day of birth and at the end of each week of life for the first six weeks of life, for a total of seven time points. These data were nested within the individual neonate and allowed the researcher to determine the growth curve over time. Level one variables in this study included illness severity scores operationalized via the SNAP-II instrument as well as weekly milk volumes ingested by the neonate each week. Milk volumes specifically included six different data points including: 1.) weekly intake of mothers' own milk measured in milliliters, 2.) weekly intake of donor human milk measured in milliliters 3.) weekly intake of all human milk (combined weekly total of mothers' own milk plus donor human milk) measured in milliliters, 4.) percentage of weekly diet that was attributed to consumption of mothers' own milk 5.) percentage of weekly diet that was attributed to consumption of donor human milk, 6.) percentage of weekly diet that was attributed to consumption of total human milk (combined total of mothers' own milk plus donor human milk).

Model Comparison

The initial step was to evaluate the graph showing the change in the dependent variable, neonatal severity of illness, over time. Growth models were constructed to evaluate a linear, quadratic, and finally a piecewise model for SNAP-II scores over time. Once the best fitting growth model was determined, the independent variables of interest (MOM, DHM, and THM) were added independently to test for statistical significance. Finally, birth weight was added to the model as a control since it is seen as a proxy for severity of illness in the literature.

The maximum likelihood estimation method was utilized in this study so that model comparisons could be done using likelihood ratio testing. Although restricted maximum likelihood estimation produces a less biased result, one cannot compare models with this method and therefore it was not utilized. Maximum likelihood estimation method was also selected because it is a robust estimation method when dealing with some non-normality in the dataset. Likelihood ratio testing was calculated by subtracting the negative two log likelihood scores, also known as deviance scores, for the comparison model from the baseline model. Then the number of parameters for the comparison model were subtracted from the parameters from the baseline model to determine the degrees of freedom used. The likelihood ratio test is distributed as a chi-square and comparison was made to the critical values to determine if significant change occurred between models. Models were also compared using goodness of fit testing including: Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC). A better model was noted when the respective AIC or BIC score decreases for the comparison model.

Table 5

Correlations Among Study Variables Averaged Over Six Weeks

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. meanSNAPII	1	.924**	-.398*	-.076	-.479**	-.035	-.000	-.044	-.049	-.001	-.579**	.108	-.011
2. meanLg10SNAPII	-	1	-.384*	-.090	-.472**	.004	-.022	-.014	-.073	-.024	-.629**	.055	-.060
3. meanMOMml	-	-	1	-.417**	.831**	.827**	-.494**	.621**	-.443**	-.493**	.362*	-.053	-.002
4. meanDHMml	-	-	-	1	.158	-.530**	.953**	.131	.956**	.956**	-.042	.204	-.165
5. meanTHMml	-	-	-	-	1	.574**	.047	.756**	.104	.049	.368*	.067	-.103
6. meanMOM%	-	-	-	-	-	1	-.603**	.747**	-.560**	-.601**	-.113	-.054	.040
7. meanDHM%	-	-	-	-	-	-	1	.080	.946**	.999**	-.101	.229	-.179
8. meanTHM%	-	-	-	-	-	-	-	1	.087	.082	-.225	.123	-.099
9. meanLg10DHMml	-	-	-	-	-	-	-	-	1	.957**	-.051	.245*	-.179
10. meanLg10DHM%	-	-	-	-	-	-	-	-	-	1	-.098	.234	-.181
11. meanBirthweight	-	-	-	-	-	-	-	-	-	-	1	-.171	-.100
12. meanSteroids	-	-	-	-	-	-	-	-	-	-	-	1	-.024
13. meanChorio	-	-	-	-	-	-	-	-	-	-	-	-	-1

*-$p < .05$ **-$p < .00$

Note. meanSNAPII = Mean Score for Neonatal Acute Physiology-II; meanLg10SNAPII = Mean log 10 transformed Score for Neonatal Acute Physiology score; meanMOMml = Mean mother's own milk volume intake measured in milliliters; meanDHMml = Mean donor human milk volume intake measured in milliliters; meanTHMml = Total human milk volume intake measured in milliliters; meanMOM% = Mean percentage of mother's own milk intake; meanDHM% = Mean percentage of donor human milk intake; meanTHM% = Mean percentage of total human milk intake; meanLg10DHMml = Mean Log 10 transformed donor human milk intake measured in milliliters; meanLg10DHM% = Mean Log 10 transformed percentage of donor human milk; meanBirthweight = Mean birthweight; MeanSteroids = Mean steroids; meanChorio = Mean chorioamnionitis; Measured for 67 babies over time.

