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Examining the Relationship of Blood Transfusions and Acute Morbidity in Preterm Infants

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DEDICATION

This dissertation is dedicated to my boys, Johnathan and Easton. There is never a day that your love and support cease to amaze me.

My husband Johnathan, you have seen me through every step of my educational journey and have never said no to my dreams. You have pushed and praised me, even at times I did not deserve it. I love you forever, and always. Sideways 8.

My sweet boy Easton. You have no idea how much you motivated me in the pursuit of my PhD. I hope my drive shines in you, and you always reach for the stars. The world is yours baby boy! I love *you* more than anything! (I win)

"Don't Stop Believin"
-Journey

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ABSTRACT

Preterm infants, those that are born less than 37 weeks gestational age, often suffer major morbidity and mortality during hospitalization in the neonatal intensive care unit due to their prematurity; one of the major morbidities is Necrotizing Enterocolitis, a devastating gastrointestinal disease. The exact aspects that cause preterm infants to develop Necrotizing Enterocolitis are unknown; however, our hypothesis is preterm infant thermal stability and/or preterm infant stress around packed red blood cell transfusions are etiological factors in the relationship between these necessary transfusions and morbid outcomes such as Necrotizing Enterocolitis.

This dissertation includes an in-depth background and introduction of various morbid conditions that preterms are predisposed to because of their preterm physiology which is covered in Chapter 1. Chapter 2 presents the current state of the science through a completed scoping literature review that identifies studies revealing varying conclusions as to the relationship between packed red blood cell transfusions and Necrotizing Enterocolitis in preterms. Chapter 3 features the study team's evaluation, selection, and adaptation of a conceptual framework that was driven by nursing theory to study the relationship of acute morbidity and packed red blood cell transfusions in preterms. Chapters 4 and 5 cover the method, design, and results of the two-phased dissertation study examining the relationship of blood transfusions and acute morbidity in preterm infants.

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LIST OF SYMBOLS

°C	Degree Celsius
°F	Degree Fahrenheit
$	Dollar or Peso sign
n=	Population size
%	Percent
I	Roman numeral 1
II	Roman numeral 2
III	Roman numeral 3
IV	Roman numeral 4
®	Registered Trademark

LIST OF ABBREVIATIONS

ABT.....ABDOMINAL TEMPERATURE

ANN.....ACADEMY OF NEONATAL NURSING

BPM.....BEATS PER MINUTE

CBC.....COMPLETE BLOOD COUNT

CDC .....CENTERS FOR DISEASE CONTROL AND PREVENTION

CINAHL .....CULULATIVE INDEX TO NURSING AND ALLIED HEALTH LITERAUTURE

CON ..... COLLEGE OF NURSING

CONS..... COAGULASE NEGATIVE STAPHYLOCOCCUS

CPTD .....CENTRAL PERIPHERAL TEMPERATURE DIFFERENTIAL

EMR..... ELECTRONIC MEDICAL RECORD

FT.....FOOT TEMPERTURE

GA.....GESTATIONAL AGE

GBS..... GROUP B STAPHYLOCOCCUS

G/DL ..... GRAM PER DECILITER

GI ..... GASTROINTESTIONAL

HCT..... HEMATOCRIT

HGB ..... HEMOGLOBIN

HIPAA .....HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT

HR.....HEART RATE

ID .....IDENTIFICATION

IRB.....INSTATUTIONAL REVIEW BOARD

ISC .....INCUBATOR SERVO CONTROL

MESH .....MEDICAL SUBJECT HEADINGS

ML/KG..... MILLILITER PER KILOGRAM

ML/KG/DAY .....MILLILITER PER KILOGRAM PER DAY

MOM..... MOTHER'S OWN MILK

NEC..... NECROTIZING ENTEROCOLITIS

NICU.....NEONATAL INTENSIVE CARE UNIT

NPO.....NOTHING BY MOUTH

PDA.....PATENT DUCTUS ARTERIOSIS

PHD.....DOCTOR OF PHILOSOPHY

PICC..... PERIPHERALLY INSERTED CENTRAL CATHETER

PIV .....PERIPHERAL INTRAVENOUS CATHETER

PRBC ..... PACKED RED BLOOD CELL

PRISMA..... PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META ANALYSES

REDCAP..... RESEARCH ELECTRONIC DATA CAPTURE

SAS .....STATISTICAL ANALYSIS SYSTEM

SD .....STANDARD DEVIATION

SPARC.....SUPPORT TO PROMOTE ADVANCEMENT OF RESEARCH AND CREATIVITY

TPN ..... TOTAL PERENTAL NUTRITION

UAC ..... UMBILICAL ARTERIAL CATHETER

UOFSC ..... UNIIVERSITY OF SOUTH CAROLINA

US ..... UNITED STATES

UVC ..... UMBILICAL VENOUS CATHETER

WHEAT ..... WITHHOLDING ENTERAL FEEDS AROUND PACKED RED BLOOD CELL TRANSFUSIONS

WHO ..... WORLD HEALTH ORGANIZATION

CHAPTER 1

BACKGROUND OF THE PRETERM INFANT

INTRODUCTION

Over 100,000 preterm infants, (nearly 10% of all births) are born annually in the United States, and this statistic continues to increase (Martin et al., 2020). Prematurity is a leading cause of death within the first month of life (Glass et al., 2015). Preterm infants are predisposed to morbidity and mortality due to their immature physiology and neonatal complications (Platt, 2014). Preterm birth is a major contributing factor in more than 75% of pediatric deaths during the first four weeks of life (Glass et al., 2015). Prematurity is associated with learning and motor disabilities and with visual and hearing impairment, contributing to approximately half of disabilities in children (Glass et al., 2015).

The costs of medical care in the Neonatal Intensive Care Unit (NICU) have an inverse relationship with the gestational age (GA) of the infant (Cheah, 2019). The cost of a NICU admission varies anywhere from $90-2,500 per day and this cost varies dependent of the degree of care the infant will require and GA (Deepak and Murki, 2019). It is reported that nearly 75 % of NICU admissions in the United States are related to prematurity (being born less than 37 weeks GA) and 25% are term newborns (born greater than 37 weeks GA) with varying physiological needs (Muraskas and Parsi, 2008). Preterm infants admitted to the NICU need numerous medical interventions depending on the GA and clinical condition such as: mechanical ventilation, noninvasive ventilation,

airway protection, central lines, total parenteral nutrition (TPN), and abundant medications. The care provided for the preterm infant in the NICU is life saving and essential; however, does not come without consequence. The everyday, life sustaining tasks performed in the NICU can pose stressful to a preterm infant and inadvertently lead to morbid conditions (Peng et al, 2013). Some stress inducing care situations will be further expounded upon in the following sections.

NUTRITION

Optimal nutrition in the preterm infant is a critical aspect of neonatal care (Dutta et al., 2015). However, feeding preterms can pose many difficulties as their gastrointestinal system (GI) is very immature. The overall goal is to reach full feeding volume safely in the shortest amount of time while avoiding negative complications that can accompany rapid feeding volume advancement. Full feeding volumes, approximately 150-180ml/kg/day, will allow the infant to gain weight daily and grow (Dutta et al., 2015). Preterms grow and thrive best on human milk (Gephart et al., 2018). Mothers' own milk (MOM) or donor human milk is recommended and encouraged in the NICU; however, not every preterm receives human milk. Determination is ultimately left to parent's discretion. Trophic feeds, or minimal volume, for preterms is 10ml/kg/day, in conjunction with TPN. Enteral feedings are facilitated using a feeding tube, either nasogastric or orogastric. Preterm infant feeding frequency and methods are determined per each NICU protocol. Enteral feeding frequency in this population may be continuous or intermittent, varying from one to three hours, based upon metabolic needs. Literature advises against routine checking of gastric residual and abdominal girth, as they are deemed unimportant findings (Dutta et al., 2015). However, it should be noted that

emesis or residual gastric fluid with evidence of blood is a critical finding and can be indicative of GI complications such as Necrotizing Enterocolitis (NEC), as some NICUs still utilize this practice (Gephart et al., 2018).

THERMAL REGULATION

A neonatal complication commonly found soon after delivery is thermal instability (Knobel & Holditch-Davis, 2010). Because preterms are inefficient in heat production, they are more susceptible to heat loss resulting in thermal instability such as, hypothermia (Knobel-Dail et al., 2017). The World Health Organization (WHO) defines hypothermia as a core temperature below 36.5°C (WHO, 1997). The mechanisms through which preterms can lose heat include: ***Radiation***: preterm infant's bare skin is exposed to environmental factors and heat is lost to a warmer environment; ***Evaporation***: preterms lose heat through their thin skin as insensible water is lost in to the air; ***Conductive***: preterms lose heat when they make physical contact with a cool surface or object and/or ***Convective***: preterms lose heat when their warm heat molecules from the skin surface are carried away by cooler air currents (Knobel & Holditch-Davis, 2010).

Preterms are unable to shiver to create heat as do term infants older than 12 months of age; however term infants and preterms greater than 32 weeks GA generate heat through non-shivering thermogenesis (Knobel-Dail et al., 2017). Infants less than 32 weeks GA have inefficient heat production due to their immature physiology, which may lead to to decreased oxygention, hypoglycemia and acidosis when heat loss is great and hypothermia results (Knobel-Dail et al., 2017). Hypothermia has been determined a

major cause for infant mortality and morbidity (WHO, 1997) and thus a critical component of neonatal care.

ANEMIA AND BLOOD TRANSFUSIONS

Red blood cell counts vary by GA and low amounts of red blood cells occur more rapidly and frequently in preterms. Due to their inability to produce red blood cells quickly and preterm frequent laboratory testing, preterms experience anemia. Anemia in the preterm has been described as a decrease in hemoglobin (Hgb), which is a component of the red blood cell. Hematocrit (Hct) is a test to measure the packed cell volume of the red blood cell. The acceptable ranges of Hgb are >10.0 g/dl and Hct > 30% (Polin et al., 2017); however, this threshold can vary between standards used in NICUs (Jeon & Sin, 2013). Normal Hgb and Hct levels in preterms are difficult to define as a preterms may present with other confounding issues and these infants are not considered healthy newborns (Jopling et al., 2009).

In the preterm, the average red blood cell life span is 40 to 60 days compared to 120 days in the adult (Jeon & Sin, 2013). The preterm also experiences mineral and electrolyte imbalances resulting in low counts of red blood cells. Additionally, preterm infants have low iron stores because they are born prior to the bulk iron transport from the mother's placenta, fetal bone marrow stimulation of erythropoietic activity, and a fully functional liver (Jeon & Sin, 2013).

In addition to their prematurity, preterms are subject to anemia due to frequent laboratory testing to maintain homeostasis (Widness et al., 2005). To correct their anemia, preterms frequently receive packed red blood cell (PRBC) transfusions, often when they are at a critical and fragile stage (Widness et al., 1996). PBRCs, concentrated

red blood cells, are the standard transfusion of choice for preterms as PRBCs are the component of whole blood that provides the red blood cells needed to increase the Hgb and Hct when anemia is identified while safely limiting transfusion volume (Basu & Kulkarni, 2014).

NECROTIZING ENTEROCOLITIS

NEC was first described and investigated in 1969 by Dr. John Stevenson (Stevenson et al., 1969). Since this time, NEC has become the most common and devastating GI complication in the preterm with more frequent occurrence in lower gestation (less than 34 weeks) and lower weight (less than 1500 grams) preterms (Knell et al., 2019). The incidence of NEC in preterms is as high as 13%, indiscriminate of sex, race, or ethnicity (Nino et al., 2016). NEC has an associated mortality rate of 20-30% and as high as 50% if surgery is indicated. A diagnosis of NEC can complicate and extend a hospitalization more than 6 months to a cost of nearly $500,000 if surgical intervention is required. Unfortunately, NEC may result in the preterm infant's death (Fitzgibbons et al., 2009).

The pathophysiology of NEC is affected by several risk factors such as prenatal events (preeclampsia, absent or reversed end-diastolic flow, hypoxia), immediate postnatal events (hypothermia, asphyxia, respiratory distress syndrome), and neonatal events (formula versus maternal milk feeding, congenial heart disease, apnea (Hall, Eaton, & Pierro, 2013). The primary and most agreed upon risk factor for the development of NEC is prematurity due to immature mucosa and immune response (Kliegman & Fanaroff, 1984).

The presentation of NEC can differ in each preterm and symptoms can include abnormal changes in lab values (complete blood count, blood gas), increased abdominal girth, discoloration of abdomen, increased gastric residual (contents in the stomach before the next scheduled enteral feeding) and/or the presence of blood in the stool (Nino et al., 2016). To rate the degree of NEC experienced by the preterm, the Bells' scoring system was utilized (Bell, et al., 1978). A few years later, there was a modification to this scoring system and was termed, *The Modified Bells' Scoring System* and is still the current the standard method of NEC classification (Zani & Pierro, 2015). Table 1.1 depicts this system.

Table 1.1 Modified Bells' Scoring System (Zani & Pierro, 2015)

Stage	Clinical Findings	Radiological Findings	GI Findings
IA	Apnea/Bradycardia Thermal instability	Normal or intestine dilation, mild ileus	Gastric residuals, mild abdominal distention, emesis
IB	Same as above	Same as above	Bright red blood per rectum
IIA	Same as above	Intestine dilation, ileus, pneumatosis	Grossly bloody stool. Defined abdominal distention, no bowel sounds
IIB	Mild metabolic acidosis and mild thrombocytopenia	Widespread pneumatosis, ascites, portal-venous gas	Abdominal wall edema with tenderness and loops
IIIA	Mixed acidosis, oliguria, hypotension, coagulopathy	Definite ascites, no free air	Generalized peritonitis, abdominal wall edema, redness, induration
IIIB	Shock, systemic deterioration	Pneumoperitoneum	Same as IIIA

SIGNFICANCE TO NURSING SCIENCE

As a standard, when a preterm requires a blood transfusion, a small amount of PRBCs (usually 10ml/kg) is sent from the blood bank freezer to the NICU for

transfusion. This blood may be warmed to room temperature before the nurses uses a pump device to infuse the PRBC liquid through a peripheral or centrally inserted venous catheter into the preterm over 1-4 hours. Other times, the PRBCs are immediately infused to the preterm by the nurse giving a slow push of the liquid through a syringe. The decision to warm the PRBCs prior to infusion or not, is unit specific. Researchers have anecdotally noted that infants have associated central hypothermia during PRBC transfusions (Knobel & Holditch-Davis, 2010). ***We hypothesize that preterm infant thermal instability and/or preterm infant stress around PRBC transfusions are etiological factors in the relationship between PRBC transfusions and morbid outcomes such as NEC.*** It is known that NEC is not idiopathic, rather complicated and confounded by other variables (Nino et al., 2016). NEC has been investigated for over 30 years without identifying a definitive causation; therefore, preterms are still experiencing NEC and dying from this complication. This dissertation explores the complicated associations between PRBC transfusions, feedings, body temperature, infant stress, and NEC.

GUIDING THEORETICAL FAMEWORK

The theoretical framework that guides the hypothesis and objectives for the proposed dissertation study is based on a modified version of Neuman's Systems Model (Neuman & Fawcett, 2011). Neuman's Systems Model describes how extrinsic factors (environment, culture) and intrinsic factors (age, sex, ethnicity) can influence and modify a system (person) thus altering homeostasis. Figure 1.1 is the ***modified model*** of Neuman's System Theory (The NEC Systems Model) which we developed to inform this dissertation research.

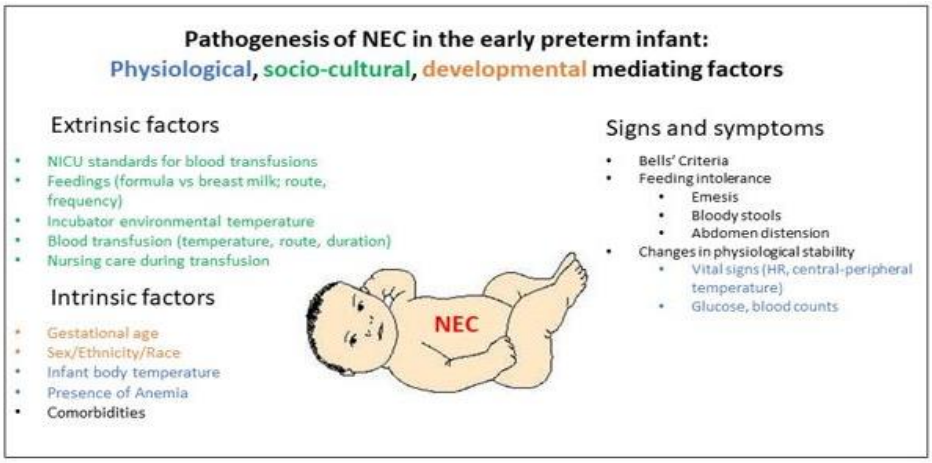

Figure 1.1 The NEC Systems Model

This conceptual model describes the extrinsic and intrinsic factors that may contribute to the pathogenesis of NEC in preterms who receive blood transfusions. As a standard, clinicians look for signs and symptoms of feeding intolerance and distress, which may or may not lead to NEC; however, there is no clear guideline to predict the pathogenesis of NEC. This model defines the factors that may lead to NEC and can serve as a guide for research studies to examine possible pathogenic pathways between these factors and the diagnosis of NEC. The intrinsic and extrinsic factors that influence *the system (preterm infant)* can lead to NEC depending on their contribution to the etiological pathway between PRBC transfusions and morbid outcomes such as: hypothermia, feeding intolerance, and NEC as diagnosed per Bells' stage (Bell et al., 1978). Neuman's System Model explores interacting variables from physiological interacting variables from physiological, psychological, sociocultural, developmental, and spiritual domains (Neuman & Fawcett, 2011). This model includes the physiological, socio-cultural and development domains. This model and our goal to explore pathways to NEC that may include PRBC transfusions, feedings, and hypothermia led to the scoping

literature review to be discussed in Chapter 2 of this dissertation. The NEC Systems Model will be further explained in Chapter 3.

SPECIFIC AIMS

To begin to understand acute and chronic morbid outcomes associated with PRBC transfusions, the intrinsic and extrinsic variables around the blood transfusion in a preterm need intensive study to identify relationships. This two-phased dissertation study examined PRBC transfusion practices through a national survey of neonatal nurses (Phase 1) and a secondary analysis of 16 transfusion cases in preterm infants, using mixed methods in an intensive, multiple case study design (Phase 2). The specific aims are as follows:

Aim 1. Examine standards in current practice for PRBC transfusions for preterm infants in NICUs across the United States through a national survey of neonatal nurses.

Research Questions:

1. What are the determining variables indicating an infant should be transfused with PRBCs?
2. What are the standards for feeding infants before, during, and/or after transfusion of PRBCs?
3. Are PRBC transfusions warmed prior to infusion and if so, how is this accomplished?
4. How are infants assessed physiologically before, during and after PRBC transfusions?

Aim 2. Examine preterm infant stability before, during and after PRBC transfusions in relationship to quantitative data (continuous body temperature, heart rate, oxygen saturation, lab values) and qualitative data (health record data: feeding status, presence of anemia, disease processes, medical treatments) in 16 infant transfusion cases using within

case analysis and between case comparison to synthesize case data for possible etiological links between PRBC transfusions and morbid conditions including hypothermia, feeding intolerance, NEC.

Research Questions:

1. How do physiological variables vary within infants before, during, and after PRBC transfusions?
2. Do infants have any signs/symptoms of stress or instability including hypothermia, feeding intolerance and/or acute morbid changes before, during or after PRBC transfusions?
3. How does infant condition during and after PRBC transfusions vary by infant age, sex, and race?

CHAPTER 2

EXAMINING ETIOLOGICAL PATHWAYS TO NECROTIZING ENTEROCOLITIS IN VERY PRETERM INFANTS: A LITERATURE REVIEW[1]

INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal (GI) complication that can occur in the first few months of life in this vulnerable population (Marin & Strickland, 2013). Nearly 13% of preterms are affected by NEC which is accompanied by extended hospitalization and cost (Nino, et al., 2016). Although a major cause of preterm morbidity and mortality, the exact etiology of NEC is still elusive to researchers (Marin & Strickland, 2013). The pathogenesis of NEC is multifactorial with gastrointestinal (GI) tract immaturity, microbial colonization, and GI ischemia playing major contributory roles (Knell et al., 2019).