Growth models. Growth models were examined in a stepwise fashion to compare each model and determine the best fitting growth model for SNAP-II scores over time (See Table 6). The first model was the unconditional model, which was used as the baseline. The second model was linear and the model fit was improved by adding the level one predictor of time (γ_{week} = -.182, $p < .001$). Model two explained variance at level one increased by 54% (.543506 for σ^2) and model fit improvement was supported (Deviance = 444.481, $\Delta\chi^2(df)$ = 310.819(1), $p < .001$, AIC = 452.481, BIC = 469.015). Model three was quadratic and included two parameter estimates for time including week (γ_{week} = -.393, $p <$. 001) and week^2 (γ_{week^2} = -.035, $p <$. 001). Model three explained variance at level one increased by an additional 13.7% as compared to model 2 (.136934 for σ^2). Model three also demonstrated improved model fit as compared to model two (Deviance = 386.371, $\Delta\chi^2(df)$ = 58.11(1), $p < .001$, AIC = 396.371, BIC = 417.038). Finally a piecewise model was created by visually examining the weekly mean SNAP-II scores (See Figure 4.) This graph indicated that the average slopes for SNAP-II scores were different at three time points and therefore three "pieces" or three linear relationships were examined. Piece one was defined as starting at birth (time point zero) and ending at the end of week one of life (time point 1). Piece two was defined as starting at the end of week one of life (time point 1) and ending at the end of week 2 of life (time point 2). Piece three was defined as starting at the end of week 2 (time point 2) and extending through the end of the sixth week of the study (time point 6). The parameter estimates for the piecewise model were significant for piece two (γ_{piece2} = -.711, $p < .001$) and piece three (γ_{piece3} = -.083, $p < .001$), but was not statistically significant for piece one (γ_{piece1} = .051, $p > .05$). The piecewise model explained variance increased by an additional 13.7% (.136818 for σ^2). Finally, the piecewise growth model demonstrated the best model fit (AIC = 340.480, BIC = 365.280). Therefore the piecewise growth model was used as

the new baseline model for additional testing used to answer the specific research questions for this study.

Table 6

Fixed and Random Effects Estimates for Severity of Illness Growth Models

Parameter	Model 1 Unconditional	Model 2 Linear - Week	Model 3 Quadratic - Week^2	Model 4 Piecewise
		Fixed Effects		
Intercept	.463263**	1.003921**	1.181277**	1.043209**
Week	-	-.181760**	-.393319**	-
Week^2	-	-	.035385**	-
Piece1	-	-	-	.050719
Piece2	-	-	-	-.711111**
Piece3	-	-	-	-.082830**
		Random Effects		
σ^2	.277029**	.126462**	.109145**	.094212**
T_{00}	.031602*	.051575**	.054009**	.056265**
Deviance	755.300	444.481	386.371	328.480
Parameters	3	4	5	6
$\Delta \chi^2$ (1)	-	310.819**	58.11**	-
AIC	761.300	452.481	396.371	340.480
BIC	773.700	469.015	417.038	365.280
Explained Variance (σ^2)	-	.543506	.136934	.136818

Note. * $p < .05$ **$p < .001$

Analysis of the Research Questions

Research question one. What is the relationship between mothers own milk (MOM) intake and neonatal severity of illness of very low birth weight and extremely low birth weight infants over the first six weeks of life? The relationship between MOM and neonatal severity of illness was explored in models five, six, and seven (See Table 7). MOM was explored as a level one independent variable in two ways: 1.) as a volume measured in milliliters and 2.) as a percentage of all enteral nutrition.

Model five explored adding MOM(mL) into the piecewise growth model. The parameter estimate for MOM(mL) ($\gamma_{MOM(mL)} = -.000105$, $p < .05$) was statistically significant and indicated

that as the neonate's intake of MOM increased by one milliliter, the neonatal severity of illness decreased by .000105. By adding MOM(mL) to model five, additional variance was explained (.000676 for σ^2) and a better model fit was demonstrated as compared to model four (Deviance = 319.241, $\Delta\chi^2(df) = 9.239(1)$, $p < .05$, AIC = 333.241, BIC = 362.175).

Since model five demonstrated a statistically significant relationship between MOM(mL) and SNAP-II scores, an additional parameter of birth weight was added to model six as a control variable to determine if the relationship between MOM(mL) and severity of illness remained statistically significant after adding this additional level two predictor variable to the model. In model six, the parameter for birth weight ($\gamma_{\text{Birth weight}} = -.000727$, $p < .001$) indicated that as a neonate's birth weight increased, the severity of illness score decreased. With the addition of this expected, statistically significant effect of birth weight in the model, MOM(mL) remained statistically significant ($\gamma_{\text{MOM(mL)}}) = -.000079$, $p < .05$). Model six, provided additional explanation of variance at level two (.463422 for τ_{00}) and a better model fit (Deviance = 287.862, $\Delta\chi^2(df) = 31.38(1)$, $p < .001$, AIC = 303.862, BIC = 336.930) as compared to model five.

Model seven evaluated the relationship between the percentage of MOM in the neonates' diet and neonatal severity of illness. In contrast, adding MOM(%) as a level one predictor to the piecewise model failed to demonstrate statistical improvement ($\gamma_{\text{MOM(\%)}}) = -.025263$, $p > .05$). Model seven provided a minimal amount of explained variance (.000817 for σ^2), but failed to demonstrate a better fitting model as the AIC and BIC increased in size and the chi-square test was not statically significant (Deviance = 328.267, $\Delta\chi^2(df) = .213(1)$, $p < .7$, AIC = 342.267, BIC = 371.201). Therefore, no statistically significant relationship was demonstrated between MOM(%) and neonatal severity of illness and no further statistical tests were performed.

Table 7

Fixed and Random Effects Estimates for Piecewise Models with MOM

Parameter	Model 4 Piecewise	Model 5 Piecewise MOM(mL)	Model 6 Piecewise MOM(mL) Birth Weight	Model 7 Piecewise MOM(%)
		Fixed Effects		
Intercept	1.043209**	1.043324**	1.816148**	1.043319**
Piece1	.050719	.059516	.057805	.072385
Piece2	-.711111**	-.655280**	-.669021**	-.711835**
Piece3	-.082830**	-.072145**	-.075094**	-.084582**
MOM(mL)	-	-.000105*	-.000079*	-
MOM(%)	-	-	-	-.025263
Birth Weight			-.000727**	
		Random Effects		
σ^2	.094212**	.093575**	.093334**	.094135**
T_{00}	.056265**	.049825**	.026735**	.056392**
Deviance	328.480	319.241	287.862	328.267
Parameters	6	7	8	7
$\Delta \chi^2$ (1)	-	9.239*	31.38**	.213
AIC	340.480	333.241	303.862	342.267
BIC	365.280	362.175	336.930	371.201
Explained Variance	-	.000676 (σ^2)	.463422 (τ_{00})	.000817 (σ^2)

Note. * $p < .05$ **$p < .001$

Research question two. What is the relationship between donor human milk (DHM) intake and neonatal severity of illness of very low birth weight and extremely low birth weight infants over the first six weeks of life? The relationship between DHM and neonatal severity of illness was explored in models eight and nine (See Table 8). DHM was explored as a level one independent variable in two ways: 1.) as a volume measured in milliliters and 2.) as a percentage of all enteral nutrition.

Model eight explored the relationship of DHM(mL) and neonatal severity of illness by adding it as an additional predictor to the piecewise model. The addition of DHM(mL) failed to demonstrate a statistically significant relationship with neonatal severity of illness ($\gamma_{DHM(mL)}$ = -

.000089, $p > .05$). Furthermore, model eight did not demonstrate a better fitting model as the BIC increased in size and the chi-square test was not a statically significant (Deviance = 325.575, $\Delta\chi^2(df) = 2.91(1)$, $p < .09$, AIC=339.575, BIC=368.509). Therefore, no statistically significant relationship was demonstrated between DHM(mL) and neonatal severity of illness.