In the last several years, researchers have reported three other factors that have been associated with increased NEC in preterms: (1) anemia; (2) packed red blood cell (PRBC) transfusions; and (3) enteral feedings before, during or after the blood

[1] Everhart, K., Donevant, S., Wirth, M., & Dail, R. B. (2020). Examining etiological pathways to necrotizing enterocolitis in very preterm infants. *Journal of Neonatal Nursing,* 27(2), 77-81. https://doi.org/10.1016/j.jnn.2020.07.003

transfusions (Marin & Strickland, 2013 ; Gephart, et al., 2018). Our ***team postulates another contributing factor for the development of NEC in the preterm, which may interact with GI tract immaturity, microbial colonization, GI ischemia, is thermal instability and the associated decreased central temperature (hypothermia) and changes in perfusion that is associated with blood transfusions. The presence of feedings and or anemia may play a role as well.***

OBJECTIVE

The objective of this literature review is to examine the variables of interest: hypothermia, enteral feedings, and blood transfusions, in relationship to the eventual development of NEC or signs and symptoms leading to NEC in the preterm. Through this scoping review, we hope to identify potential contributing factors associated with NEC in the preterm and answer the research question, "What is the state of the science around the relationship between PRBC transfusions, body temperature, and enteral feedings with the incidence of NEC in preterms?"

METHODS

The Cumulative Index of Nursing and Allied Health Literature (CINAHL) and PubMed databases were used to search for original reports of research and case studies related to PRBC transfusions with or without enteral feedings and incidence of NEC in the preterm, while also searching for any reference to anemia and/or hypothermia. The search was initially limited to neonates in the NICU; however, was further limited to very preterm infants in the NICU on the final search as this population is most vulnerable to NEC (Petrosyan, et al., 2009). Other inclusion criteria for the search included primary studies and/or meta-analyses written in English. No exclusion was implemented as to the

date of publication. When meta-analyses were identified, the primary studies within the meta-analyses were not reviewed independently as results from each meta-analysis included synthesis of these primary studies. All studies incorporated quantitative methods as no studies using qualitative methods were found in the search. The search terms used for CINHAL and PubMed were infant, newborn", "blood transfusion", "hypothermia", "body temperature regulation", "enteral feeding", "enterocolitis necrotizing", and "infant, preterm". Table 2.2 depicts the search and MeSH (medical subject headings) terms used.

Table 2.2 Search and MeSH terms

Database	Search Filters	Search/ MeSH	Citations Returned
CINAHL	English	"infant, newborn", "blood transfusion", "hypothermia", "body temperature regulation", "enteral feeding", "enterocolitis necrotizing", and "infant, preterm"	82
PubMed	English	"infant, newborn", "blood transfusion", "hypothermia", "body temperature regulation", "enteral feeding", "enterocolitis necrotizing", and "infant, preterm"	764

RESULTS

From the literature search, there were 846 published articles identified. We removed 749 of the articles through title screening and duplication. After secondary review, 42 full study reports were read and assessed. After title and abstract review, an additional 25 articles were excluded because they were review articles, not relevant to the topic of interest, or non-English language. There were 17 research reports partially related to the search terms used; however, none of the articles included all search terms together: "blood transfusion, neonate/infant/preterm, enteral feedings, and temperature." Of these 17 articles, there were three meta-analyses and seven other studies not included in any of the metanalyses. The search results are depicted in a PRISMA Flow Diagram

(Shamseer et al., 2015) in Figure 2.2. The three meta-analyses and seven independent studies were reviewed and synthesized for common themes and gaps in the literature. The literature demonstrates mixed conclusions on the relationship of PRBC transfusions and NEC in preterms. The etiology of this devastating disease is still elusive.

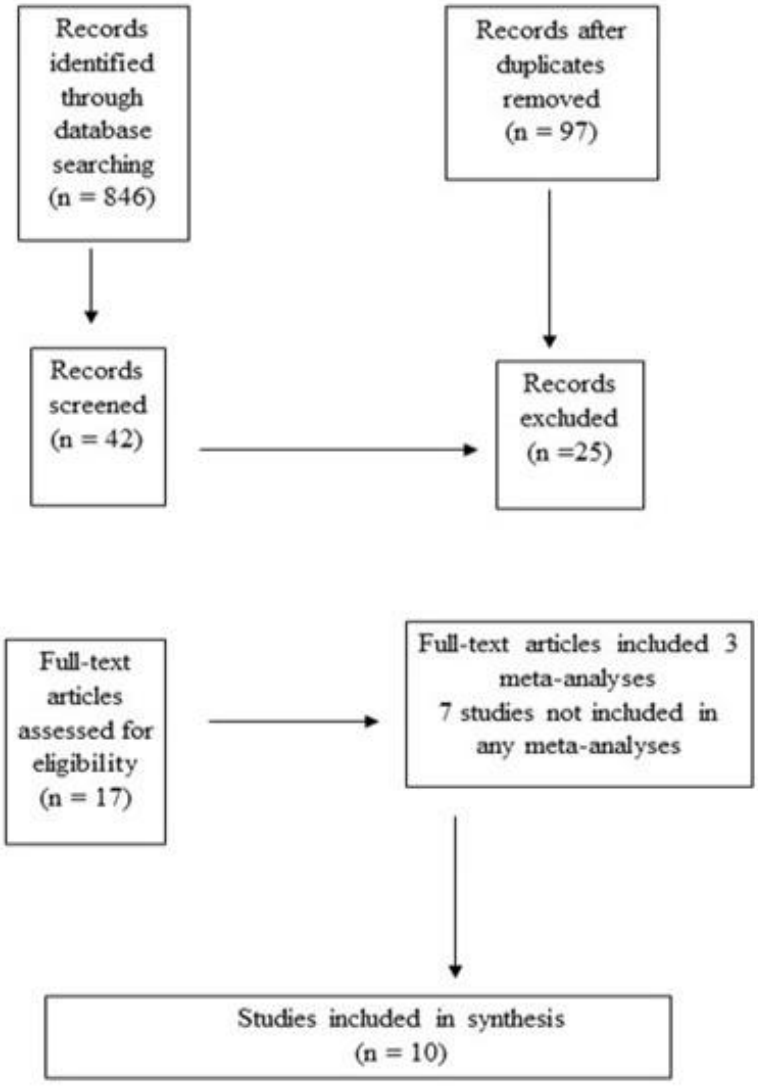

Figure 2.2 PRISMA Flow Diagram

META-ANALYSES

Mohamed and Shah's meta-analysis was published in March 2012. The analysis focused on transfusion associated NEC and identified eleven retrospective-case-controlled studies and one cohort study. These authors identified a relationship between recent PRBC transfusions and the incidence of NEC (Mohamed & Shah, 2012). The authors reported that infants who developed transfusion associated NEC were at higher risk for NEC, and in general had smaller birthweights and younger GAs. These infants were also more likely to have a patent ductus arteriosus (PDA) and were sicker than those infants who did not experience transfusion associated NEC or NEC without transfusions (Mohamed & Shah, 2012). In addition, Mohamed and Shah (2012) reported that only two of the studies described withholding feeds or reduction of feeding volume during the PRBC transfusion and thus, not enough evidence to suggest a relationship. However, Mohamed and Shah (2012) discuss extreme anemia could be associated to transfusion associated NEC as it leads to altered GI blood flow and changes in visceral vascular response to feeds as a result of an immunologic reaction and thus a reperfusion injury.

Amin et al., (2012) conducted a meta-analysis in October of 2012 which included all eleven studies from Mohamed and Shah's 2012 meta-analysis in addition to three new articles and identified the same findings of the previous analysis of transfusion associated NEC studies (Amin et al., 2012). The authors noted there could be a causal link between PRBC transfusions and NEC based on previous reviews and noted that preterms who experience transfusion associated NEC were more preterm with a more complex clinical course. The authors also assert there is increased morbid outcomes in preterms who experience transfusion associated NEC in comparison to non-transfusion associated NEC.

One limitation identified was lack of current studies on the topic and authors suggest caution on supporting this association. The authors recommend a large, multi-site study to explore this plausible association of PRBC and NEC in preterms (Amin et al., 2012).

Garg et al. (2018) conducted a meta-analysis of seventeen observational studies with reports of PRBC transfusions and NEC cases. The authors define the incidence of NEC after PRBC transfusions as transfusion-associated NEC, which is defined as any report of NEC within 48 hours after PRBC transfusion (Garg et al., 2018). Importantly, these authors did not find any association between PRBC transfusions and NEC. Garg and colleagues (2018) suggest changes in transfusion practices within NICUs may account for this finding as well as the multifactorial nature contributing to the etiology of NEC. In addition, they suggest attention needs to be given to other contributory causes of NEC such as the degree of anemia that leads to changes in GI blood flow. Finally, they also assert that PRBC transfusions are a common occurrence in the event of a NEC diagnosis and therefore could be misrepresented as an important link to NEC (Garg et al., 2018). Garg et al. reported that most studies reviewed for their meta-analysis did not report feeding practices during the transfusion time (Garg et al., 2018).

OBSERVATIONAL STUDIES

The seven additional observational studies identified that were not included in the three meta-analyses, were grouped by the search terms used and synthesized based on their subject content. The studies that discussed PRBC transfusions and NEC were consistent in their claims of an association between PRBC transfusions and NEC. They all revealed that the preterms who developed NEC and received a PRBC transfusion had lower GAs and birthweights (Cunningham et al., 2017; dos Santos et al., 2011; Jeon &

Sin, 2013). The preterms GA and birthweight are important factors to consider when examining an association between PRBC transfusions and NEC. Since the preterm is predisposed to needing PRBC transfusions based on their immature circulatory systems, it is plausible that receiving a PRBC transfusion is just a common association that occurs at/or around the time of a NEC diagnosis. Additional research is needed to establish a correlation between PRBC transfusions and NEC.

Another possible cause of NEC mentioned is the degree of anemia in the preterm (Jeon & Sin, 2013). Jeon and Sin (2013) attributed lower GA and birthweight with the degree of anemia; however, when adjusted for these variables, it was found that blood loss due to laboratory testing was the main cause of anemia in preterms. The authors explain that PBRC transfusions are treatment for anemia, and it is important to examine whether the preterm is symptomatic from anemia. They recommend preventing the anemia and subsequent PRBC transfusion by decreasing laboratory testing, both the number of tests and frequency (Jeon & Sin, 2013).

Marin et. al (2013) used near-infrared spectroscopy to investigate the relationship of PRBC transfusions and NEC. These researchers explicitly defined transfusion associated NEC as NEC symptom onset within 48 hours following a PRBC transfusion (Marin et al., 2013). The authors aimed to quantify transfusion associated NEC by means of mesenteric tissue oxygenation. Despite a small sample size (n=8), they were able to show a variation in mesenteric oxygenation patterns between the groups (non-PRBC vs PRBC). This also supports the claim Marin and Strickland (2013) used to develop their conceptual framework for transfusion-related NEC (Marin & Strickland, 2013). The preterms that developed NEC after receiving PRBCs received a larger PRBC volume and

more frequent PRBC transfusions (Marin et al., 2013). This concept could be coupled with the degree of anemia in preterms to explore further relationships.

Lastly, of the studies that discussed both PRBC transfusions and NEC, one group of researchers found a *decreased risk of acquiring NEC* in the presence of a PRBC transfusion (Sood et al., 2016). The authors assert there are limitations in other studies that have examined PRBC transfusions and the incidence of NEC because of other confounding factors to be considered such as medication regimens, feeding practices before, during, and after PRBC transfusions and the lack of comparison to preterms who did not develop NEC after PRBC transfusions. During this study, examining only PRBC transfusions and the incidence of NEC while controlling for other variables showed a decreased incidence of NEC compared to other study outcomes. The authors stated that these findings are unable to be generalized to all preterms. Larger cohorts and randomized clinical trials are needed to replicate their findings (Sood et al., 2016).

Another aspect of associating PRBC transfusions and NEC outcomes that needs to be examined is how preterms are fed around transfusion time. Several studies have reported an association between enteral feedings during PRBC transfusions and NEC; however, there is no standard of care related to this topic. The retrospective study by Doty et al. (2016) examined preterms over a 3-year period who had received a PRBC transfusion (n=180) and identified diverse feeding practices. Sixty-four of the 180 preterms did not receive enteral feedings during the PRBC transfusion, and the remaining 116 preterms received enteral feedings during at least one of their PRBC transfusions (Doty et al., 2016). While there was a lower number of NEC diagnoses in preterms who had enteral feedings withheld during PRBC transfusions compared to those who did not,

the overall study did not find a statistically significant difference ($p = 0.33$) between the groups (Doty et al., 2016). Although there was no statistical difference noted, the authors described the need for further studies to evaluate this relationship.

The last study report reviewed was of an improvement initiative to decrease the incidence of NEC in preterms (Talavera et al., 2016). These authors aimed to decrease the NEC rate from 8% to less than 4% in eight NICUs. The quality improvement measures utilized were restriction of certain medication usage, decreasing the number PRBC transfusions with more selective thresholds, and early human milk enteral feedings in the preterm in relation to the incidence of NEC (Talavera et al., 2016). The team found that after the initiation of these quality improvement measures there was a reduction of NEC cases from 8% to 3.1%. (Talavera et al., 2016). It is unclear which of the measures or a combination of the measures were responsible for the decrease in NEC. Table 2.3 depicts a summary of selected studies for review.

Table 2.3 Summary of selected studies

Author/Year	Level of Evidence	Quality Rating	Comments
Santos et al. (2011)	IV	Good	Relationship Recommends changes in transfusion guidelines
Mohamed & Shah (2012)	I	Good	N=12 studies Relationship Sicker infants
Amin, Remon, Subbarao & Maheshwari (2012)	I	Good	N=10 studies Plausible connection between PRBC and NEC
Won Jeon & Sin (2013)	IV	Good	N=50 Association of anemia, smaller birthweights and sicker.
Marin et al. (2013)	IV	Good	N=4, small sample All infants with PRBC transfusion had altered mesenteric blood flow
Sood et al. (2016)	IV	Fair	N=627 Claims less hazard of PRBC and NEC, but other clinical factors still had significance
Doty et al. (2016)	IV	Good	N=108 NEC lower when feeds held. No statistical significance however clinically significant
Talavera et al. (2016)	IV	Good	Human milk and conservative feeding patterns during PRBC reduced NEC cases Feeding held during but not before and after
Garg, Pinotti, Lal & Salas (2016)	I	Good	N=17 studies Claims no association NEC is multifactorial
Cunningham et al. (2017)	IV	Good	N=115 Association with lower gestational age and birthweight Claims association bias

No studies were found that included body temperature as a variable when examining precursors to NEC.

DISCUSSION

In a preterm, the body organs and systems are under-developed which can complicate clinical research when trying to assert causality or even associations. Some researchers attribute the state of anemia as a variable contributing to the development of NEC because anemia leads to decreased mesenteric flow (Jeon & Sin, 2013). Other researchers examined other external factors such as feedings; however, evidence around this variable was not definitive (Doty, 2016; Talavera, 2016). All factors presented, such

as low mesenteric oxygen levels, anemia related to prematurity and laboratory sampling, and feeding practices during PRBC transfusions potentially can each lead to morbid outcomes independently. Therefore, the medical community and the preterm population would benefit from ongoing research to identify causal relationships.

There are common themes of NEC causation identified through these studies. Yet, there is still no definitive answer to the question "what causes NEC in preterms?" This disease process has been investigated intensely for over 30 years with no clear answer.

A large research effort which is currently taking place in the United Kingdom to reduce the incidence of NEC in preterms is the "Withholding Enteral Feeds Around Packed Red Cell Transfusions (WHEAT) trial" (Gale et al., 2019). The research team conducting this multi-center randomized pilot study hopes to use information already collected by clinicians via a point-of-care testing scheme to determine whether withholding enteral feedings before, during, and after PRBC transfusions decreases the incidence of NEC (Gale et al., 2019). Findings from this study could inform the state of the science around NEC in the preterm and update care practice in NICU settings for preterms.

One aspect of NEC in the preterm that was missing from literature searched in this review was any associations between body temperature, PRBC transfusions and NEC in the preterm. Hypothermia was seen anecdotally in previous research (Knobel et al., 2013) in which preterm's body temperatures decreased during PRBC transfusions. Thus, our team asks-could the body temperature of a preterm during a blood transfusion have a contributory effect with the incidence of NEC? With decreased central body temperature,

comes decreased blood flow and perfusion (Dudgeon, et al., 1980). Decreased central body temperature, or hypothermia, may result from infusing PRBC fluid which may be cold having been delivered from the hospital blood bank freezer, typically stored at 0°C. PRBC transfusions are usually only allowed to sit and warm up to the environmental room temperature, which is largely 21°C to 24°C (70°F to 75°F). In our current study of in five NICUs, four of them allow blood to sit for several minutes at room temperature before transfusing while one NICU has implemented warming of PRBC transfusions prior to infusing. A review of standard NICU protocol for administering PRBC transfusions is needed. Studies are also needed to examine the relationship between a preterm's body temperature, blood transfusions and the incidence of NEC due to the gap in the literature around this topic.

CONCLUSION

Numerous research studies have focused on the incidence and etiology of NEC in preterms. There are no studies examining relationships among preterm body temperature, PRBC transfusions and enteral feedings given to the preterm before, during and/or after the transfusion in relationship to central hypothermia and NEC outcomes, which exposes a gap in the existing literature. This review reveals there is still a gap in our knowledge of and understanding of the factors that cause NEC in preterms. More research is needed to investigate transfusion practices and the possible relationship with NEC in preterms, as well as how those practices may affect body temperature, which could potentially contribute to the pathogenesis of NEC.

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CHAPTER 3

EXPLORING CONTRIBUTING FACTORS TO THE PATHOGENESIS OF NECROTIZING ENTEROCOLITIS IN VERY PRETERM INFANTS: AN ADAPTATION OF NEUMAN'S SYSTEMS THEORY[2]

INTRODUCTION

Incorporating models and theories in nursing care helps cultivate nursing knowledge (Sadeghnejad, et al., 2011). Theory provides the foundation for appropriate application of research efforts (Mahmoudzadeh-Zarandi, et al., 2010). The purpose of this paper is to describe and relate nursing theory to the area of preterm morbidity and mortality, especially as it relates to devasting diseases such as necrotizing enterocolitis (NEC). NEC is a devastating complication occurring in over 10% of preterms in the first few months of life (Knell et al, 2019). Although a major cause of preterm infant morbidity and mortality, the exact etiology of NEC remains vague (Marin & Strickland, 2013). NEC is multifactorial characterized with the triad of gastrointestinal immaturity, microbial colonization, and central ischemia playing major contributory roles (Knell et al, 2019). There is evidence that suggests blood transfusions are associated with an increased

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incidence of NEC, although the etiological pathway is still unknown (Marin & Strickland, 2013). Some speculated factors include stress of the blood transfusion along with the interaction of feedings before, during and/or after the blood transfusion as well as the presence of anemia (Jeon & Sin, 2013). An appropriate theoretical model to guide research and care of the preterm is Betty Neuman's "Neuman's Systems Model" (Neuman & Fawcett, 2011). The focus of this model is stress and the stress responses of the patient (system) which lends itself well to the neonatal intensive care unit (NICU) environment of the vulnerable preterm population, especially when examining health outcomes. Peng et al, 2013, describes neonatal hospitalization as stressful with environmental stimulation causing "sensory over-load", which is contradictory to the caring environment that neonatal clinicians are trying to accomplish within the NICU for the care of a preterm infant (Peng et al, 2013). Stressors are those events or actions during care that can alter certain preterm infants' physiological responses such as heart rate, respiration rate, and oxygen saturation (Peng et al., 2009). Environmental stressors in the NICU, such as light, noise, handling, and procedures (blood transfusions or feedings), can "overstimulate" a preterm infant and increase energy expenditures; metabolic energy is an essential component of living and thriving which is found in low reserves in the preterm infant (Peng et al., 2011; Peng et al., 2013; Peng et al., 2014).

Understanding the contributing factors of stress in early preterm infants and how to mitigate this stress to restore a state of hemostasis is a critical care aspect of their care to prevent morbidity and mortality.