Model nine examined the relationship between DHM(%) and neonatal severity of illness by adding DHM(%) as a predictor to the piecewise model. Model nine did not demonstrate a better fitting model as the AIC and BIC increased in size and the chi-square test did not demonstrate a statistically significant decrease (Deviance = 326.739, $\Delta\chi^2(df) = 1.74(1)$, $p < .2$, AIC = 340.739, BIC = 369.673). Therefore, no statistically significant relationship was demonstrated between DHM(%) and neonatal severity of illness ($\gamma_{DHM(\%)} = -.094057$, $p > .05$).

Initial correlations of aggregated means for infants failed to demonstrate a statistically significant relationship between SNAP-II and DHM(mL) as well as between SNAP-II and DHM(%). These findings were supported with the statistically insignificant parameter estimates for DHM(mL) and DHM(%) above as well as the rejection of model eight and nine as they did not provide model improvement as compared to the piecewise model alone. Therefore the null hypothesis was accepted and no further analysis was continued.

Research question three. What is the relationship between total human milk intake (THM) (combined total of MOM and DHM) and neonatal severity of illness of very low birth weight and extremely low birth weight infants over the first six weeks of life? The relationship between THM and neonatal severity of illness was explored in model 10, 11, and 12 (See Table 9). THM was explored as a level one, independent variable in two ways: 1.) as a volume measured in milliliters and 2.) as a percentage of all enteral nutrition.

Table 8

Fixed and Random Effects Estimates for Piecewise Models with DBM

Parameter	Model 4 Piecewise	Model 8 Piecewise DHM(mL)	Model 9 Piecewise DHM(%)
		Fixed Effects	
Intercept	1.043209**	1.042903	1.042934**
Piece1	.050719	.052012	.058807
Piece2	-.711111**	-.703655**	-.710619**
Piece3	-.082830**	-.079512**	-.081030**
DHM(mL)	-	-.000089	-
DHM(%)	-	-	-.094057
		Random Effects	
σ^2	.094212**	.093630**	.093773**
T_{00}	.056265**	.055867**	.056436**
Deviance	328.480	325.575	326.739
Parameters	6	7	7
$\Delta \chi^2$ (1)	-	2.91	1.74
AIC	340.480	339.575	340.739
BIC	365.280	368.509	369.673
Explained Variance (σ^2)	-	.006178	.004660

Note. * $p < .05$ **$p < .001$

Model 10 added the predictor variable of THM(mL) to the piecewise model to examine the relationship between THM(mL) and severity of illness. THM(mL) demonstrated a statistically significant relationship with severity of illness ($\gamma_{THM(mL)} = -.000150$, $p < .001$). This result indicated that as neonates increased their intake of THM by one milliliter, their severity of illness decreased by .000150. Model 10 demonstrated an additional 1.9% of explained variance at level one (.018957 for σ^2). Also, model 10 demonstrated a better model fit as compared to the piecewise model alone (Deviance = 310.139, $\Delta\chi^2(df) = 18.34(1)$, $p < .001$, AIC = 324.139, BIC = 353.073).

Since model 10 demonstrated a statistically significant relationship between THM(mL) and neonatal illness severity, birth weight, a known proxy for illness severity in the literature,

was added to the next model as a control. Model 11 demonstrated an expected statistically significant relationship between birth weight and illness severity ($\gamma_{\text{Birth weight}} = -.000698$, $p < .001$). In addition, the statistically significant relationship between THM(mL) and illness severity ($\gamma_{\text{THM(mL)}} = -.000127$, $p < .001$) persisted with the addition of the control variable. The parameter estimate for THM(mL) in model 11 indicated that as neonates increased their intake of THM by one milliliter, their severity of illness decreased by .000127. Model 11 also provided additional explanation of variance at level two (.461730 for τ_{00}) as well as a better model fit as compared to model 10 (Deviance = 279.280, $\Delta\chi^2(df) = 30.859(1)$, $p < .001$, AIC = 295.280, BIC = 328.347).