DEVELOPMENT OF THEORY

Neuman's Systems Model was first presented in the 1970's and is constructed from General Systems Theory (Alligood & Marriner-Tomey, 2014). Neuman's Systems Model describes the open relationship of the system and the environment. The "system" has a unique structure of a center "core" and the lines of resistance and defense to stressors around that central core. The lines can be fixed, normal, or flexible in response to the stressor. Figure 3.3 depicts "the system" and "lines of defense" portion of Neuman's Systems Model.

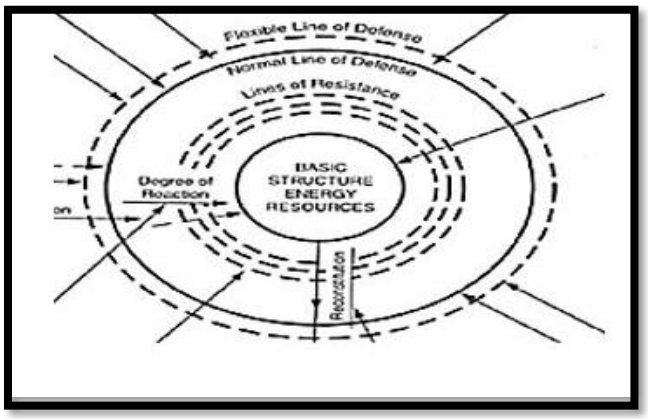

Figure 3.3 "System" and "Lines of resistance and defense" of Neuman's Systems Model

MAJOR ASSUMPTIONS

For a theory to be creditable, there should be assumptions provided by the theorist which are based upon their own values and beliefs to provide a foundation for the theory (Marchione, 1993). There are many assumptions in Neuman's Systems Model; however, specific appropriate major assumptions for the neonatal population interaction with their intensive care environment were selected for this paper. The selected major assumptions of Neuman's System Model are (Peptiprin, 2016):

-Each patient (system) is a unique makeup of factors and characteristics stored within a range of responses. This assumption describes how each infant (system) will present with their own distinct demographic and genomic make up and, therefore, cannot be standardized as a system or in their response to a stressor.

- There are many known, unknown, and universal stressors. They each differ in their potential for disruption of an infant (system) usual stability level. This assumption refers to the numerous stressors that can affect the system and cause dysfunction. There are well known stressors to any given population; however, there are those that are still unknown and need to be studied.

- Each infant (system) has a normal range of responses to the environment referred to as the "normal line of defense" and can be used as a standard by which to measure health deviation. This assumption describes the structure of the system that is comprised of "lines of defense" some that are fixed and others that are flexible and any response that does not lie within this "normal" can be considered an abnormality. With these assumptions stated and described, the remainder of this paper will demonstrate the theoretical and conceptual adaptation and application of Neuman's Systems Model to the exploration of contributing factors to the pathogenesis of NEC in very preterm infants.

THEORETICAL CONCEPTS

Neuman's Systems Model describes the intra, inter, and extrapersonal relationship of the internal and external stressors on the system, and the barriers, or "lines of resistance and defense" that the system has within to aide protection for the system (Fawcett & Foust, 2017). Intrapersonal stress is defined as stress within the system, interpersonal stress is stress between systems (person-to- person), and extrapersonal

stress is stress from the environment. Appropriate theoretical adaptation of Neuman's System Model to the exploration of contributing factors to the pathogenesis of NEC in early preterm infants begins by first understanding each of the stressors described by Neuman in the context of our "system", preterm infants.

THEORETICAL ADAPTATION

***Intrapersonal Stressors are described as the stress within the system*.** In this population, the "system" or the early preterm infant is vulnerable, fragile, and critical due to their preterm state. These "systems" have not fully developed in utero (40 weeks gestation) and, yet, after birth they are challenged to adapt to life within the NICU environment as best as they can. Some examples of preterm intrapersonal stressors include gestational age, sex, and race as there are instances in which differences in demographics of the preterm can influence health outcomes (Glass et al., 2015). These intrapersonal stressors are those that cannot be altered and therefore must be considered when caring for the preterm.

Another intrapersonal stressor can be the clinical context of an infant. There are often instances of "waxing and waning" states in the clinical course for preterms. (Glass et al., 2015). It would be fair to say that some days are better than others and overtime, this internal struggle can become burdensome on the lines of resistance and defense as defined by Neuman's Systems Model. The internal stressors of the preterm may be so taxing on the "system" that the lines of resistance and defense are broken, and this can lead to poor outcomes and even death. Figure 3.4 depicts the first adaptation of Neuman's Systems Model to the exploration of contributing factors to the pathogenesis of NEC in early preterm infants This adaptation begins to conceptualize the system and the

intrapersonal stressors by illustrating the system being preterm. The intrapersonal stressors are often characteristics that we as care providers or researchers cannot alter such as gestational age, sex, and/or race. For the purpose of research or clinical care, these intrapersonal variables (stressors) are physiological, developmental, and mediating components that may perpetuate the development of morbid conditions and outcomes.

Interpersonal Stressors are described as stress between systems. To care for this population effectively, care providers must possess a keen eye to the details of physiologic and behavioral changes in the preterm and tailor the care delivered to the individual infant. The focus of a neonatal care provider is to keep the "system" cared for and well. There are several factors that influence decisions in the care of the preterm.

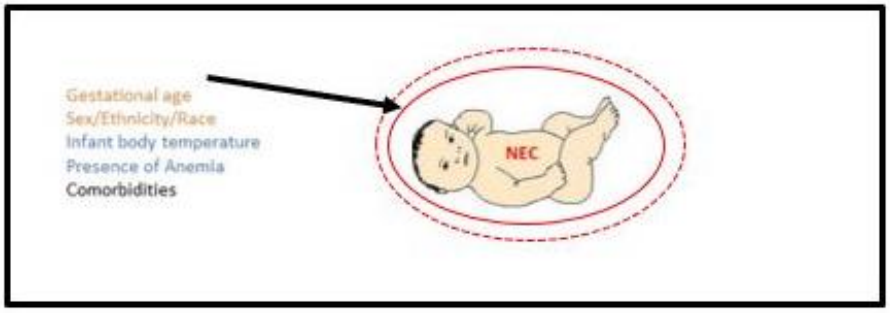

Figure 3.4 First adaptation of Neuman's Systems Model

These factors can present interpersonal stressors to the system because the system is underdeveloped and not prepared to handle interpersonal stress (Peng et al., 2011; Peng et al., 2013; Peng et al., 2014). These interpersonal stressors in addition to the intrapersonal stressors, continue to weaken the preterm's lines of defense and resistance, thus complicating the core response. In the context of this preterm infant system and the exploration of contributing factors to the pathogenesis of NEC in early preterm infants, the interpersonal variables are of socio-cultural domains that may perpetuate morbid conditions and outcomes.

Extrapersonal Stressors are described as stress from the environment. The NICU environment is comprised of specially trained clinical care providers who are prepared to adapt care to mimic intrauterine life as much as possible. Even with technological advances to optimize healthy outcomes for this system, this is not a perfect nor seamless process. There are specialty beds that preterms "live in" during their hospital stay that are designed to keep them warm, there are developmental tools (bedding) that are used to aid in correct anatomical positioning, and the expectation of quiet is known to all care providers and visitors; however, there are still extrapersonal stressors which challenge the health of the preterm infant. The extrapersonal stressors conceptualized for the purpose of examining a preterm infant within this environment have been grouped within the extrinsic factors and are of socio-cultural domains that may perpetuate an NEC diagnosis. The stressors include but are not limited to: NICU standards of care, feedings, environmental temperature, and nursing care (procedures, handling). These stressors were selected based upon the completed literature review variables blood transfusions, feedings, body temperature, and NEC, a conceptual analysis of environmental stress in the preterm infant, and NICU nursing experience (Everhart et al, 2020). The key findings to the literature review which examined etiological pathways to necrotizing enterocolitis in very preterm infants and the conceptual analysis of stress in the preterm infant, were that preterms endure a constant battle to maintain homeostasis and this ongoing stress, which can weaken and eventually break through the lines of defense, can lead to the core response as identified by poor neonatal health outcomes. These findings, in conjunction with the conceptualization of Neuman's Systems Model as a guiding framework for research efforts for preterm infants, exposes the need more

insight on the differing levels of stressors, as defined by Neuman's Systems Model. Figure 3.5 depicts the second adaptation of Neuman's Systems Model to the exploration of contributing factors to the pathogenesis of NEC in preterm infants. This adaptation adds the interpersonal and extrapersonal stressors in the model to conceptualize the relationships of the system's intrapersonal stressors, coupled with interpersonal (between systems) and extrapersonal (stress from the environment) stressors.

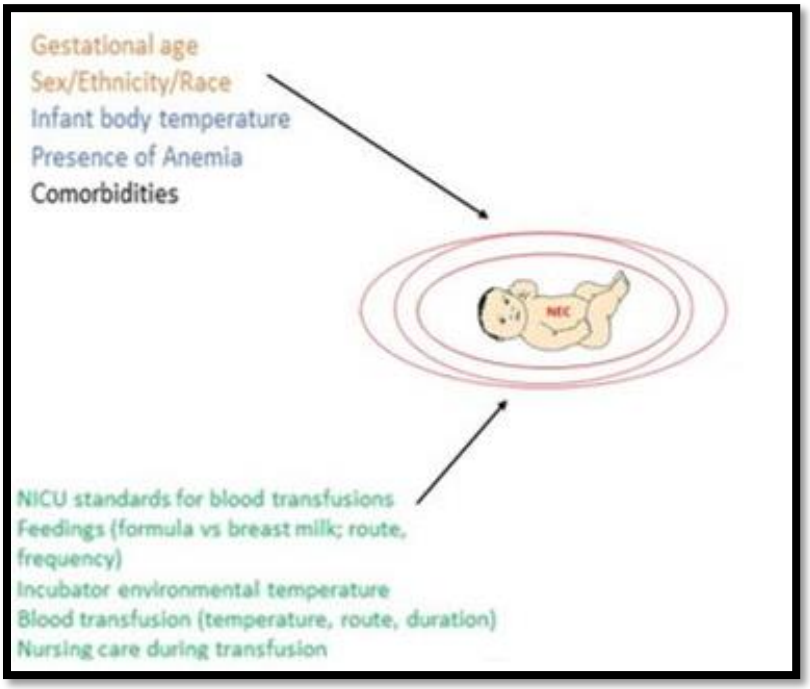

Figure 3.5 Second adaptation of Neuman's Systems Model

DISCUSSION

When the lines of resistance and defense are broken, there is a systematic breakdown. This breakdown is the difference between the state of wellness and illness for the "system" (Neuman & Fawcett, 2011). The system possesses a dynamic makeup of responses and relationships with the stressors of that system. Neuman's Systems Model

explains that wellness is a delicate balance of utilization and conservation of the energy available in the system and this balance must not be disturbed if optimal system stability is to be obtained. Neuman's System Model explores many interacting variables from physiological, psychological, sociocultural, developmental, and spiritual domains (Neuman & Fawcett, 2011).

For the case of the preterm infant, this breakdown could lead to infant stress and morbid conditions such as, but not limited to pathways or symptoms leading to hypothermia, decreased oxygenation, hypoglycemia, acidosis, feeding intolerance and/or a diagnosis of NEC (Bell et al, 1978; Nino et al, 2016; & Dani et al., 2017). The varying levels of ongoing stress on the preterm infant in the NICU, can have acute, long-term, or even fatal consequences. These consequences are a result of "over-burden" of the system which can lead to instability, such as those described by Neuman's Systems Model (Neuman & Fawcett, 2011). A model case example will illustrate for the audience the consequences of one type of stress, environmental stress, on the preterm infant being cared for in the NICU.

MODEL CASE

Consider bath nights in the NICU. The preterm infant has an axillary temperature reading of 97.4°F (36.3°C) on assessment. The nurse decides to forego the sign of a below acceptable axillary temperature reading by the World Health Organization (1997) of 36.5°C and proceeds to bathe the cold preterm infant. The preterm infant is crying and yawning during the bath. Following the bath, the preterm infant's incubator is alarming due to low infant temperature, and there have been bradycardic episodes noted by the nurse. This model case reflects how environmental stress (care, handling, and bathing)

can influence poor outcomes for preterm infants. In conjunction with the hypothesis that thermal instability, a form of stress, could be an etiological pathway to NEC, it is evident that Neuman's Systems Model and our adaptation of the model, it a sound fit to guide this research.

The final adaptation completes, depicted as Figure 3.6, a new model including the physiological, socio-cultural and development domains in relationship to the preterm. This model explains how extrinsic factors (inter and extrapersonal stressors) and intrinsic factors (intrapersonal stressors) can influence and modify a system (preterms) and may present an etiological pathway through signs, symptoms, and/or a diagnosis of NEC. After the lines of resistance are weakened, they can become broken. This event can cause a systematic breakdown in which there will be varying signs and symptoms of less-than-optimal wellness within the system. Morbid conditions are shown in the model, (See Figure 3.5) as signs and symptoms that indicate a change in homeostasis. This model is named The NEC Systems Model. The signs and symptoms include but are not limited to, NEC systems as defined by Bells' Criteria (Bell, et al., 1978) feeding intolerance defined by emesis, blood present in stools, abdominal distension (Nino et al., 2016), and alteration in physiological stability such as changes in vital signs and laboratory values (Platt, 2014).

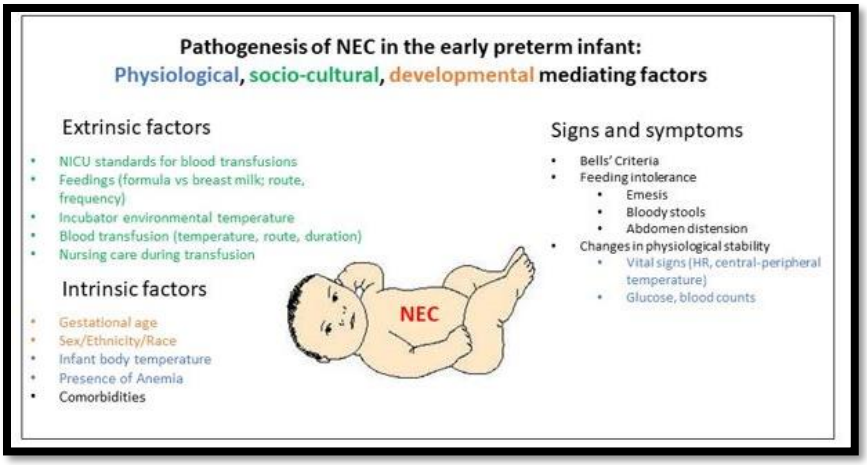

Figure 3.6 The NEC Systems Model

The application of Neuman's Systems Model to research and care of the preterm infant is a sound fit as the model addresses varying aspects of stress that can affect a "system". This model, when guiding preterm infant care and research, puts emphasis on the "system" and the response of that system. For the preterm infant, the use of this model allows the researcher and clinician to not only answer the research question or address the current clinical picture, but to approach the preterm infant holistically and understand that this population is multi-faceted and requires the system to be cared for on the intra, inter, and extrapersonal level.

CONCLUSION

Neuman's System Model provides a holistic approach to nursing care of the "system" (Neuman and Fawcett, 2011). The model provides focus on the "system" and their individual responses to the intrapersonal, interpersonal, and extrapersonal stressors they endure. The overarching goal of the model is *optimal system wellness* to maintain homeostasis within the "system" (Neuman and Fawcett, 2011).

The preterm infant will endure stressors of all domains as defined in both models as a result of their prematurity. With this adaptation of Betty Neuman's Systems Model, we intend to explore the relationship of the neonatal environment on the overall "system" health and how these stressors may lead to signs and symptoms of NEC, or an eventual diagnosis of NEC. Using Neuman's System Model to develop conceptual and theoretical frameworks to examine infants within their systems and the associated stressors, will guide clinicians and researchers to improve neonatal morbidity and mortality in the future.

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CHAPTER 4

EXAMINING STANDARD PRACTICES USED FOR PACKED RED BLOOD CELL TRANSFUSIONS FOR PRETERM INFANTS IN NEONATAL INTENSIVE CARE UNITS ACROSS THE UNITED STATES: A NATIONAL SURVEY

INTRODUCTION

In 2019, there was a 2.6% rise (from 10.02 to 10.28%) in preterm infants born in the United States (US) alone (Martin et al, 2020). According to the Centers for Disease Control and Prevention (CDC), the incidence and associated complications of preterm birth continue to be a national health crisis (Centers for Disease Control and Prevention [CDC], 2020). Preterms are considered one of the most vulernable populations due to their immature physiology (Behrman et al., 2007). A preterm can acquire an infection nearly anywhere on or in their body such as the blood, urine, skin, or eyes (Polin et al., 2017). Preterms are also predisposed to a devastating gastrointestinal (GI) complication known as Necrotizing Enterocolitis (NEC). Nearly 13% of preterm infants are affected by NEC, which extends and complicates the hospitalization and increases costs (Nino et al., 2016).

The pathogenesis of NEC is described by a triad of contributing factors that include GI tract immaturity, microbial colonization, and GI ischemia (Knell et al., 2019). The Bell and modified Bells' Scoring System can be used to describe the extent of

severity of NEC disease with “stages” based on the presenting symptoms (Bell et al.,1978, Zani & Pierro, 2015). The Bell stages include: Stage I (Mild/Suspected) with nonspecific radiological findings; Stage II (Moderate) with radiological findings of pneumatosis or portal venous gas and abdominal distention, tenderness, and thrombocytopenia; and Stage III (Severe) with radiological findings of a pneumoperitoneum, worsening of symptoms from stage II in addition to hypotension, peritonitis or severe metabolic shock and acidosis (Bell et al, 1978). The initial presentation of NEC can vary, and symptoms include abnormal changes in lab values (complete blood count, blood gas), increased girth or discolorations of abdomen, increased gastric residuals (contents in the stomach before the next scheduled enteral feeding) and/or blood in the stool (Nino et al, 2016). Many infants can present with the signs and symptoms of NEC, but never receive a diagnosis of NEC; however, these subtle signs and symptoms can lead to stopped feedings, decreased infant growth, and longer hospitalizations. Although defined as a major contributor to preterm infant morbidity and mortality, the exact etiology of NEC is still vague (Marin & Strickland, 2013). Therefore, there is a critical need for more research to be done on the etiological factors contributing to NEC. Current research shows that NEC is not an idiopathic process, but a rather complicated disease process confounded by other variables (Nino et al., 2016). Researchers have been investigating NEC for over 30 years without identifying an etiology and preterms are still experiencing NEC and dying from this complication (Marin & Strickland, 2013).

Due to an immature circulatory system and frequent, yet, necessary laboratory testing, preterms may experience anemia, a noticeable decrease in hemoglobin and

hematocrit (Jeon & Sin, 2013). Often, mineral and electrolyte imbalances can lead to decreased red blood cell counts in preterms. Preterms are also born prior to the bulk iron transport from the mother's placenta and have poor fetal bone marrow stimulation of erythropoietic activity due to immature liver function, which all can lead to altered blood counts (Jeon & Sin, 2013). As a result, preterms often receive repeated blood transfusions with packed red blood cells (PRBC) over their hospitalization (Howarth et al., 2018). PRBCs are the gold standard to correct hemoglobin and hematocrit imbalance. These red blood cells increase hemoglobin and hematocrit levels and eliminates giving extra fluid volume (Basu & Kulkarni, 2014).

Recent evidence suggests PRBC transfusions could be associated with the onset of NEC in preterms; but researchers have not determined the exact causal pathway. One potential explanation for NEC is the degree of anemia present in the preterm. Other possible explanations include the overall stress of the PRBC transfusion on the preterm and/or the involvement of feeding practices before, during and/or after the PRBC transfusion. Another theory related to the PBRC transfusion is the temperature of the PRBCs during the transfusion (Knobel & Holditch-Davis, 2010). Researchers have anecdotally noted central hypothermia in preterms after PRBC transfusions in previous studies (Knobel & Holditch-Davis, 2010). Some of the possible explanations include the stress experience of the blood transfusion and the involvement of feeding practices before, during and/or after the PRBC transfusion. There has also been conversation as to the degree of anemia present in the preterm being a factor in the etiology of NEC. Generally, PRBCs are sent from the blood bank freezer to the neonatal intensive care unit (NICU) for transfusion; however, there are variations in most NICU protocols which

could, or could not specify if the PRBC transfusion syringe can warm to room temperature before infusing to the fragile preterm infant. Some NICU protocols dictate the use of a blood warmer on these small transfusions, where others do not. NICU practice trains nurses infuse PRBCs over 1-4 hours and monitor infant stability during the transfusion (Lau, 2017). Further the NICU protocols dictate whether the preterm infant continues to receive feedings during the PRBC transfusion. Currently, there are no published standards for NICU nurses administering PRBC transfusions to preterm infants resulting in inconsistent practices. Based upon these gaps in the existing literature and standards of practice surrounding PRBC transfusions in preterms, we wanted to examine the standard practices used for PRBC transfusions for preterm infants in NICU across the United States. The purpose of this study was to identify 1) clinical indicators for a PRBC transfusion, 2) warming practices of PRBC before and during a transfusion, 3) feeding practices of the preterm infant before, during and after a PRBC transfusion, and 4) assessment of the preterm infant during the PRBC transfusion.

METHODS

Online Survey Our team developed a 23-item survey in Research Electronic Data Capture (REDCap; Harris et al., 2009). REDCap offers a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (Harris et al., 2009). The team developed the survey questions based on our team's neonatal clinical

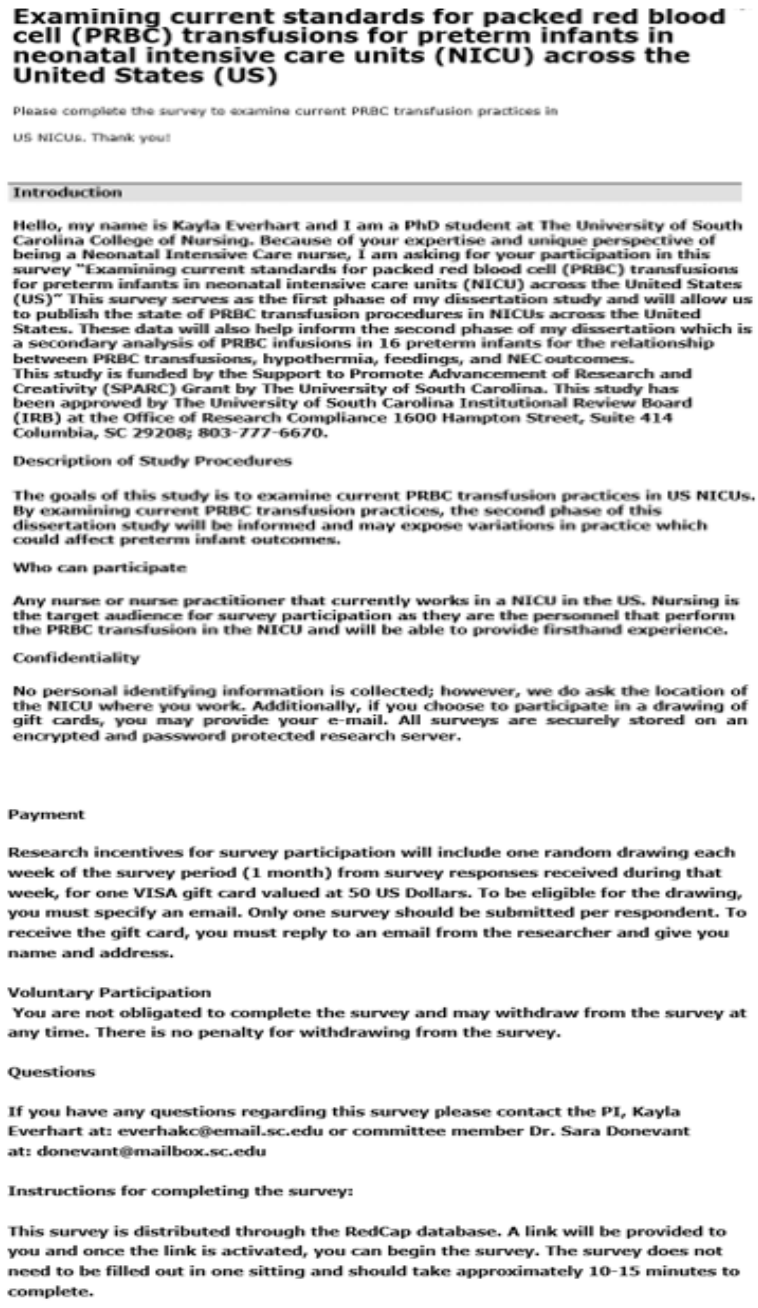
experience and a literature review on this subject, presented in Chapter 2 (Everhart et al, 2020).

Research has demonstrated that feeding practices may be a factor in the relationship between PRBC transfusions and the development of NEC in preterm infants; however, findings are not conclusive. Therefore, we wanted to explore feeding practices before, during, and after PRBC transfusions in preterms. In this survey, we did not ask what they were feeding, as this concept will be examined in future research. We are more interested in *how* NICU nurses feed preterms around the time of PRBC transfusions. Generally, PRBC transfusions are infused over 1-4 hours (Lau, 2017) and so the amount of time the infants are made NPO during the transfusion would be based on their NICU protocol.

For the questions on the preterm assessment, we stratified preterm infants based on gestational age (GA) using groups as 1 (23-27 weeks gestation) and 2 (28-32 weeks gestation). The intention with separating groups by GA was to investigate if more complex and fragile preterm infants received more frequent assessments in relationship to the PRBC transfusion. Respondents were asked to comment on assessment of physiological variables including heart rate, respiratory rate, oxygen saturation, blood pressure, and body temperature.

Content validity was assessed by a nurse scientist with clinical background as a neonatal nurse and practitioner with over 10 years as a neonatal researcher and an academic researcher with expertise in internet surveys. Based upon her feedback, the survey was refined prior to study initiation. The questions included yes/no, select all that apply, and short open narrative responses to provide specific detail for analysis.

Participants could access and complete the survey using an internet connection in 10-15 minutes. The response options were derived from the team members' NICU nursing experiences. Figure 4.7 is an example of the invitation letter that was included at the beginning of the survey. The entire survey is located in Appendix A.



Examining current standards for packed red blood cell (PRBC) transfusions for preterm infants in neonatal intensive care units (NICU) across the United States (US)

Please complete the survey to examine current PRBC transfusion practices in US NICUs. Thank you!

Introduction

Hello, my name is Kayla Everhart and I am a PhD student at The University of South Carolina College of Nursing. Because of your expertise and unique perspective of being a Neonatal Intensive Care nurse, I am asking for your participation in this survey "Examining current standards for packed red blood cell (PRBC) transfusions for preterm infants in neonatal intensive care units (NICU) across the United States (US)" This survey serves as the first phase of my dissertation study and will allow us to publish the state of PRBC transfusion procedures in NICUs across the United States. These data will also help inform the second phase of my dissertation which is a secondary analysis of PRBC infusions in 16 preterm infants for the relationship between PRBC transfusions, hypothermia, feedings, and NEC outcomes.
This study is funded by the Support to Promote Advancement of Research and Creativity (SPARC) Grant by The University of South Carolina. This study has been approved by The University of South Carolina Institutional Review Board (IRB) at the Office of Research Compliance 1600 Hampton Street, Suite 414 Columbia, SC 29208; 803-777-6670.

Description of Study Procedures

The goals of this study is to examine current PRBC transfusion practices in US NICUs. By examining current PRBC transfusion practices, the second phase of this dissertation study will be informed and may expose variations in practice which could affect preterm infant outcomes.

Who can participate

Any nurse or nurse practitioner that currently works in a NICU in the US. Nursing is the target audience for survey participation as they are the personnel that perform the PRBC transfusion in the NICU and will be able to provide firsthand experience.

Confidentiality

No personal identifying information is collected; however, we do ask the location of the NICU where you work. Additionally, if you choose to participate in a drawing of gift cards, you may provide your e-mail. All surveys are securely stored on an encrypted and password protected research server.

Payment

Research incentives for survey participation will include one random drawing each week of the survey period (1 month) from survey responses received during that week, for one VISA gift card valued at 50 US Dollars. To be eligible for the drawing, you must specify an email. Only one survey should be submitted per respondent. To receive the gift card, you must reply to an email from the researcher and give you name and address.

Voluntary Participation

You are not obligated to complete the survey and may withdraw from the survey at any time. There is no penalty for withdrawing from the survey.

Questions

If you have any questions regarding this survey please contact the PI, Kayla Everhart at: everhakc@email.sc.edu or committee member Dr. Sara Donevant at: donevant@mailbox.sc.edu

Instructions for completing the survey:

This survey is distributed through the RedCap database. A link will be provided to you and once the link is activated, you can begin the survey. The survey does not need to be filled out in one sitting and should take approximately 10-15 minutes to complete.

Figure 4.7 REDCap Invitation Letter

SAMPLE

The inclusion criteria included any nurse or nurse practitioner currently working in a NICU in the US. As nurses perform the PRBC transfusion, we selected them to provide firsthand insight on the processes and protocols. No personal identifying information was collected during the survey. However, the survey included demographic information such as age, years of nursing and NICU experience, education level, and location of the NICU where the respondents worked. This survey research study was approved by the University of South Carolina (UofSC) institutional review board (IRB).

DATA COLLECTION

We employed a variety of recruitment methods including social media and an email blast from Academy of Neonatal Nursing (ANN), a professional neonatal nurses' organization. Research team members promoted the survey through social media accounts (Facebook and Twitter). Upon approval from the leadership of ANN, an email and survey link were sent to each ANN member as a onetime dedicated email blast for a nominal fee with funds from the Support to Promote Advancement of Research and Creativity (SPARC) grant, an internal UofSC grant. ANN's policies require distribution in this manner as member email data are confidential. The email blast from ANN occurred approximately 3 weeks after the survey was first promoted on social media.

To increase the response rate, we offered $50 US dollar gift cards as an incentive with one weekly random drawing for a gift card for four weeks. If the participants wished to participate in a drawing of gift cards, they provided their email information for entry in the drawing during the week of their response. We used a random number generator

using the completed survey identification (ID) numbers to select the weekly winners. In total, the survey was active for 4 weeks duration.

DATA ANALYSIS

We exported the results from REDCap into Microsoft Excel for analysis using the following: 1) descriptive statistics (average, standard deviation [SD], range) for continuous variables. The categorical data were analyzed with 2) frequencies and percentages for categorical data and 3) tests of normality for continuous numerical data. Two members of the team independently analyzed the narrative and short answer responses for themes.

RESULTS

Over the 2 weeks of promotion on social media, we received 687 responses. An additional 70 responses were received after the onetime ANN email for a total of 757 survey responses. Of the surveys submitted, 521 had complete data which were used in the analyses.

DEMOGRAPHICAL DATA

Of the 521 valid responses, all responses included the NICU level of care: 48% (n=249) were from level IV NICUs, 49.7% (n=258) were level III NICUs and 2.3% (n=12) were from level II NICUs. There were no responses from nurses working in a Level I NICU. The mean age of respondents was 32 years old (range = 21-66 years; SD = 9.5) with 8 years of NICU nursing experience on average (range = 1-43 years, SD = 9). Educational degrees obtained by respondents ranged from Associate to Doctoral Degrees. Respondents worked across the US with 47 of the 50 states represented.

CLINICAL INDICATORS

We asked about the clinical indicators used to determine if a preterm received a PRBC transfusion. The participants selected all answers that applied from the following options: 1) apnea/bradycardia, 2) low hematocrit (HCT), 3) abnormal vital signs, 4) hypotension, 5) hypovolemia, and 6) other. Of the clinical indicators for a PRBC transfusion in preterms, participants reported low HCT most frequently 96% (n=501) followed equally by hypovolemia and apnea/bradycardia at 63.3% (n=330). Abnormal vital signs (%) and hypotension (%) were the least reported clinical indicators amongst the survey respondents.

WARM PRBC TRANSFUSIONS

The majority 74% (n=386) of participants reported not warming PRBC transfusions. Only 10.2% (n=53) of participants indicated they warm PRBC transfusions. However, only 2.1% (n=11) reported using a blood warmer to warm PRBCs. Other warming processes included 1) allowed the PRBCs to "sit out", 2) "warm by ambient air", or 3) "using my own body heat."

FEEDING PROTOCOLS

The majority of nurses (66%, n=343) reported they alter feedings during a PRBC transfusion which demonstrates variation in care for preterms. Next, we asked *how* the feedings were altered. Almost 41% (n=212) of participants indicated preterms are not fed or made nothing by mouth (NPO) ***before*** the PRBC transfusion. However, the research team did not ask how much time prior to the transfusion and assume this included any time prior to the PRBC transfusion. Most nursing respondents, 57.6% (n=300), indicated the infants are made NPO ***during*** the transfusion.

One important finding in the open-ended questions was how practice may vary within the same NICU in relationship to feeding orders and PRBC transfusions based on the provider writing the orders. Multiple nurses stated, “Feed orders depend on which doctor or practitioner is giving the orders.” The nurses explained PRBC transfusion practices within their NICU can also vary based on GA of the preterm, varying thresholds of vital signs and laboratory values, and clinical presentation.

ASSESSMENT OF PRETERM INFANTS

Participants’ responses indicated most NICUs have consistency in the physiologic assessment of preterms regardless of GA during PRBC transfusions. The perterms were routinely assessed every 2-4 hours when not receiving PRBC transfusions. However, 97% (n=505) of participants indicated their NICU employs a specific assessment policy during PRBC transfusion, as in the frequency of the variable assessments (heart rate, respiratory rate, temperature, blood pressure) and an hourly (at a minimum) visualization of the PRBC infusion site.

TRANSFUSION ACCESS

Need a sentence explaining what you were asking. Survey answer options for infusion access included: 1) peripheral IV (PIV), 2) peripherally inserted central catheter (PICC), 3) umbilical arterial catheter (UAC), 4) umbilical venous catheter (UVC), 5) broviac/central venous line, and 5) do not know. Almost all (99%, n=515) of respondents indicated that a PIV was the preferred administration site for PRBC transfusions. If this was not possible, the next most preferred site was UVC (74.5%, n=388). Some respondents (25%, n=130) indicated that UACs are used for PRBC transfusions., as this is not a frequented practice (U.S. National Library of Medicine, 2021).

DISCUSSION

In this survey, we found that PRBC transfusion practices vary in NICUs across the US. There was great inconsistency in answers regarding warming PRBCs versus not warming PRBCs for routine transfusions. However, some nurses do use artificial means to warm PRBCs prior to transfusion. Often nurses conduct work arounds to accomplish tasks to achieve the outcome, even when knowing this is not evidence-based or best practice (Debono et al., 2013). For example, using "your own body heat" to warm a syringe of PRBCs to give a preterm is practical but may not necessarily reflect evidence-based practice. In a previous survey designed to elicit practices for decreasing heat loss in the delivery room, our team found that nurses knew plastic wrapped around an infant would decrease heat loss. Yet one respondent reported using the plastic package bag from the manual resuscitator (ambu bag) envelop a preterm (Knobel, Vohra, & Lehmann, 2005). These examples of workarounds may potentially place the preterm at greater risk. Research is needed to provide the best evidence so that clinicians can standardize practice, improve consistency, and decrease complications in these vulnerable infants.

There was difference in access site for PRBC transfusions. The literature states that UACs *can* be used for PRBC transfusions; however, this is not the preferred route as there is an increased risk of thrombosis (U.S. National Library of Medicine, 2021). The participants also reported using PICCs as a means for PRBC transfusions, but the access comes with an associated risk of hemolysis due to the small-bore catheter (Pettit, 2006).

Because there is variation among NICU practices, we do not know if NICU protocols dictate that preterms are completely NPO or if some will reduce feeding volumes around the time of PRBC transfusion. Our survey respondents reported that their

NICU protocols often do not alter feedings before, during, or after PRBCs; however, some respondents indicated they "do not know" how feedings were altered. Feeding practices elicited some confusing responses which did not assist in identifying when feeds are held and/or reduced in volume in relationship to the time before, during and after the PRBC transfusion. Feeding practices and PRBC transfusions are variables targeted in ongoing research studies for preterm infants and the incidence of NEC. Currently, there is a large trial underway in the United Kingdom, "Withholding Enteral Feeds Around Packed Red Cell Transfusions (WHEAT) trial" (Gale et al., 2019). This multi-center randomized pilot study is using previously collected data to determine whether withholding enteral feedings before, during, and after PRBC transfusions decreases the incidence of NEC (Gale et al., 2019). This research along with more local efforts will have great benefits and will contribute to science and the health outcomes of preterms.

Our team inquired about PRBC transfusion methods and warming versus not warming because of our hypothesis that hypothermic body temperatures due to cold PRBCs may be an etiological factor in the incidence of NEC. A recent literature review found no published studies exploring associations of body temperature, PRBC transfusions, feedings, and NEC in the preterm (Everhart et al, 2020). Research is needed to determine if body temperature, or more specifically hypothermia in a preterm during a blood transfusion, has a contributory effect on the incident of NEC after feedings are resumed. Our findings show warming these small and frequent PRBC transfusions is uncommon and may potentially result in cold stress in the preterm by producing hypothermia.

CONCLUSIONS AND LIMITATIONS

The purpose of this national survey was to examine standard practices used for PRBC transfusions for preterm infants in NICUs across the US. The research team aimed to understand what current practices are occurring from the nursing perspective. By examining current PRBC transfusion practices, we can inform future research and may variations in practice that may affect preterm outcomes. The results demonstrated a vast variations PRBC transfusion practices, a frequent intervention in this vulnerable population. For example, irregular and inconsistent practices (body heat) in warming PRBC transfusions did not reflect evidence-based practice and possibly contribute to morbid outcomes in preterms. Interesting, general practice for oral and enteral feedings includes warming prior to administration to a preterm. It is unclear why feedings are warmed, but not PRBC transfusions. Based upon this significant gap, our next step is to examine 16 PRBC transfusion cases in a secondary analysis to explore variables that might exemplify possible etiological relationships between morbid outcomes and PRBC transfusions in preterm. In our program of research, we hope to contribute to policy to standardize procedures for PRBC transfusion practices in preterms and decrease morbidity.

CHAPTER 5

IS THERE A RELATIONSHIP BETWEEN PACKED RED BLOOD CELL TRANSFUSIONS AND ACUTE MORBIDITY IN PRETERM INFANTS? A SECONDARY ANALYSIS

INTRODUCTION

In 2018, there were over 100,000 preterm births. The current rate of preterm births in the United States (US) is staggering and still on the rise (Martin et al., 2020). Due to their prematurity, these preterm infants (preterms) experience an increased risk for morbidity due to infection, hypothermia, feeding intolerance, cardiovascular and respiratory instability, and hematologic abnormalities (Polin et al., 2017). Preterms also encounter a high risk of Necrotizing Enterocolitis (NEC). NEC, a form of neonatal infection that begins in the gastrointestinal tract (GI), can evolve into overwhelming sepsis if not diagnosed and treated in a timely manner (Bell et al., 1978). NEC affects nearly 13% of preterms, requires surgery in 20 to 40% of cases, and leads to mortality in 25 to 50% of cases (Shulhan, 2017).

Preterms require continuous and complex care by specialized medical professionals to combat these conditions (Brodsky & Quinn, 2014). Because of frequent laboratory testing and immaturity, preterm infants often require packed red blood cell

(PRBC) transfusions to correct iatrogenic anemia and anemia of prematurity (Widness et al, 2005). Researchers found an association between the incidence of NEC and treatment of preterms receiving PRBC transfusions (Santos et al., 2011). However, this association is disputed in the research (Amin et al., 2012; Sood et al., 2016), as reported in the literature review presented in Chapter 2. To build on data found through the survey of PRBC transfusion practices as described in Chapter 4, the purpose of this study is to: ***Examine preterm infant stability before, during and after PRBC transfusions in relationship to quantitative data (continuous body temperature, heart rate, oxygen saturation, lab values) and qualitative data (infant and caregiver status through video observation and health record data: feeding status, presence of anemia, disease processes, medical treatments) in 16 infant transfusion cases using within case analysis and between case comparison to synthesize case data for possible etiological links between PRBC transfusions and morbid conditions including hypothermia, feeding intolerance, NEC.***

Research questions include:

1. How do physiological variables vary within infants before, during, and after PRBC transfusions?

2. Do infants have any signs/symptoms of stress or instability including hypothermia, feeding intolerance and/or acute morbid changes before, during or after PRBC transfusions?