Model 12 evaluated the relationship between THM(%) and neonatal severity of illness. Although model 10 and 11 demonstrated a statistically significant relationships between THM(mL) and SNAP-II, the parameter estimate for THM(%) was not statistically significant ($\gamma_{\text{THM(\%)}} = -.101846$, $p > .05$) and model 12 did not improve the model fit as compared to the piecewise model alone (Deviance = 325.732, $\Delta\chi^2(df) = 2.748(1)$, $p < .1$, AIC = 339.732, BIC = 368.666) as demonstrated by a larger AIC, BIC, and a non-significant chi-square test.

Table 9

Fixed and Random Effects Estimates for Piecewise Model with THM

Parameter	Model 4 Piecewise	Model 10 Piecewise THM(mL)	Model 11 Piecewise THM(mL) Birth Weight	Model 12 Piecewise THM(%)
		Fixed Effects		
Intercept	1.043209**	1.042887**	1.785647**	1.043357**
Piece1	.050719	.065477	.063611	.146819
Piece2	-.711111**	-.618534**	-.632631**	-.713494**
Piece3	-.082830**	-.061900**	-.065356**	-.087945**
THM(mL)	-	-.000150**	-.000127**	-
Birth Weight	-	-	-.000698**	-
THM(%)	-	-	-	-.101846
		Random Effects		
σ^2	.094212**	.092426**	.092152**	.093430**
T_{00}	.056265**	.046107**	.024818**	.056944**
Deviance	328.480	310.139	279.280	325.732
Parameters	6	7	8	7
$\Delta \chi^2$ (1)	-	18.34**	30.859**	2.748
AIC	340.480	324.139	295.280	339.732
BIC	365.280	353.073	328.347	368.666
Explained Variance	-	.018957 (σ^2)	.461730 (τ_{00})	.008300 (σ^2)

Note. * $p < .05$ **$p < .001$

CHAPTER FIVE

DISCUSSION

Discussion of Findings

The purpose of this secondary data analysis was to explore the relationships between neonatal severity of illness and human milk, specifically mother's own milk, donor human milk, and total human milk over the first six weeks of life in VLBW and ELBW infants. This study contained two major areas of focus: 1.) human milk (MOM, DHM, THM) as the independent variable of interest and 2.) neonatal severity of illness as the dependent variable of interest.

Human milk. A growing body of evidence supports that human milk is the best nutrition for babies and that vulnerable populations should be provided with human milk to help mitigate illness and improve overall neonatal health. One consideration regarding measuring the effect of human milk is the ability to measure small effect sizes and ensure that small, yet statistically significant effects are not missed and therefore avoiding type II errors. The mean volume of human milk consumption changes greatly over the first few days and weeks of life and this was demonstrated in the current study. This variation was also demonstrated via the large standard deviation noted for each human milk volume ($SD_{MOM(mL)}$ = 668.94, $SD_{DHM(mL)}$ = 354.36, $SD_{THM(mL)}$ = 699.92).

The volume of nutritional intake for neonates is routinely documented in milliliters, therefore the parent study used this same measurement. Furthermore, this means that the parameter effects of human milk were estimated based on the effect of the neonate ingesting one

milliliter of human milk. One milliliter is a very small amount; therefore the corresponding effect per milliliter is anticipated to be small as well.

There are two approaches that can be used to ensure that the researcher does not miss this small, yet statistically significant effect: 1.) take the numerical value out additional decimal places so that the very small coefficients are still observed or 2.) compute a new variable for human milk by multiplying by a larger number to magnify the effect, essentially changing the comparison from the effect of ingestion of one milliliter to the ingestion of a larger amount of human milk. In this study, the primary investigator choose to keep the comparison at one milliliter as these fragile neonates often start enteral feeds one milliliter at a time. Also, many NICUs are now providing oral care with drops of human milk for these fragile infants before enteral feeds are started. A recent randomized clinical trial provided evidence that using 0.2mL of colostrum (the first human milk that is produced) for oral care every three hours, for three days, starting at 48 – 96 hours of life was associated with a statistically significant decrease in sepsis (Lee et al., 2015). Therefore, determining the effect of ingesting one milliliter of human milk can be a powerful way to let clinicians as well as new moms know the beneficial effects when these fragile infants ingest even small amounts of human milk. Mother's are more likely to provide human milk if they are empowered with the knowledge and clinicians are also more likely to promote and protect breastfeeding and human milk provision in the NICU when they are empowered with this knowledge as well.