3. How does infant condition during and after PRBC transfusions vary by infant age, sex, and race?

METHODS AND SAMPLE

DESIGN

This study is a secondary analysis of data using a multi-case, within case analyses using mixed methods (Polit & Beck, 2017, Zainal, 2007), with an exploratory look across cases. Case data were obtained from the parent study (NIH/NINR:1R15NR012157-01) conducted at Duke University Hospital from 2010-2013. (Knobel et al., 2013; Knobel-Dail et al., 2016; Knobel-Dail et al., 2017).

INSTITUTIONAL REVIEW BOARD (IRB)

The parent study was approved by the Duke University Hospital IRB in 2010. Dr. Dail, dissertation chair, transferred these data to University of South Carolina (UofSC) College of Nursing (CON) under a transfer agreement and a new protocol was opened through the UofSC IRB. These secondary analyses were approved by the UofSC IRB.

SAMPLE

Parent data were reviewed to identify all PRBC transfusions among the 30 preterms in the parent study. We identified 13 preterms in the study with a total of 16 PRBC transfusions. Table 5.4 presents the demographic data of the 13 infants.

Table 5.4 Case infant demographics

Infant	GA at Birth	Race	Sex
1	26 0/7	B	M
2	26 1/7	B	F
3	27 5/7	B	F
4	25 3/7	B	M
5	27 4/7	B	F
6	27 ¾	W	F
7	26 2/7	B	M
8	27 4/7	B	F
9	27 5/7	B	F
10	27 ¾	W	M
11	28 1/7	W	F
12	25 6/7	B	M
13	27 1/7	W	F

For this secondary analysis, a case was defined by a PRBC tranfusion, not an individual infant. The data informing each case included 4 hours prior to a PRBC transfusion, hours during the transfusion (1-4), and 4 hours after PRBC transfusion.. Table 5.5 lists the transfusion cases, which infant is linked to each case and the day of life (DOL) for the linked infant that the transfusion occurred. Data informing each case are as follows and listed in Figure 5.8.

Table 5.5 Transfusion cases

Case	DOL of case
1	7
2	11
3	8-9
4	1
5	6-7
6	10-11
7	6-7
8	8-9
9	10
10	7
11	13
12	13-14
13	20
14	5
15	11
16	11-12

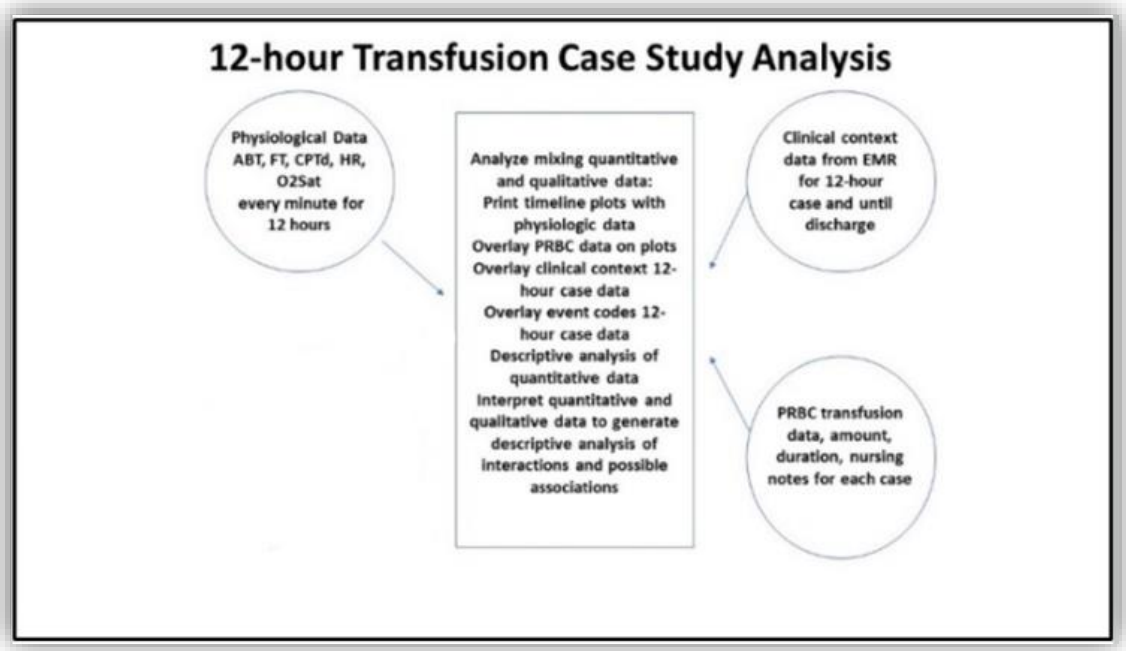


Figure 5.8 12-hour transfusion case study analysis

TEMPERATURE

During the parent study, abdominal (ABT) and foot (FT) temperatures were measured by Y Series Steri-Probe® skin temperature probes (Model 499B, Cincinnati Sub-Zero, Cincinnati, Ohio), accurate within ±0.2°C (Knobel et al, 2013). The ABT of a preterm is closely related to core temperature due to the near zero heat flux and can be used as a proxy for central temperature (Okken & Koch, 2012). Temperatures were downloaded, cleaned, then saved to a Statistical Analysis Software (SAS, Cary, NC) dataset for each infant.

For this study, ABTs were extracted from SAS datasets for each transfusion case (12-hour). Hypothermia was defined as an ABT less than 36.5°C, which corresponds to the World Health Organization definition of hypothermia (World Health Organization [WHO], 1997). Hyperthermia, any abdominal temperature greater than 37.5°C, can also negatively impact preterms (WHO, 1997).

CPTd

In the parent study, the CPTd variable was created from calculating (ABT-FT= CPTd) in SAS, which is indicative of the thermal gradient in a preterm. Thermal gradients are temperature difference between two points (Wiegand, 2015). For this study, the CPTd values were calculated in Microsoft Excel by subtracting the FT from the ABT to produce the CPTd. The CPTd value provides information to researcher as to the thermal state of a preterm infant (Lyon, 2008). An abnormal CPTd, >0°C, (or when the FT is higher than the ABT) or <2°C which is (or when the ABT is greatly increased over the FT), can be associated with instability within preterms. Researchers noted that increased CPTd values > 2º C, or a high temperature differential, is associated with

infection in preterms (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017). Other researchers have noted when the FT is higher than the ABT or CPTd values < 0º C occurs in preterm infants that are of very low GA and with stressful events (Mok et al., 1991; Lyon et al., 1997; Knobel-Dail et al., 2017).

ENTERAL FEEDINGS

Feeding data were recorded in the parent study for type of feedings the infant were receiving (breast milk or formula). Also recorded was the route of feeding (gastric or nasogastric tube intermittent or continuous feeds). There were also instances where the infants were NPO (nothing by mouth) status (no feeds).

NECROTIZING ENTEROCOLITIS (NEC)

A NEC diagnosis was confirmed from the EMR data according to the Bells' and Modified Bells' Criteria (Bell et al., 1978; Zani & Pierro, 2015). We also collected any data available around each 12-hour transfusion case indicating clinicians obtained labs or abdominal radiographs, stopped feedings, or started antibiotics due to a suspicion of NEC, feeding intolerance and/or infection. Because many infants in the parent study were under surveillance for infection or NEC during their hospitalization, these data were used to inform the case to generate hypotheses about the etiological pathway between PRBC transfusions and NEC in this case.

CLINICAL CONTEXT VARIABLES

During the parent study analyses, EMR data (infections, patent ductus arteriosus (PDA), respiratory disease, intraventricular hemorrhage, and death were obtained for the clinical context surrounding each infant to inform case analysis. These data informed the clinical context around PRBC transfusions and health outcomes until discharge for each

study infant. Some of these variables are risk factors for NEC including maternal infection (Chorioamnionitis), infant infection, GA at birth, PDA, gender, and/or Intra-Uterine Growth Restriction/small for GA (Kinsella et al, 2006).

To develop a trajectory over each PRBC transfusion timeline within the clinical context, each case was analyzed integrating qualitative and quantitative data. Each transfusion case is informed with physiologic data (ABT, FT, HR, SPO2), clinical context data (environmental temperature, feeding status and feeding intolerance, clinical diagnoses, treatments), and PRBC transfusion data (date, start/stop time, duration, infusion site, and infant tolerance). Table 5.6 displays the study variables for each transfusion case.

Table 5.6 Case study variables

Variable	Instrument	Conceptual Definition	Interval
Quantitative			
Abdominal Temperature (ABT)	Thermistor	Skin temperature (0.1°C)	Every minute
Foot Temperature (FT)	Thermistor	Skin temperature (0.1° C)	Every minute
Central-Peripheral Temperature Difference (CPTd)	ABT-FT = CPTd	Difference (0.1°C)	Every minute
Heart Rate (HR)	GE Monitor	HR by GE monitor	Every minute
Oxygen Saturation (SPO2)	Masimo Pulse Ox	SPO2 by Masimo	Every minute
Qualitative			
Enteral Feeds	EMR	Type of feeding, route	Status during 12-hour case
Blood transfusion (PRBC) data	EMR	Amount, duration, route of transfusion	Transfusion data per case
Suspicion of NEC	EMR	Rule out NEC: infant NPO, Abdominal XRAYs	Status during 12-hour case
Diagnosis of NEC	EMR	Diagnosis of NEC from EMR or Bell's Criteria	Instances prior to discharge
Suspicion of Infection	EMR	Blood cultures, antibiotics	Status during 12-hour case
Patent Ductus Arteriosus (PDA)	EMR	PDA by ultrasound	Status during 12-hour case

BACKGROUND OF PARENT STUDY

The parent study (NIH/NINR:1R15NR012157-01) was conducted in the tertiary NICU at Duke Children's Hospital between 2010-2013 (Knobel et al., 2013; Knobel-Dail et al., 2016; Knobel-Dail et al., 2017). As standard of care during the parent study, preterm infants were placed in preheated incubators upon admission with incubator servo control (ISC) set point temperatures (the temperature where infants' ABT was controlled with a feedback heat loop by incubator control system) of 36.5 ºC to 37.0 ºC, and incubator humidification of 60-80%, which is still the standard at this NICU. PRBC transfusions were given with blood sent from the blood bank freezer where it is stored at 0°C, then allowed to warm to environmental temperature near the infant's incubator.

DATA MANAGEMENT

Parent data were linked to a unique study ID and no subject identifiers were within these data. Parent data were anchored to each infants' day and time of birth. This exact date/time is designated as 0 minutes since birth (MSB). Each day consists of 24 hours of minutes for each infant; therefore, day of life (DOL) 1 was 0-1440 MSB. This timeline trajectory of data was kept for data management in this secondary data analyses and the actual dates and times of the start and end of each transfusion case were also converted to MSB to link to physiologic data (ABT, CPTd, HR, SP02).

Data were exported from SAS datasets into Microsoft Excel datasets for data cleaning and management. The Microsoft Excel datasets were saved onto a UofSC server (OneDrive account) which was password protected. No patient identifiers were contained in the data. The data for each case were saved to a case specific folder where all data

cleaning and management occurred. Only this PhD student and the dissertation committee had access to this secure OneDrive account.

DATA ANALYSIS

Within case analysis was conducted on each of 16 transfusion cases to examine preterm infant stability before, during and after PRBC transfusions in relationship to quantitative data (continuous abdominal temperature, the central-peripheral temperature difference, heart rate, and oxygen saturation) and qualitative data (health record data: feeding status, presence of anemia, disease processes, medical treatments).

Research Questions to be addressed using within case analysis are:

1. How do physiological variables vary within infants before, during, and after PRBC transfusions?
2. Do infants have any signs/symptoms of stress or instability including hypothermia, feeding intolerance and/or acute morbid changes before, during or after PRBC transfusions?

To visualize data, two different plots were created using SAS software for each case. One plot displayed minute-to-minute ABT and FT for the case duration. Another plot displayed minute-to-minute HR and SPO2 for the case duration. In both plots, the *x* axis displayed MSB data for the case duration of up to 12 hours of the case from the start of the case (4 hours pre-transfusion) to the end of the case (4 hours after transfusion) and the y axis displayed the ranges of the respective physiological variables. Each 12-hour plot was printed and inspected for the visual trajectory of physiologic variables over time. To aid in visual interpretation, clinical context data were overlaid on the plotted timeline

of physiological variables using Microsoft PowerPoint software (see figure 5.9 for an example).

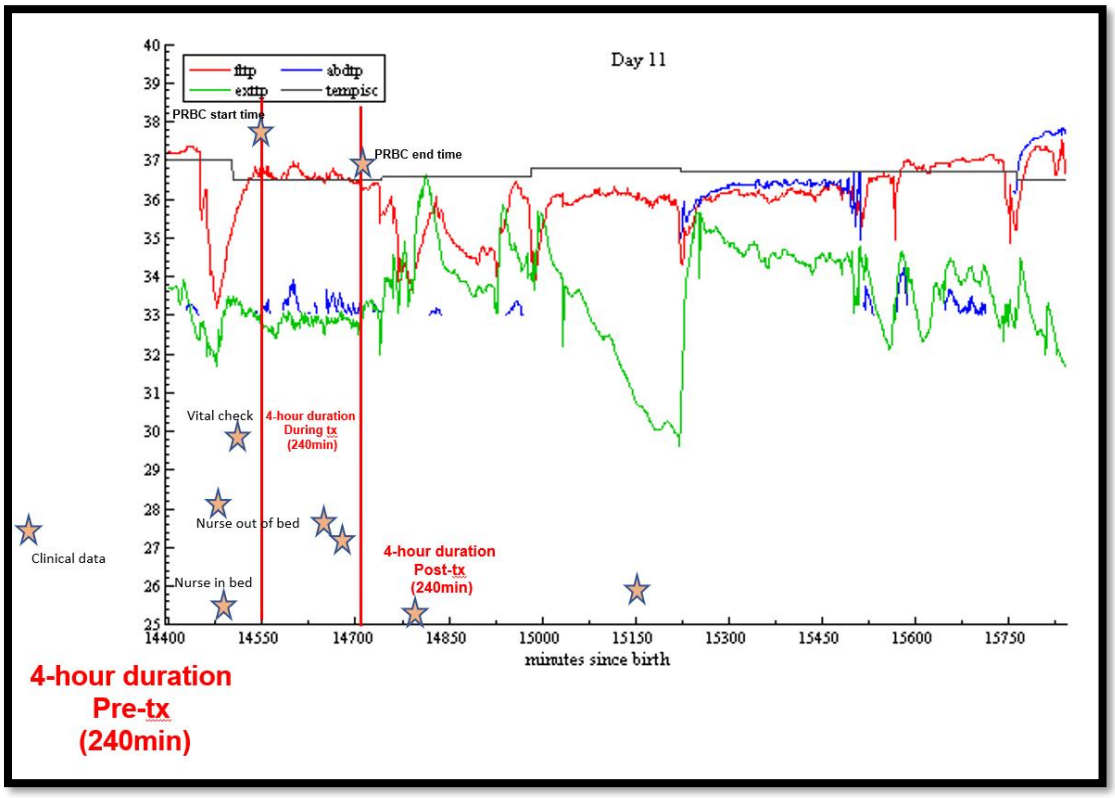


Figure 5.9 Plot example

Descriptive statistics were computed for each 4-hour interval of time (pre-transfusion, transfusion, and post transfusion) of the transfusion case to examine for infant stress before, during or after the transfusion indicated by hypothermia (<36.5 ºC) or hyperthermia (>37.5 ºC; WHO, 1997) ABT, HR that is tachycardic (>95th percentile) or bradycardic (< 5th percentile), (Alonzo et al., 2018). Also, decreased oxygen desaturations (SPO2 <85%), (American Academy of Pediatrics, 2007) and/or abnormal thermal gradients (CPTd < 0 ºC or > 2 ºC). The CPTd will be computed from minute-to minute ABT and FT or thermal gradients across the 12-hour case. Physiologic and qualitative data will be integrated and synthesized for indicators of infant stress, clinical

diagnoses and instances of feeding intolerance and acute morbidity to summarize each case.

Between case analyses will be conducted for an exploratory examination to generate hypotheses for future research studies and to answer the research question:

3. How does infant condition during and after PRBC transfusions vary by infant age, sex, and race?

RESULTS

Within Case Analysis The 16 cases of this study were each analyzed within case and the results will be reported for each case using: demographic information, clinical contextual data that occurred temporally in relationship to the case, analysis of physiological variables, variable plots, and an overall summary that integrates all data.

CASE 1

This case was linked to infant 1 (see Table 5.5), who was 26 weeks GA at birth. The transfusion occurred on the infant's DOL 7 and was transfused through a PIV over 4 hours. However, the location of the PIV is unclear from the documentation and it could be in the foot or arm.

During the assessment of this infant by an attending physician on the morning after the transfusion, the infant displayed visible loops of bowel in the abdomen, which is indicative of a stressed GI. An abdominal radiograph was obtained and showed no signs of pneumatosis (a sign of NEC). However, the infant's feedings were withheld and a Replogle tube was placed to keep the bowel decompressed. The infant was on antibiotics during this transfusion case (Ampicillin and Gentamicin) because of suspicion for

infection and pending lab tests on the day of transfusion. All cultures returned negative, and infection was not diagnosed.

The infant was kept NPO on transfusion day due to the abdominal assessment and surgical placement of a broviac central line for intravenous access. The day after transfusion, (DOL 8) the infant restarted small volume feeds of breast milk; However, later that day (DOL 8) feedings were again withheld and a Replogle suction tube reinserted after an increase of 2 centimeters in abdominal girth, indicating GI distress. One possible conclusion is the PRBC transfusion on this same day (early morning) temporally triggered GI distress and early signs of NEC. It is possible that the transfusion may have further complicated this infant's clinical course. Table 5.7 includes the descriptive statistics of variables for case 1. Figure 5.10 is the visual plot for variables for case 1.

Table 5.7 Physiological variables for case 1

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
Abt °C	36.9 (0.2) 36.25 to 37.21	36.6 (1) 33.06 to 37.29	36.6 (0.7) 33.26 to 37.27
CPTd °C	0.9 (SD 1) -1.02 to 3.7	0 (SD 1.4) -4.38 to 2.91	-0.07 (SD 0.5) -1.85 to 3.1
HR bpm (134 to 178)	132 (SD 10) 107 to 153	140 (SD 5) 130 to 151	140 (SD 8) 70 to 155
SP02 %	82 (SD 36) 0 to 100	96 (SD 12.6) 0 to 100	86 (SD 34.5) 0 to 100

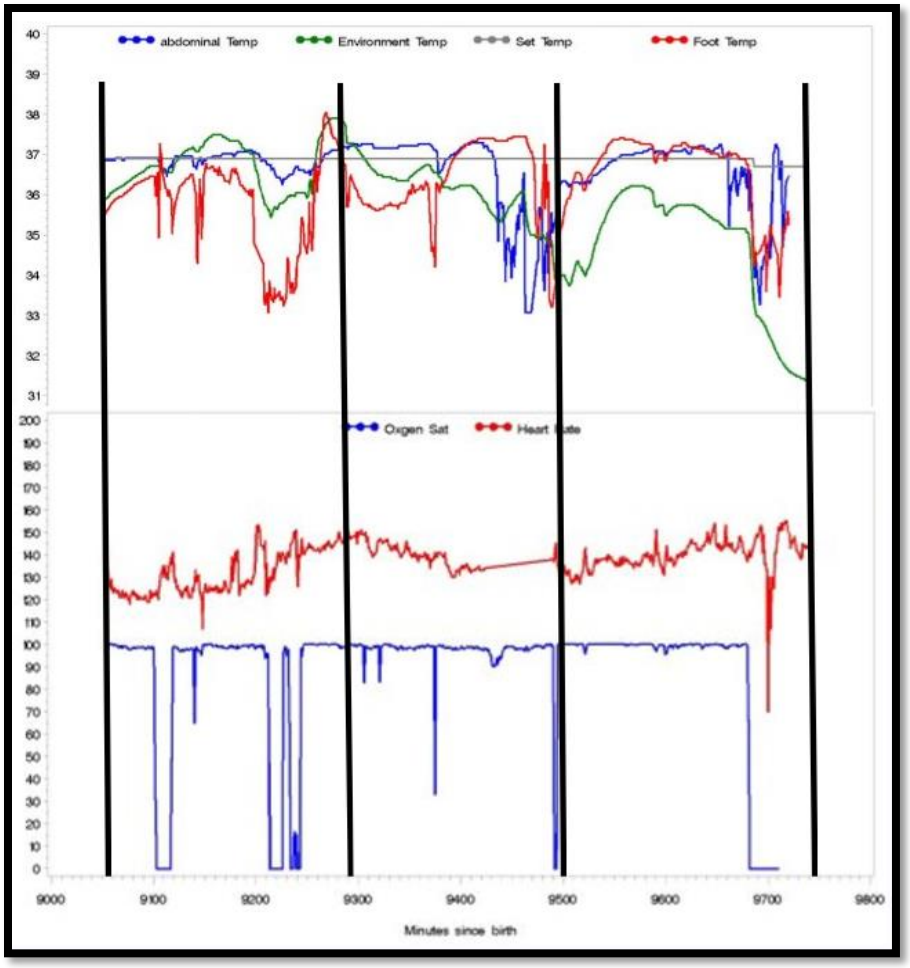


Figure 5.10: Variable plots for case 1

SUMMARY ANALYSIS FOR CASE 1

ABT: During the pre-transfusion period, the infant's thermal stability was unstable and falls into a hypothermic range (<36.5 ° C). During the transfusion period this infant showed very inconsistent thermal dynamics. The infant's ABT ranges from 33.06° C to 37.29 ° C. During the pretransfusion periods, the ABT average was normothermic, (36.6 ° C) but the infant did experience a sudden and abrupt drop in all temperature measures, which remained throughout the entire transfusion.