The most significant results of this study were the statistically significant inverse relationships demonstrated between MOM(mL) and SNAP-II scores as well as THM(mL) and SNAP-II scores. Specifically, as MOM(mL) and THM(mL) volume of intake increased, severity of illness scores decreased. However, MOM(%) and THM(%) failed to demonstrate statistically

significant relationships with illness severity. These results are discordant and require further reflection and inquiry. It was expected that if the milliliter volume of human milk was correlated to illness severity measurements, that the percentage of human milk intake would also demonstrate significant inverse relationships and provide additional evidence of a relationship between human milk and neonatal illness severity. However, no relationship was seen with any of the human milk percentage predictor variables including DHM(%). This result indicates that caution should be used when interpreting the meaning of the relationship noted between MOM(mL) ,THM(ml), and neonatal severity of illness.

In the NICU, a neonate's intake is highly regulated by the provider according to the neonate's weight and physiologic stability. If neonates are unstable, or increased feeding residuals are observed, feedings are withheld. Inversely, as neonates are doing well, feedings continue and the volume of intake steadily increases in a stepwise fashion according the neonates physiologic status and toleration of the diet. Therefore, it is possible that the relationship that was observed in this study is that of volume of intake increasing over time related to the decreasing severity of illness scores over time regardless as to whether the intake volume was human milk or an alternative nutritional source.

In addition, DHM(mL) failed to demonstrate a statistically significant relationship with severity of illness scores, which may be due to insufficient quantities of DHM(mL) intake. When compared to quantities of MOM(mL) and THM(mL) intake, DHM(mL) was minimal and on average, it only composed 10% of the neonates' diet (See Table 3). So although DHM(mL) did not demonstrate a significant relationship with severity of illness in this study, it may be due to the small amounts of DHM(mL) that the infants ingested as compared to MOM(mL) and THM(mL). Most likely this minimal intake of DHM is due to two factors: 1.) the NICU for the

parent study did not introduce the use of donor milk until about halfway through recruitment for the parent study and 2.) although DHM may provide 100% of the enteral nutrition for a neonate, it is often only used as a supplement to MOM, because MOM is still known as the best human milk that is unique to that mother/baby dyad (Bauer & Gerss, 2011). Although DHM(mL) alone did not demonstrate a significant relationship with severity of illness, the addition of DHM(mL) as a part of the sum total of THM(mL) for model 10 ($\gamma_{THM(mL)}$ = -.061900, p < .001) and model 11 ($\gamma_{THM(mL)}$ = -.000127, p <.001) provided evidence that DHM(mL) strengthen the relationship between THM(mL) and severity of illness versus MOM(mL) alone ($\gamma_{MOM(mL)}$ = -.000105, p < .001).

Neonatal severity of illness. Neonatal severity of illness, the dependent variable of interest, was operationalized by the SNAP-II instrument. Although this instrument has been used widely thoughout the globe, this study is only the third known study to date that has used the SNAP-II instrument longitudinally (Morse, Groer, Shelton, Maguire, & Ashmeade, 2015). Madan et al. (2008) examined relationships of neonatal complications with SNAP-II scores; however, no statistically significant relationships were identified. Lim and Rozycki (2008) measured SNAP-II scores daily throughout the NICU admission and examined relationships of morbidity, specifically sepsis and necrotizing enterocolitis, as well as mortality to SNAP-II scores. However, the data did not demonstrate the ability of the SNAP-II score to accurately predict morbidity and mortality at these later time points.