CPTd: Over the 12-hour transfusion case this infant displays abnormal thermal gradients where the FT is higher than the ABT. This is an abnormal finding as higher temperature in the foot than the abdomen has been related to the preterm infant's immature vasomotor tone or stress by prematurity (Mok et al., 1991; Lyon et al., 1997, Knobel et al., 2017). This stress can be a result of prematurity and/or infant disruption (this is near a vital sign check by nursing), or the infant is really beginning to show signs of true instability.

HR: Pretransfusion, the infant's mean HR is lower than the acceptable limit for GA and therefore is considered bradycardic (Alonzo et al., 2018). The remaining observations are all within normal limits for an infant of this GA.

SP02: Measures are variable the entirety of the transfusion case (American Academy of Pediatrics, 2007). The low SPO2 events correspond with abnormality in all other measures (temperatures and HR) so may be indicative of stress.

Conclusion: It is possible that the PRBC transfusion on the same day as the infant displayed GI complications, (early morning) could have compromised the infant's gut, therefore, it can be concluded this infant displayed early signs of NEC and that this transfusion case may have further complicated this infant's clinical course.

CASE 2

This case was linked to infant 1 (see Table 5.5), a 26-week GA infant, but now over a week old. This was the infant's second transfusion and occurred on the infant's DOL 11 and was infused through a PIV; no location given in documentation. This PRBC transfusion infused over 2 hours and 30 minutes.

Clinically, this infant was not feeding as feedings were stopped 3 days prior to this transfusion. Low volume feedings were restarted 4 hours after the transfusion. Later during the month of March 2011, this infant had a few instances of feedings being withheld due to due to abdominal distention. However, there was never a clinical diagnosis of NEC assigned to this infant. Table 5.8 includes the descriptive statistics of variables for case 2. Figure 5.11 is the visual plot for variables for case 2.

Table 5.8 Physiological variables for case 2

Variable	**Pre Mean (SD) Range**	**During Mean (SD) Range**	**Post Mean (SD) Range**
ABT °C	36.9 (SD 0.01) 36.25 to 37.29	36.9 (SD 0.01) 36.4 to 37.29	36.9 (SD 0.01) 36.3 to 37.31
CPTd °C	0.9 (SD 0.02) 0.07 to 2.25	0.35 9SD 0.01) 0.15 to 1.19	0.46 (SD 0.01) 0.015 to 1.2
HR bpm (134 to178)	140 (SD 0.46) 130 to 167	139 (SD 0.34) 131 to 162	134 (SD 0.38) 124 to 154
SP02 %	88 (SD 1.7) 0 to 100	97 (SD 0.72) 0 to 100	97 (SD 0.36) 32 to 100

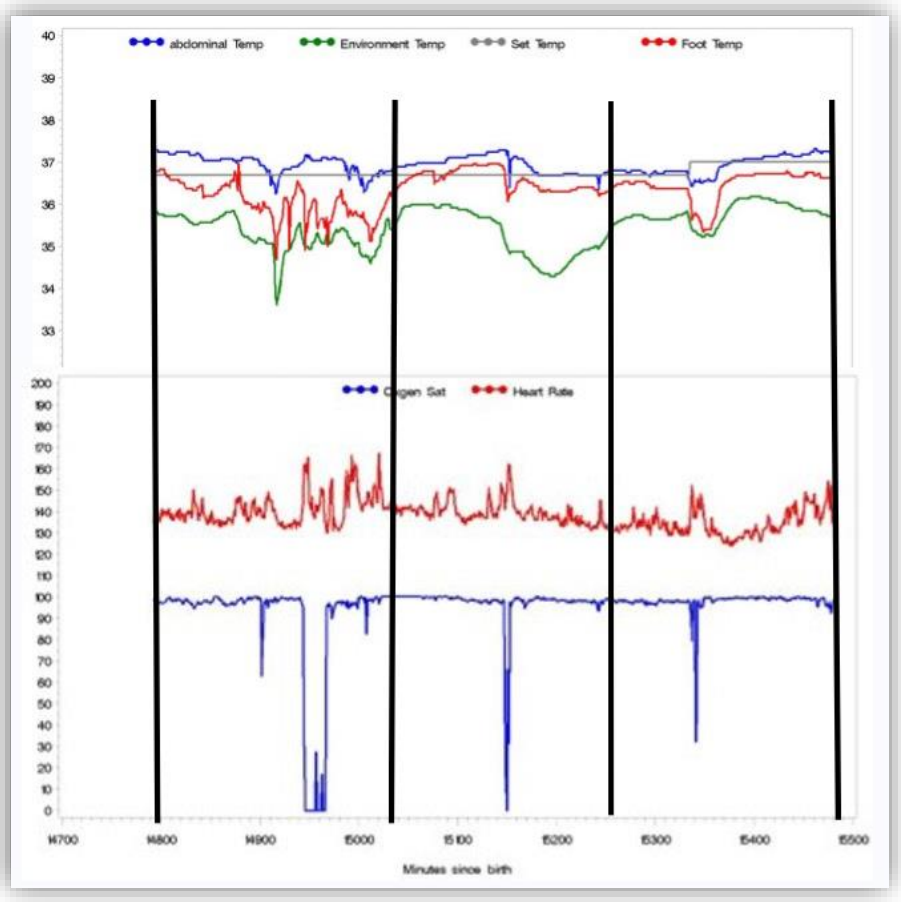


Figure 5.11: Variable plots for case 2

SUMMARY ANALYSIS FOR CASE 2

ABT: The infant is centrally normothermic for nearly the entirety of the transfusion period. The preterm only experienced hypothermia (<36.5 ^{o}C) during 4.5% of the pretransfusion period The range for central temperatures were from (36.25 ^{o}C to 37.31 ^{o}C). The mean abdominal temperature for the entirety of this case was 36.9 ^{o}C.

CPTd: These values were mainly within the normal range throughout this case period. Pre-transfusion, the infant did have a small amount of abnormal thermal gradient values (<1%).

HR: There are no instances during this case where the infant's HR falls outside the acceptable range for GA (Alonzo et al., 2018).

SP02: There are occasional decreases in the infant's SP02 during all transfusion intervals however, they were longer and lower during the pretransfusion phase. During the pre-transfusion interval, 10% of the values are below the acceptable range (85-100%). The SP02 values improve through the remainder of the case, ending with only 1% of measures outside of acceptable range (American Academy of Pediatrics, 2007).

Conclusion: This infant tolerated this PRBC transfusion; however, the infant was normothermic most of the case. The infant seemed to tolerate the PRBC well and the instances of low oxygen saturation decreased in the post transfusion period. It can be concluded that the transfusion was helpful to the infant's stability.

CASE 3

This case was linked to infant 2, born at 26 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 8-9 and was infused through a lower extremity PIV. This PRBC transfusion infused over 2 hours and 5 minutes.

Clinically, this infant had been treated with medication to close the PDA on DOL 1-3. Feedings for this infant were stopped 4-hours pre-transfusion and the infant remained NPO after the transfusion due to an emesis with blood. The infant was already on antibiotic (Ampicillin and Gentamicin) therapy on the day of the transfusion, due to a previous diagnosis of neonatal pneumonia. The infant was removed from the physiologic portion of study data collection; however, was still enrolled for clinical data collection two days later (DOL 10). On DOL 10, the infant remained NPO and underwent another laboratory investigation to rule out sepsis due to a stool with evidence

of blood and an abnormal abdominal radiograph. The infant was diagnosed with "early NEC" on DOL 11, and the infant further required treatment with an infusion for low blood pressure (Dopamine). Table 5.9 includes the descriptive statistics of variables for case 3. To be noted, there were no environmental temperatures available for this case. Figure 5.12 is the visual plot for variables for case 3.

Table 5.9 Physiological variables for case 3

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT ^{o}C	36 (SD 0.04) 34.03 to 37.07	36.5 (SD 0.01) 36.1 to 36.85	36.7(SD 0.01) 36.25 to 36.91
CPTd ^{o}C	1.4 (SD 0.04) 0.64 to 2.77	1.2 (SD 0.05) -0.89 to 2.43	0.9 (0.02) 0.33 to 1.92
HR bpm (134 to 178)	165 (SD 0.69) 123 to 194	165 (SD 0.75) 152 to 190	164 (SD 0.22) 155 to 178
Sp02 %	94 (SD 1.19) 0 to 100	97 (SD 1.06) 0 to 100	99 (SD 0.01) 99 to 100

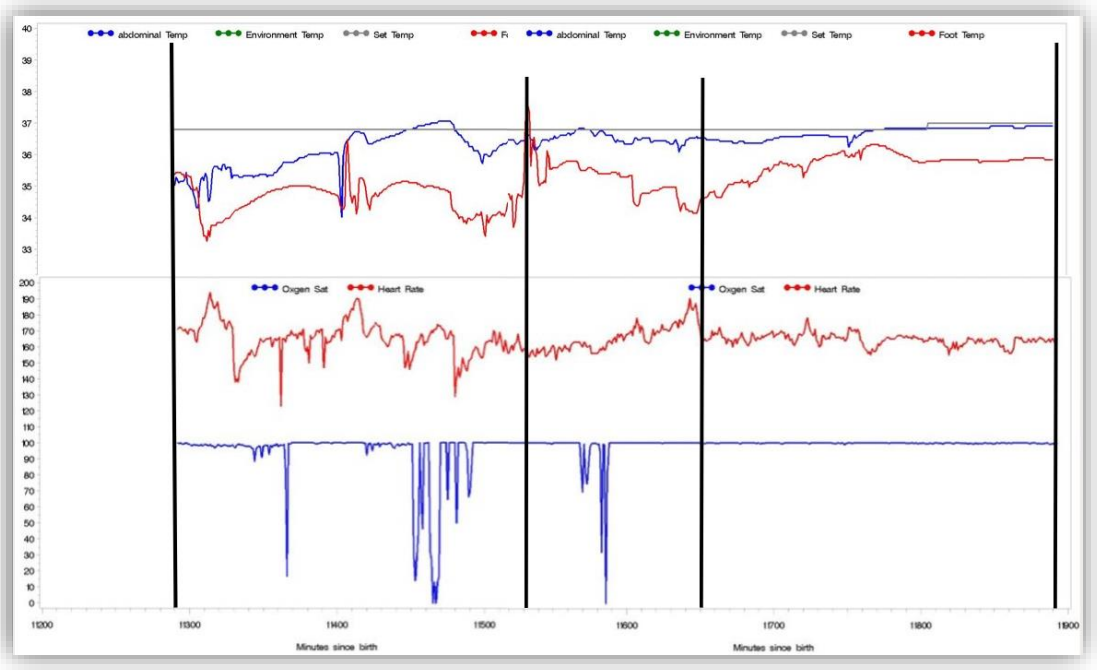


Figure 5.12 Variable plots for case 3

SUMMARY ANALYSIS FOR CASE 3

ABT: This infant had centrally hypothermic (<36.5 ºC) nearly half of the pre-transfusion period (34.03 ºC to 37.07 ºC). The infant becomes normothermic (mean of 36.5 ºC and 36.7 ºC) during the transfusion into the post transfusion period.

CPTd: During the pre-transfusion period, the infant averages a normal thermal gradient; however, there is a wide range of CPTd values (0.64 º C to -2.77 º C) and some greater than 2 º C, which can be associated with infection (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017). During the transfusion period, there are still abnormal temperature gradients (> 2 º C). Post transfusion, the infant normalized and thermal gradients are improved and fall within normal range (0.33 º C to -1.92 º C).

HR: HR means were within normal limits across the observation. However, during the pretransfusion, 10% of the HR measures fall outside (above or below) of the

acceptable limits for this infant's GA, during the transfusion, 7% of the HR measures fall outside of the acceptable limits for this infant's GA. Post transfusion, there were no HR measures that fell outside of the acceptable limits for this infant's GA (Alonzo et al., 2018).

SP02: The mean of SP02 measures for this transfusion case are within the normal limits for this measure (85-100%); however, some measures fell outside the normal limits and considered a desaturation during the pretransfusion and transfusion period (American Academy of Pediatrics, 2007).

Conclusion: The infant in this case displayed thermal and physiological improvement after receiving this PRBC transfusion. It can be concluded this transfusion helped this infant clinically. Because the infant was treated for a PDA, and had an infusion to treat hypotension, it makes since that the PRBC transfusion would be beneficial to the infant's perfusion. The thermal gradients were greater than 2 ^{o}C, which has been associated with infection; however, since there was improvement with this transfusion, it is not conclusive that this infant truly had an infection, rather that the blood may have helped with the decreased body perfusion and blood flow seen with infection.

CASE 4

This case was linked to infant 3, an infant born at 27 5/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 1. Per clinical documentation, this infant was transfused during this case through the central UVC. This PRBC transfusion infused over 3 hours and 30 minutes.

Clinically, this infant was presumed to be septic at birth due to maternal Chorioamnionitis and begun on antibiotics as a precaution when admitted to the NICU.

The infant was on antibiotics for suspected sepsis during this transfusion case with no feedings and remained NPO until DOL 3.

This infant has an eventful hospitalization requiring multiple PRBC transfusions related to apnea, bradycardic, and desaturation events. At 1 month of life, the infant had evidence of blood in the stools and radiographic findings indicating pneumatosis, which is a sign of impending NEC and so, feedings were again withheld. At that time, laboratory testing was done to rule out infection, including a blood culture and a 7-day course of antibiotic therapy. The blood culture results revealed gram+ *staphylococcus* (GBS). Table 5.10 includes the descriptive statistics of variables for case 4. To be noted there were no SP02 measures available for this case. Figure 5.13 is the visual plot for variables for case 4 (see next page).

Table 5.10 Physiological variables for case 4

Variable	Pre Mean (SD) Range	During Mean (SD) Range	Post Mean (SD) Range
ABT °C	35.8 (SD 0.01) 35.16 to 36.3	35.5 (SD 0.03) 33.69 to 35.9	34.8 (SD 0.02) 33.59 to 35.25
CTPd °C	0.009 (SD 0.01) - 0.6 to 0.6	-0.11 (SD 0.03) - 2.41 to 0.52	-1.05 (SD 0.03) - 2.09 to (-0.27)
HR bpm (134 to 178)	161 (SD 0.54) 143 to 185	154 (SD 0.4) 140 to 174	146 (SD 0.3) 139 to 174
SP02 % (not available)			

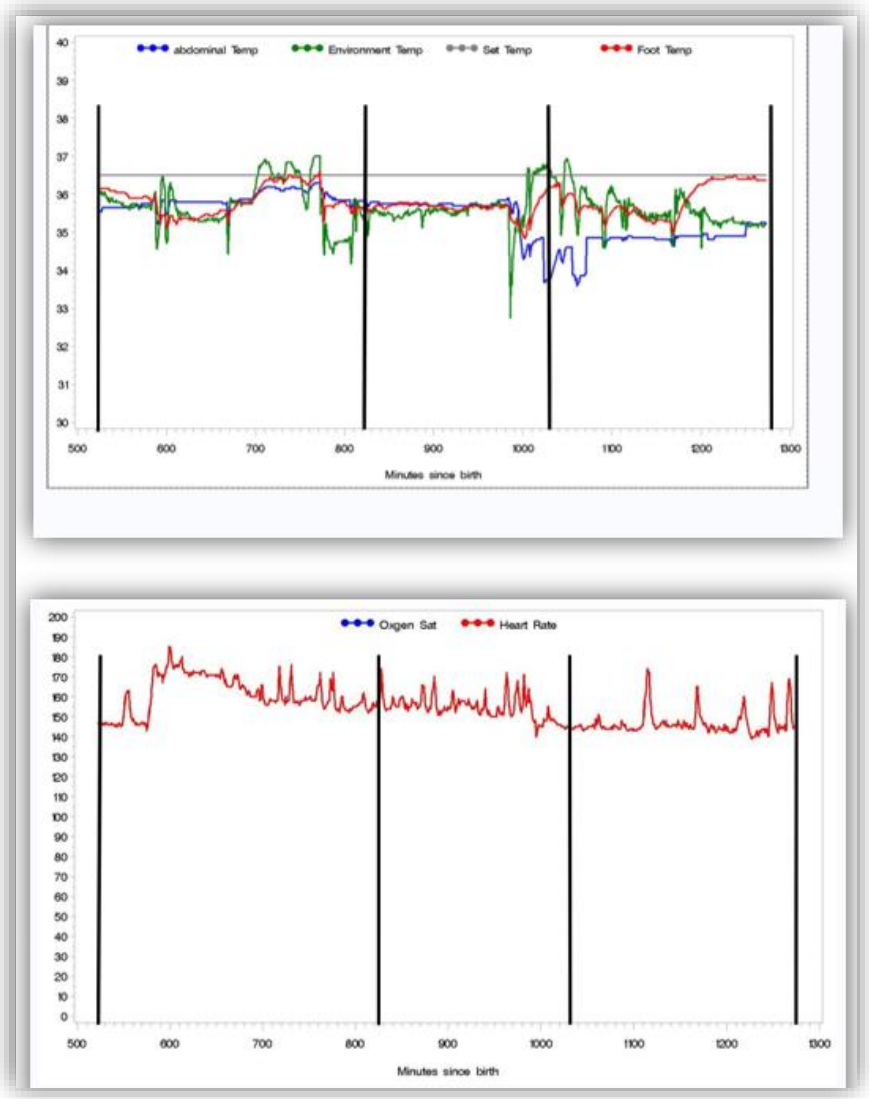


Figure 5.13 Variable plots for case 4

SUMMARY ANALYSIS FOR CASE 4

ABT: During this entire case, the infant remained thermodynamically unstable. During the pre-transfusion period, 100% of the ABT values are hypothermic with means (35.8 ºC, 35.5 ºC, 34.8 ºC) across the three intervals severely hypothermic.
This hypothermia worsens as the transfusion case progresses. This infant had a UVC placed on this transfusion day (DOL 1). It is possible that the incubator was open during this pre-transfusion time for this procedure and other stabilization procedures contributed to the severe hypothermia.

CPTd: There are abnormal thermal gradients noted where the FT becomes warmer than the ABT. The infant in this case displayed varying amounts
of CPTd throughout the case. There were worsening abnormal temperature gradients means throughout the entire observation period (0.09 ºC, -0.11 ºC, -1.05 ºC) There is no CPTd noted during the transfusion (infant more centrally warm). After the transfusion is complete, the infant displays abnormal thermal gradients and a wide CPTd.

HR: HR means were within normal limits across observation; however, during the pretransfusion, there are instances of tachycardia (< 178bpm for this infant based upon GA). During the transfusion and post transfusion period, the infant normalizes it's HR (Alonzo et al., 2018).

SP02: None available.

Conclusion: It can be concluded that the infant was unstable during this transfusion case. The infant does display improvement in CTPd during the transfusion period, however, becomes has more abnormal thermal gradients post transfusion. Could this infant had still been recovering from birth stress during this case and the increase in

volume had improved CTPd? The infant in this case became more centrally hypothermic as the transfusion progressed, which could be due to central infusion of cold PRBCs. This conclusion is evidenced by worsening mean central temperatures (35.8 ^{o}C, 35.5 ^{o}C, 34.8 ^{o}C). This transfusion case cannot be ruled out as a precursor to any of the subsequent medical events that the infant had as the infant was grossly unstable during this transfusion case of DOL 1. It seems that the infusion of possibly cold blood into an already hypothermic infant, aggravated the situation, which only decreases perfusion to the gut and may cause acute ischemia. This is one possible pathway to an NEC diagnosis.

CASE 5

This case was linked to infant 4 who was born at 25 3/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 6 and was infused through a lower extremity PIV. This PRBC transfusion infused over 3 hours.

This infant was presumed to be infected at birth due to maternal infection. Infant's mother had GBS in her urinalysis and *gram-negative rods* in her amniotic fluid. The infant completed antibiotic therapy on this transfusion day; however, it is not clear as to the time antibiotics were discontinued. This infant was receiving low volume prior to transfusion and feedings were discontinued 4 hours before starting the PRBC transfusion.

On the days following this transfusion case, the infant received Sodium Bicarbonate for metabolic acidosis and had hyperglycemia (this is indicative of infection and/or stress). The infant remained under close watch as the infant's labs values were abnormal and the abdominal girth was increasing; however, the infant was described as "stable." Therefore, the clinicians did not suspect infection and labs were not drawn to rule out infection and antibiotics were not begun until 3 days after the transfusion when

the infant still had hyperglycemia and increasing white blood cells on the complete blood count testing.

Table 5.11 includes the descriptive statistics of variables for case 5. Figure 5.14 is the visual plot for variables for case 5. It should be noted that this case was set up like all cases with a 4-hour pretransfusion period, the actual duration time of the transfusion period, and followed by a 4-hour post transfusion period. The visual plot for this case has the same axis labels; however, because this transfusion spans two of the infant's days of life, the plots had to be spliced together for visualization.

Table 5.11 Physiological variables

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT °C	36.4 (SD 0.01) 35.17-37.2	36.4 (SD 0.01) 34.63-36.72	36.6 (SD 0.01) 36.02-37
CPTd °C	0.45 (SD 0.04) -1.6 to 2.22	0.14 (SD 0.05) -1.19 to 2.86	0.69 (SD 0.05) -0.08 to 3.23
HR bpm (134-176)	146 (SD 0.29) 128-162	146 (SD 0.29) 130-165	148 (SD 0.32) 140-170
SP02 %	94 (SD 0.25) 76-96	95 (SD 0.19) 82-100	91 (SD 0.19) 79-98

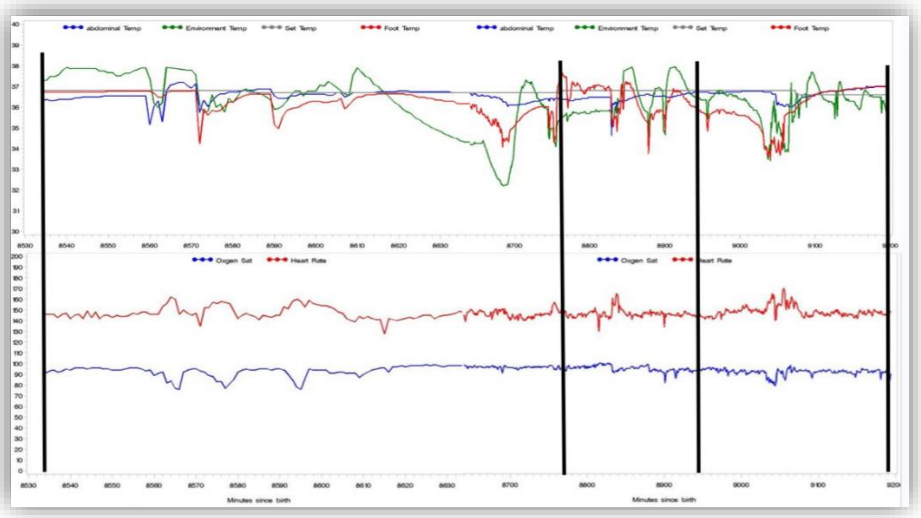


Figure 5.14 Variable plots for case 5

Summary analysis for case 5

ABT: For almost 50% of the pre-transfusion period, the infant was centrally hypothermic, with temperatures ranging from 35.17 ºC to 37.2 º C and a mean temperature of 36.4 º C. There is a notable drop in all temperatures, and it is at this time the infant begins to display an increase in abdominal temperature. During the transfusion period, the infant's mean abdominal temperature is the same as the pretransfusion however, there are instances of hypothermia noted and the range of temperatures are more extreme (34.63 º C to 36.72 º C) than during the pre-transfusion interval. As the transfusion is complete and the post transfusion period has begun, the infant has finally reached a normothermic ABT and remains warm throughout the end of the case (post transfusion abdominal mean 36.6 º C)

CPTd: Throughout the entire case, the infant displays abnormal thermal gradients. Although the mean CPTd during the transfusion is an improvement from the pre-transfusion period (0.14 º C), the range of CPTd values (-1.19 º C to 2.86 º C) are wide and concerning. Pre-transfusion, the infants CPTd ranged from -1.6 º C to 2.22 º C. Post transfusion, the mean CPTd is improved: however, still with a wide range of temperatures (-0.08 º C to 3.23 º C). Visually, there are many instances of abnormal thermal gradients across this case. The abnormal temperature gradients with the FT greater than the ABT and the large CPTd taken into consideration with the clinical data in this case could be indicative of neonatal stress.

HR: Most HR measures for this transfusion were within acceptable ranges based upon the infant's GA (Alonzo et al., 2018). There are noted values that fall below the lower 5th percentile (134bpm) however, this is not reflective of the overall case.

SP02: All mean SP02 values were within acceptable range (85-100%) over the case observation (American Academy of Pediatrics, 2007). The range of measures over each period do have values that fall outside of the acceptable range however, this is not reflective of the overall case.

Conclusion: This case became more centrally hypothermic as the transfusion progressed. There are wide CPTd values above 2 ºC, (-1.6 ºC to 2.22 ºC, -1.19 ºC to 2.86 ºC, -0.08 ºC to 3.23 ºC). A CPTd of >2º C has been associated with neonatal infection (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017). In this case, due to the infant's clinical condition, there was a clinical need for this PRBC transfusion; however, it is possible that this transfusion may have further stressed the infant due to hypothermia. It is difficult to tell if this infant's condition improved or worsened in relationship to this PRBC transfusion.

CASE 6

This case was linked to infant 4 in Case 5, a 25 3/7 weeks GA infant at birth but now over one week old (see Table 5.5). The transfusion occurred on the infant's DOL 10 and was infused through an upper extremity PIV over 3 hours and 15 minutes.

Clinically, this infant had metabolic acidosis during the time of transfusion. Due to hypotension, the healthcare team started Dopamine on transfusion day (DOL 10). Laboratory studies showed elevated white blood cell (WBC) count (exact value not given in EMR data) and hyperglycemia (>300g/dL) requiring insulin administration, which is a sign of stress or infection. The attending physician suspected a fungal infection but did not start antibiotics or antifungals at this time. The healthcare team tested for infection five days later (DOL 15) when bowel loops were observed on the abdominal radiograph,

which resulted in the start of antibiotics. However, the infant continued to receive feedings. On DOL 16, the infant remained hypotensive and was diagnosed with a PDA. Treatment was administered to help close the defect resulting in stopped feedings for three days. This case is further complicated by possible concerns of early signs and symptoms of NEC. Feedings were stopped again followed by another infection workup. The infant had a urinary tract infection from *Klebsiella* bacteria. Table 5.12 includes the descriptive statistics of variables for case 6. Figure 5.15 is the visual plot for variables for Case 6. It should be noted that this case was set up like all cases with a 4-hour pre-transfusion period, the actual duration time of the transfusion period, and followed by a 4-hour post transfusion period. The visual plot for this case has the same axis labels however because this transfusion spans two days for this infant, the plots needed to be spliced together for visualization.

Table 5.12 Physiological variables for case 6

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT ^{o}C	35.7 (SD 0.02) 34.85 to 36.42	36.1 (SD 0.02) 34.7 to 36.54	36.2 (SD 0.01) 36.07 to 37.28
CPTd ^{o}C	0.04 (SD 0.02) - 0.88 to 1.27	-0.32 (SD 0.02) - 1.32 to 0.92	-0.22 (SD 0.02) - 0.62 to 0.9
HR bpm (134 to 178)	176 (SD 0.59) 158 to 201	179 (SD 0.26) 170 to 188	173 (SD 0.5) 162 to 190
SP02 %	91 (SD 0.4) 55 to 99	91 (SD 0.3) 75 to 96	91 (SD 0.3) 69 to 96

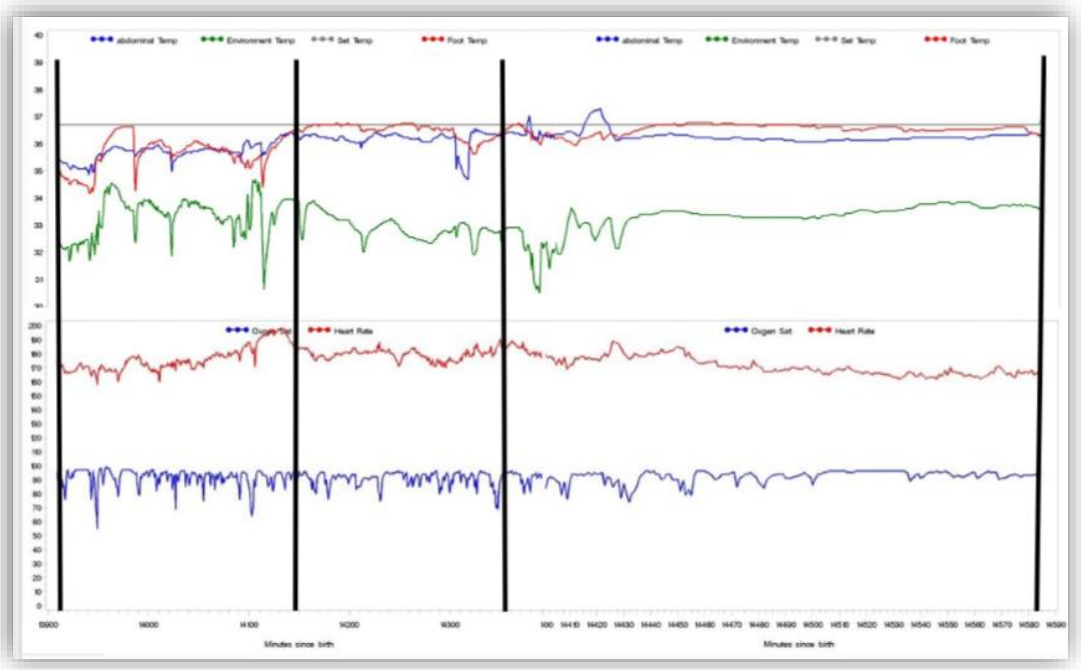


Figure 5.15 Variable plots for case 6

SUMMARY ANALYSIS FOR CASE 6

ABT: ABT are consistent with central hypothermia in this infant during the entire case. Mean ABT remains low (pre: 35.7 ^{o}C during: 36.1 ^{o}C post: 36.2 ^{o}C) throughout all time periods of the transfusion. Although still hypothermic, the infant's abdominal temperature does increase as the transfusion progresses. The infant's ABT is almost normothermic near the end of the post transfusion period.

CPTd: There is only a 30-minute time frame during the entire case observation where the ABT is greater than the FT; however, still the infant is still hypothermic. The CPTd values worsen from pre transfusion into the transfusion period with a mean of 0.04 ^{o}C and range of -0.88 ^{o}C to 1.27 ^{o}C. There are larger differences, although abnormal between the ABT and FT, with a mean of -0.32 ^{o}C and range of -1.32 ^{o}C to 0.92 ^{o}C.

Although still an abnormal thermal gradient, the CPTd improved slightly post transfusion.

HR: All HR means were within acceptable range, however all in the higher normal range for this infant based upon GA (Alonzo et al., 2018) throughout this case. The normal range for an infant of this gestation is 134 bpm to 178 bpm (Alzonzo, 2018). These higher HR ranges in all periods of the case could be a result of how critically ill this infant is and requiring Dopamine.

SP02: All SP02 means were within acceptable range (85 to100%) for this infant during this case (American Academy of Pediatrics, 2007). Some lower values were noted in the range of measures, but this is not reflective of the case.

Conclusion: Case 6 was the second transfusion in this critically ill infant with the first transfusion summarized in Case 5. In Case 5, the infant received a PRBC transfusion while sick and hypothermic. As concluded in Case 5, this situation may set up an infant for further GI problems because a hypothermic central temperature leads to gut ischemia. In this case, the infant remained critically ill, continued to have hypothermic central temperatures, and abnormal CPTd values possibly indicating stress or infection. Despite the clinical evidence of potential infection (temperature, physiological measure, and clinical patterns), the infant continued to feed. Antibiotics and/or antifungals were not started.

CASE 7

This case was linked to infant 5, an infant born at 27 4/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 6 and was infused through a central UVC over 3 hours and 30 minutes.

This infant appeared to be stable despite leukopenia (a low white blood cell count) and thrombocytopenia (a low platelet count) on admission to the NICU. These abnormal laboratory results were attributed to maternal preeclampsia and seven days of antibiotics were given in case of early onset sepsis. All cultures remained negative thus ruling out infection. The infant was given two doses of Indocin around this transfusion case for a PDA; however, only received two of the three doses due to low urine output. The healthcare team kept the infant NPO for the transfusion due to the suspicion of infection and receiving antibiotics. Low volume trickle feeds were started two days after this initial transfusion. There were no concerns for feeding intolerance following this case or during hospitalization. Table 5.13 includes the descriptive statistics of variables for Case 7. Figure 5.16 is the visual plot for variables for Case 7. It should be noted that this case was set up like all cases with a 4-hour pretransfusion period, the actual duration time of the transfusion period, and followed by a 4-hour post transfusion period. The visual plot for this case has the same axis labels however, because this transfusion spans two days, the plots were spliced together for visualization.

Table 5.13 Physiological variables for case 7

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT ºC	36.3 (SD 0.03) 33.56 to 36.57	36.6 (SD 0.01) 36.12 to 37.12	36.7 (SD 0.01) 36.42 to 37
CPTd ºC	0.5 (SD 0.03) -2.04 to 2.32	0.4 (SD 0.02) -0.23 to 1.32	0.27 (SD 0.02) -0.41 to 2.72
HR bpm (131 to 176)	154 (SD 0.3) 126 to 172	157 (SD 0.5) 130 to 182	156 (SD 0.4) 140 to 180
SP02 %	94 (SD 0.2) 62 to 98	90 (SD 0.5) 16 to 96	90 (SD 0.7) 0 to 97

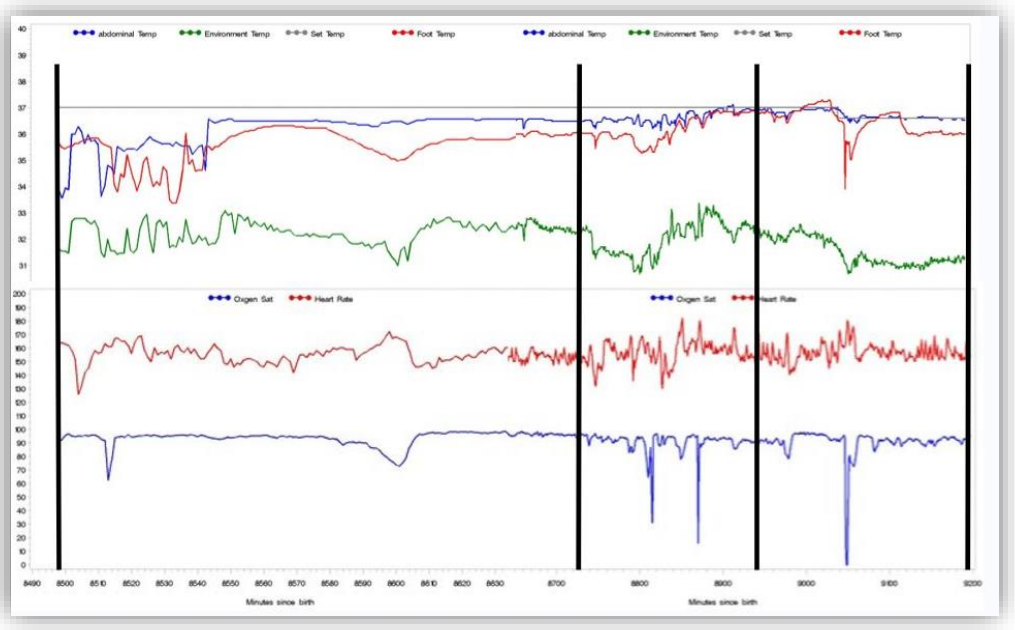


Figure 5.16 Variable plots for case 7

SUMMARY ANALYSIS FOR CASE 7

ABT: Pre-transfusion, this infant was hypothermic overall with a mean of 36.3º C and range of (33.56 º C to 36.57 º C). The preterm became both centrally (ABT) and peripherally (FT) warmer with a transfusion interval mean ABT of 36.6 º C. The infant continued to improve thermally after the transfusion with a mean abdominal temperature of 36.7 º C and a more normothermic range (36.42 º C to 37 º C).

CPTd: Over this transfusion case, the mean CPTd remain normal for pre, during and post transfusion (0.5 º C, 0.4 º C, 0.27 º C). However, the range of CPTd values are indictive of abnormal thermal gradients with the pre-transfusion period (-2.04 º C to 2.32 º C) as the most abnormal. This range reveals abnormal thermal gradients and a wide CPTd, indicating immaturity, stress, or infection. During the transfusion, the range was -0.23 º C to 1.32 º C, which was almost within normal ranges. After the transfusion, the

range of CPTd values continued to be abnormal with a range of -0.41 ºC to 2.72 ºC, indicating both CPTd values below 0 ºC and above 2 ºC. It should be noted that this infant may have underlying birth stress before the transfusion that resolved with the transfusion; however, there could be a suspicion of infection with the CPTd values greater than 2 ºC.

HR: All HR means were within the acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some lower values noted in the range of measures, however this is not reflective of the case.

SP02: All SP02 means were within acceptable range (85 to 100%) for this infant during this case. There are some lower values noted in the range of measures, however this is not reflective of the case (American Academy of Pediatrics, 2007).

Conclusion: The infant in this case was slightly hypothermic pre-transfusion and improved throughout the transfusion. The infant reached normothermia and continued to increase the body temperature, requiring the set temperature of the incubator to be turned down by clinicians. There are instances of abnormal thermal gradient noted throughout the case, however, much improved during the transfusion case. Ranges remained with abnormal values after the transfusion. The case reveals that the infant appeared to physiologically improve during the transfusion but there are still suggestions of a possible infection. It may be possible that the infant improved because of improved perfusion from the PRBC infusing into central circulation. Only more time would tell if there were an infection looming in this infant.

CASE 8

This case was linked to infant 6, born at 27 3/4 weeks GA (see Table 5.5). This was the infants first transfusion. The transfusion occurred on the infant's DOL 8-9 and was infused through a lower extremity PIV over 3 hours and 30 minutes.