Another concern identified by Lim and Rozycki (2008) was that 92% of the SNAP-II scores in their study were zero, indicating that there was no severity of illness identified in these at risk neonates. The current study also found a high percentage of null value SNAP-II scores; specifically 57.7% (n=266) of the SNAP-II scores in this study were zero. In addition, another

119 null values were not accounted for in the 57.7% since these participants (n=17) were eliminated prior to data analysis because they had a SNAP-II score of zero at all seven time points. Furthermore, when evaluating the SNAP-II scores by week, the frequency of null values increases over time from a low of 4.5% (n=3) on week one to a high of 89.6% (n=60) for week five.

A potential contributing factor to a high number of null SNAP-II values in the parent study is the lack of arterial blood gas data especially for later time points. If the neonate was not physiologically unstable enough to require an arterial line or an arterial blood gas sampling, then the value assigned was zero for the subscale. Although this practice is questionable, other studies indicated this same limitation (Lim & Rozycki, 2008). So although the SNAP-II score has robust data to support its utility as a measure of initial neonatal illness severity, the current study provides evidence that caution should be exercised when using this instrument to measure neonatal severity of illness over time. However, it is also imperative that the researcher considers the natural trajectory of illness scores over time during a NICU journey. It is reasonable to expect that most babies will improve during their NICU stay. Therefore indicating an expectation that the illness scores will decrease over time as the baby improves and moves towards a plan to discharge home. This may account for many of the null values at later time points as babies may be reaching discharge dates. However, this inquiry is beyond the scope of this dissertation.

An additional concern that was identified with the SNAP-II values was a violation of the assumption of normal distribution. Specifically, positive skewness and positive kurtosis was observed. Log10 transformation was conducted for correction; however it is more useful in correcting skewness versus kurtosis. Additionally, the large number of null scores as discussed

above impact this distribution. Further residual analyses with histograms and Q-Q plots were conducted on the final models to demonstrate normal distribution of the residuals.

Finally, the last major limitation of this dissertation was the inability to report a measure of validity for the SNAP-II measurement instrument. Although the researcher intended to calculate the Cronbach's alpha coefficient for the SNAP-II instrument for this sample of VLBW and ELBW neonates, it was not possible with the current data available in SPSS for this secondary data analysis. During the parent study, the SNAP-II scores were input into SPSS as a total score versus inputting each of the six subscales independently. Without the individual subscale values for the instrument, it is impossible to calculate this statistic. This was unfortunate because reliability data on the SNAP-II instrument has not been published (Morse et al., 2015).

Conclusions

The current study utilized a de-identified, existing data set to examine the relationship between human milk and neonatal severity of illness. Multilevel modeling was selected as the statistical measurement approach due to the time variant data that were nested within individual neonates. Six milk variables were explored including: MOM(mL), MOM(%), DHM(mL), DHM(%), THM(mL) and THM(%). Of these, only MOM(mL) and THM(mL) demonstrated a relationship with SNAP-II scores. The best model of fit for MOM(mL) was model six (See Table 7) and demonstrated that as MOM(mL) intake increased, neonatal severity of illness decreased. The best model of fit for THM(mL) was model 11 (See Table 9) and this demonstrated that as MOM(mL) and DHM(mL) were combined, each increase in THM(mL) consumption was inversely related to a decrease in the neonatal severity of illness score. However, no relationships were demonstrated with MOM(%), DHM(%), or THM(%). Although

statistically significant relationships were demonstrated between MOM(mL) and severity of illness as well as THM(mL) and severity of illness, these results must be interpreted with caution as the percentages of intake of MOM(%) THM(%) failed to demonstrate the same relationship.

Implications for Future Research

A growing body of evidence supports human milk as the best nutrition for neonates. This study provides additional support that a relationship between neonatal illness severity and human milk intake exists. Furthermore, due to this relationship and the known benefits of human milk consumption, human milk should remain a focus of ongoing research due to its potential to mitigate risk for the most fragile populations in the NICU. However, a more precise instrument may be needed to assess for subtle changes in illness severity over time when examining relationships between human milk and illness severity. The large percentage of null values for the SNAP-II score may indicate that the SNAP-II instrument is not precise at measuring very subtle changes in severity of illness. Future research should explore the development of a tool that is able to detect more subtle changes in severity of illness. Furthermore, the increased null SNAP-II values at later time points indicate a need for a precise instrument in order to detect the subtle changes in severity of illness that occur over time during a NICU admission. The ability to detect these subtle changes in illness severity will help researchers to continue to explore the relationships discussed in this study, yet the implications expand well beyond this research to all areas of neonatology.

Currently, the SNAP-II instrument is used mainly as a tool for research at the population level versus the individual patient level. With the increased use of the electronic medical record (EMR), it would be advantageous to create an automatically calculated illness severity score based on the routine input of assessment data by clinicians. An automatically calculated score

based on real time data would provide researchers with a plethora of information. Big data studies are increasing in popularity and a daily auto calculated illness severity score would provide a tremendous amount of information for researchers as they explore the data for relationships.

In addition, auto calculating illness severity scores would be beneficial for bedside clinicians as an illness severity surveillance tool that could be used in combination with their physical assessment skills and intuition. This researcher believes that if more EMR measurement tools were available for ongoing use by staff nurses, nurse practitioners, and neonatologists, this would empower clinicians with an additional tool to provide the best care for their current patients.

Finally, by incorporating EMR measurement instruments for daily use by bedside clinicians, researchers would be engaging more clinicians to become active partners in translational research. Research findings are often slow at being integrated into clinical practice. Additional collaboration among clinicians and researchers could help to decrease this gap of time from knowledge discovery to implementation. Together researchers and clinicians can make a difference in the lives of these fragile babies.

Acknowledgement

These data were collected as a part of a grant funded by the National Institutes of Health (R21NR013094).

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APPENDICES

Appendix A: IRB Exemption Letter

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11/10/2015

Shannon Morse
College of Nursing
1047 Kit Court
Lutz, FL 33549

RE: **Not Human Subjects Research Determination**
IRB#: Pro00023629
Title: Exploring the Relationship Between Severity of Illness and Human Milk Volume in Very Low Birth Weight and Extremely Low Birth Weight Infants Over Six Weeks

Dear Ms. Morse:

The Institutional Review Board (IRB) has reviewed your application and determined the activities do not meet the definition of human subjects research. Therefore, this project is not under the purview of the USF IRB and approval is not required. If the scope of your project changes in the future, please contact the IRB for further guidance.

All research activities, regardless of the level of IRB oversight, must be conducted in a manner that is consistent with the ethical principles of your profession. Please note that there may be requirements under the HIPAA Privacy Rule that apply to the information/data you will utilize. For further information, please contact a HIPAA Program administrator at 813-974-5638.

We appreciate your dedication to the ethical conduct of research at the University of South Florida. If you have any questions regarding this matter, please call 813-974-5638.

Sincerely,

VJorgensen MD

E. Verena Jorgensen, M.D., Chairperson
USF Institutional Review Board

Appendix B: SNAP-II and SNAPPE-II Instruments

Score for Neonatal Acute Physiology-II (SNAP-II)

Subscales		Point Value
Mean BP	≥ 30	0
	20 – 29	9
	< 20	19
Lowest Temperature	> 96 °F	0
	95 – 96 °F	8
	< 95 °F	15
PO_2/FIO_2	> 2.49	0
	1.0 – 2.49	5
	0.3 – 0.99	16
	< 0.3	28
PH	≥ 7. 2	0
	7.10 – 7.19	7
	<7.10	16
Multiple Seizures	No	0
	Yes	19
Urine Output (mL/kg.hr)	≥ 1	0
	0.1 – 0.9	5
	<0.1	18
Total Score Possible		115

Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II)

Subscales		Point Value
Apgar	≥ 7	0
	<7	18
Weight	≥ 1000g	0
	750 – 999g	10
	< 750g	17
SGA	>3%	0
	<3%	12
Total PE Score Possible		47
Total SNAPPE Score Possible		162

Footnote: "Reprinted from Journal of Pediatrics, 138 /1, Richardson, D.K., Corcoran, J.D., Escobar, G. J., Lee, S. K., SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores, 92-100., (2001), with permission from Elsevier." doi:10.1067/mpd.2001.109608
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Appendix C: Copyright Permission Letters

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