Clinically, this infant required resuscitation measures following birth (chest compressions for two minutes) and was on antibiotic therapy during this case (Ampicillin and Gentamicin). The infant had hyperglycemia (laboratory value missing in EMR) during this case requiring an insulin drip and this is most often from acute stress. The infant was not fed because of insulin administration for high blood sugars and remained NPO until DOL 9, (day after case). Table 5.14 includes the descriptive statistics of variables for case 8. Figure 5.17 is the visual plot for variables for case 8.

Table 5.14 Physiological variables for case 8

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT ºC	36.9 (SD 0.01) 36.19 to 37.28	36.8 (SD 0.01) 36.74 to 36.9	36.9 (SD 0.01) 35.54 to 37.23
CPTd ºC	0.5 (SD 0.01) - 0.23 to 1.43	0.7 (SD 0.01) 0.57 to 1.01	0.8 (SD 0.03) - 1.13 to 2.93
HR bpm (131 to 176)	154 (SD 0.2) 146 to 171	157 (SD 0.2) 150 to 164	157 (SD 0.4) 149 to 178
SP02 %	96 (SD 0.1) 81 to 99	94 (SD 0.09) 90 to 98	90 (SD 0.1) 78 to 94

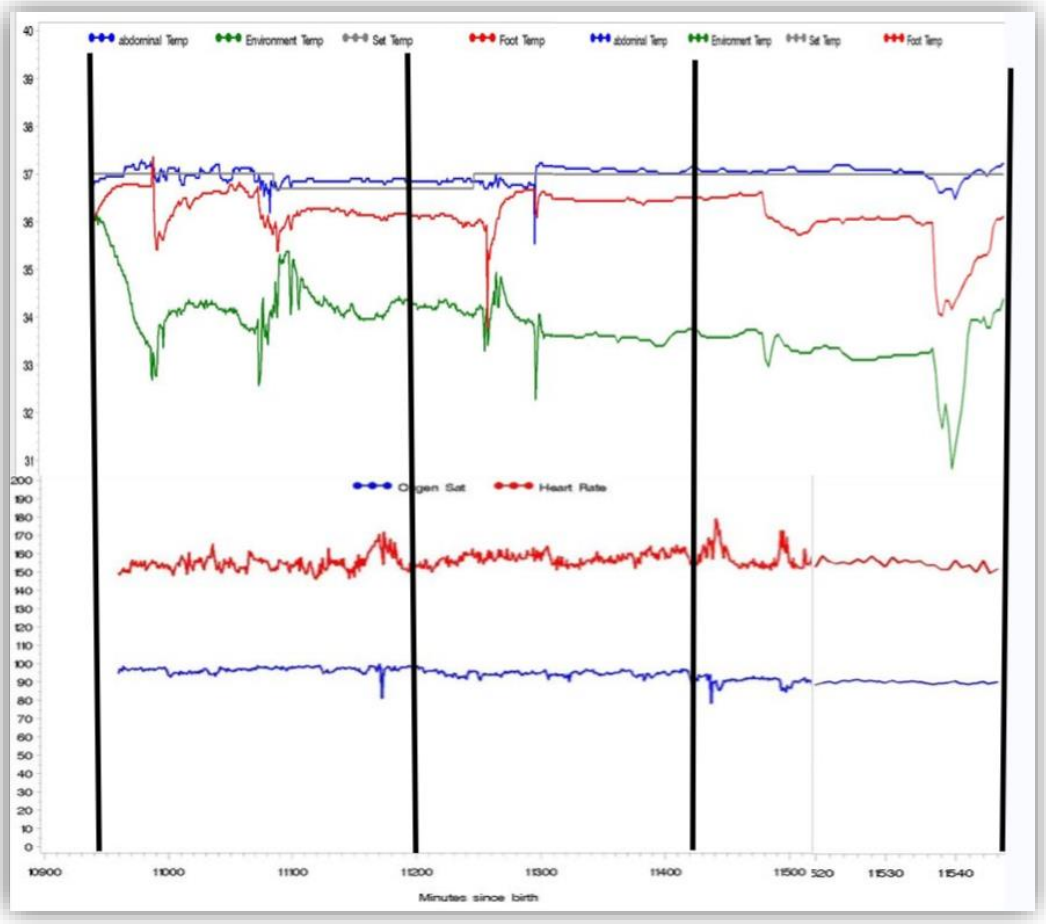


Figure 5.17 Variable plots for case 8

SUMMARY ANALYSIS FOR CASE 8

ABT: The infant in this case appears normothermic during the entire transfusion case, but a closer look at the ranges of ABTs reveal some indication of brief hypothermia pre-transfusion with a range of 36.19 ºC to 37.28 ºC, a more normothermic period during the transfusion with a range of 36.74 ºC to 36.9 ºC, and some hypothermia in the post transfusion period with a range of 35.54 ºC to 37.23 ºC. Mean abdominal temperatures were (36.9 ºC, 36.8 ºC, 36.9 ºC).

CPTd: Plot visualization shows there are no instances with the FT greater than the ABT. CPTd means are normal (0.5 ºC, 0.7 ºC, 0.8 ºC) for all three intervals;

however, the ranges widen over the course of this case. A closer look at the ranges is informative. The range of CPTd values pre-transfusion is mostly normal (-0.23 ºC to 1.43 ºC), during the transfusion the range (0.57 ºC to 1.01 ºC) is completely normal. After the PRBC transfusion, the range has many abnormal thermal gradients (-1.13 ºC to 2.93 ºC), having values both below 0 ºC and above 2 ºC.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case.

SP02: All SP02 means were within acceptable range (85 to 100%) for this infant during this case; however, like the ABT and CPTd trends, lower averages and values are seen after the transfusion. (American Academy of Pediatrics, 2007).

Conclusion: Overall, it is difficult to say if this infant tolerated the PRBC transfusion well. There were subtle trends towards abnormal values in the post transfusion interval. The infant was already ill and being treated, so only time would tell if the infant worsened temporally in the days after the transfusion.

CASE 9

This case was linked to infant 7 born at 26 2/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 10 and was infused through a lower extremity PIV over 4 hours.

This infant was born to a mother with who was positive for Group B Staphylococcus (GBS) and who was also diagnosed with Chorioamnionitis. The infant received two days of antibiotic treatment (Ampicillin and Gentamicin) to cover a possible infection; however, this current antibiotic course was changed to Vancomycin and

Gentamicin for broad spectrum coverage awaiting culture results as the infant was presumed septic due to an increase bradycardia and apnea spells.

This infant was also hypotensive at birth which required treatment with Dopamine to increase blood pressure; however, it was discontinued on day of transfusion case. This infant did not have a PDA and had not been fed since birth during this transfusion case. Low volume feeds were started how many days after this case and per case notes, the infant did not have feeding intolerance following this transfusion. Table 5.15 includes the descriptive statistics of variables for case 9. Figure 5.18 is the visual plot for variables for case 9.

Table 5.15 Physiological variables for case 9

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT ^{o}C	36.05 (SD 0.05) 33.11 to 36.83	36.3 (SD 0.04) 33.04 to 36.91	36.69 (SD 0.01) 36.15 to 37.03
CPTd ^{o}C	-0.14 (SD 0.05) -3.19 to 1.05	0.5 (SD 0.03) -1.9 to 1.5	0.08 (SD 0.01) 0.18 to 2.09
HR bpm (134 to 178)	155 (SD 0.6) 117 to 183	157 (SD 0.6) 95 to 188	159 (SD 0.5) 109 to 179
SP02 %	92 (SD 0.1) 87 to 98	93 (SD 0.3) 45 to 99	93 (SD 0.4)16 to 100

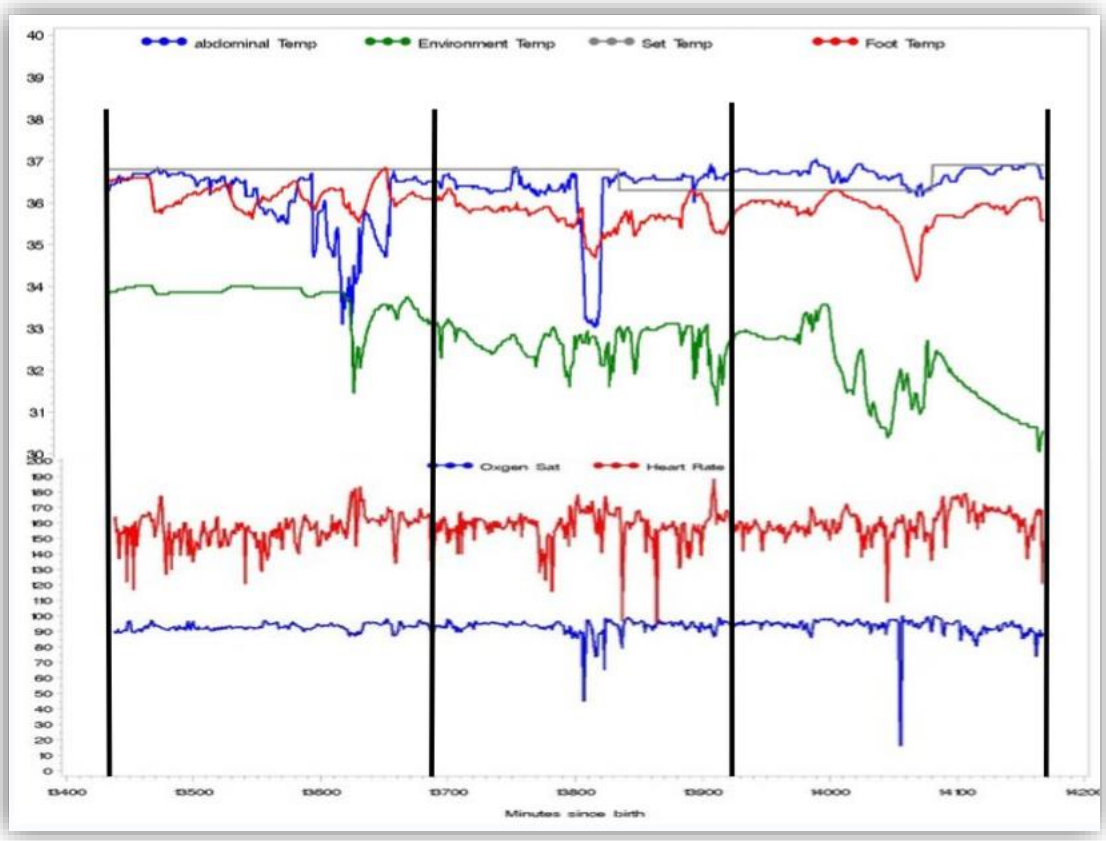


Figure 5.18 Variable plots for case 9

SUMMARY ANALYSIS FOR CASE 9

ABT: During the pre-transfusion period of this case, the infant was having instances of varying thermal dynamics. The infant's ABT is near the set incubator temperature; however, is hypothermic (36.05℃) with very low temperatures in the range (33.11 ℃ to 36.83 ℃) and begins to drop even further. Near the beginning of the transfusion period, there is a notable event where all temperatures drop and there are abnormal thermal gradients. The infant shows signs of increasing thermal stability after the transfusion begins until MSB 138200. At this time, the infant's temperature dipped resulting in abnormal thermal gradients in the middle of the transfusion period. ABT values continue to be hypothermic with the range (33.04 ℃ to 36.91 ℃) and a mean of

36.3℃. Post transfusion, the infant recovers and reaches normothermia (36.69 ℃) and the range is more in the normal limits (36.15 ℃ to 37.03 ℃). The infant rises above the set incubator temperature where it is seen the clinician decreases the set temperature.

The infant maintains a normothermic temperature reading a until the time following this set temperature change, the environmental temperature decreases, and the ABT and FT soon follow. The infant experiences a large decrease in both temperature and physiological measures at MSB 14700-1480. This decrease triggered an increase in the infant set incubator temperature and an increase towards normothermia by the end of the case.

CPTd: During the pre-transfusion period, the infant displayed abnormal and widened thermal gradients with a mean of -0.14 °C, and a range of -3.19 °C to 1.05 °C. During the transfusion, the CPTd values continue to be abnormal with a mean of 0.5 ℃ and a range of -1.9 ℃ to 1.5 ℃. However, as the transfusion progresses, the CPTd improves greatly overall. After the transfusion, the CPTd values end up normal with a mean of 0.08 ℃ and range of 0.18 ℃ to 2.09 ℃. There are instances where small amounts of abnormal thermal gradients-but mostly the infant shows improvement.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. During the transfusion, there are some bradycardic measures noted; however, the HR measures remain normal post transfusion.

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case. (American Academy Pediatrics, 2007). There are some brief desaturations with low SPO2 values during and after the transfusion, but overall, the infant remained with normal SPO2 values.

Conclusion: The infant in this case was hypothermic prior to and during the transfusion periods. There was improvement in the infant's abdominal temperature during the post transfusion period; however, there were many abnormal thermal gradients throughout this case. The thermal gradients continue to be abnormal during the transfusion but resolve after the transfusion and end up normal. Overall, the infant shows improvement from the start of the case to the end and it appears that the PRBC transfusion was beneficial to the infant's physiologic condition.

CASE 10

This case was linked to infant 8, born at 27 4/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 7. During this case, the infant had both an upper and a lower extremity PIV. It is unclear from the EMR data which site was used for this transfusion. This PRBC transfusion infused over 3 hours and 15 minutes.

This infant was born to a mother who tested positive for Group B Staphylococcus (GBS) and also had a positive urine drug screen for marijuana during her pregnancy with this infant. The mother denies smoking or alcohol use. Clinically, this infant was not on antibiotic therapy, treatment for blood pressure, or feeding during this case. The infant did have some GI concerns with a bilious gastric residual and visible loops of bowel in the abdomen two days prior to this case that was ruled benign. The infant was diagnosed with a PDA; however, was not treated during this case and the PDA later closed. Table 5.16 includes the descriptive statistics of variables for case 10. Figure 5.19 is the visual plot for variables for case 10.

Table 5.16 Physiological variables for case 10

Variable	Pre Mean (SD) Range	During Mean (SD) Range	Post Mean (SD) Range
ABT °C	37.32 (SD 0.04) 36.02 to 38.2	36.8 (SD 0.01) 36.09 to 37.2	36.6 (SD 0.00) 36.39 to 36.92
CPTd °C	1.27 (SD 0.048) 0.3 to 3.76	1.48 (SD 0.04) 0.28 to 3.55	1.81 (SD 0.03) 0.08 to 3.39
HR bpm (131 to 176)	162 (SD 0.7) 95 to 186	153 (SD 0.3) 130 to 176	154 (SD 0.33) 145 to 171
SP02%	90 (SD 1.6) 0 to 100	92 (SD 0.9) 0 to 100	69 (SD 2.8) 0 to 99

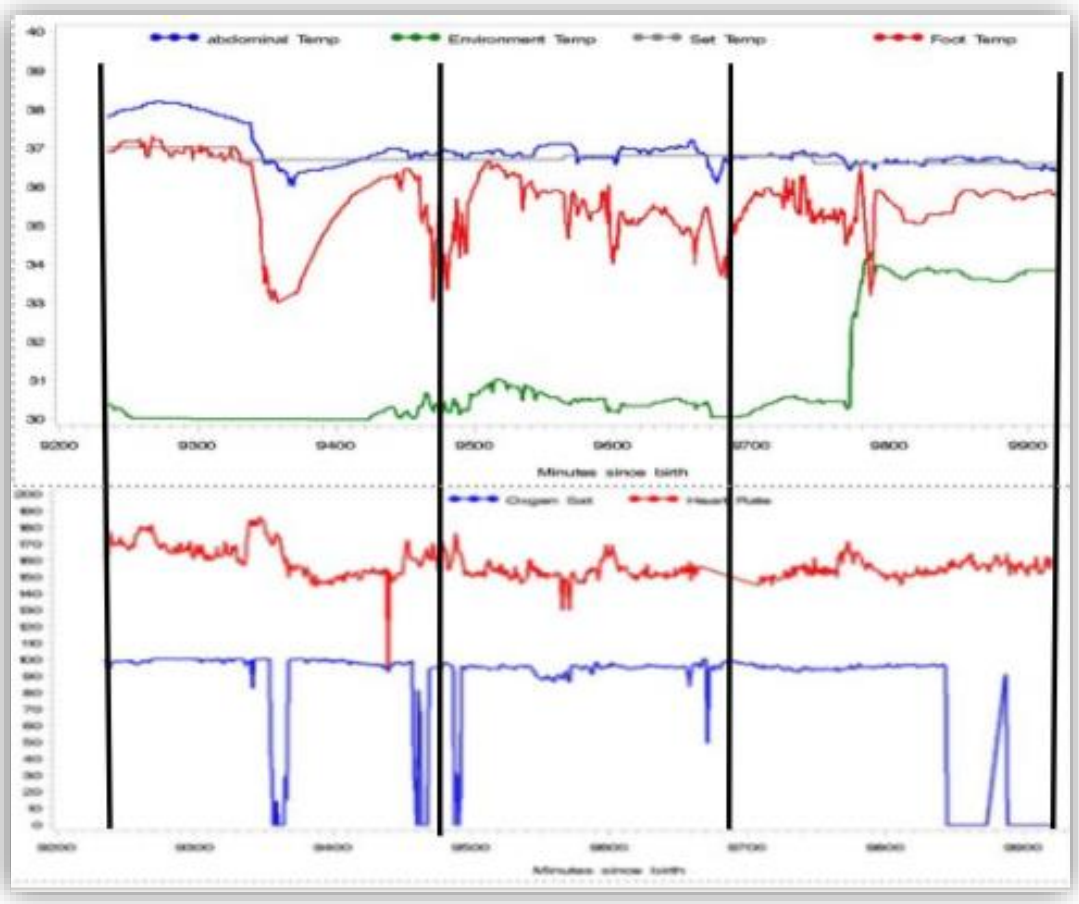


Figure 5.19 Variable plots for case 10

SUMMARY ANALYSIS FOR CASE 10

ABT: The infant in this case had some thermal instability during the pre-transfusion interval with a mean of 37.32 °C and range of 36.02 °C - 38.2 °C indicating both brief hypothermic values and normothermic values. During the transfusion, the mean was 36.8 °C, with a range of 36.09 °C to 37.2°C. After the transfusion, the ABT normalizes, with a mean of 36.6°C and a range of 36.39 °C to 36.92 °C. Interestingly, for each point there is a decrease in temperature, there is corresponding changes in the physiological measures (increase in HR or drop in SP02).

CPTd: The CPTd values in the case were abnormal in all intervals. During the pretransfusion interval, the mean values were 1.27 °C, and the range was 0.3 °C to 3.76 °C, during the transfusion values were nearly the same with a mean of 1.48 °C, and range of 0.28 °C to 3.55 °C. Post transfusion, the mean was 1.81°C with a range of 0.08 °C to 3.39 °*C*. Overall, the means stay within normal limits but are approaching 2 °C, which is the upper limit of a normal CPTd; however, there are many abnormal CPTd values within each interval. A wide CPTd can indictive of infection (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017).

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some lower values noted in the range of measures, however this is not reflective of the case.

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case (American Academy of Pediatrics, 2007). There are some lower values noted in the range of measures, however this is not reflective of the case.

Conclusion: Overall, the infant had hyperthermia and hypothermia periods pre-transfusion, and some hypothermia during the transfusion. Temperatures normalized after the transfusion. The CPTd values remained abnormal over the entire case; however, the means stayed within normal limits. It is important to note that following minute to minute longitudinal data is more revealing of abnormalities rather than aggregating data to means, which is commonly done in care. This infant had values greater than 3 °C, and these abnormal thermal gradients (>2 °C) can be associated with infection (Leante-Castellanos et al., 2012). This infant was not receiving antibiotic treatment. With the abnormally large CPTd values seen, one can conclude that *something* is going on with the infant in this case. The infant did later receive an antibiotic regimen on two different occasions post transfusion case for increased bradycardia and desaturation events with Ampicillin and Gentamycin. From these septic workups, there was no growth on any cultures collected by clinicians. This case is an example of when measuring CPTd values could be beneficial as predictive values to act detect something is amiss within a preterm and begin to quickly investigate.

CASE 11

This case was linked to infant 9 born at 27 5/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 13. This transfusion was infused through an upper extremity PIV. This PRBC transfusion infused over 2 hours and 30 minutes.

The infant in this case received antibiotics for 48 hours to rule out infection due to preterm delivery although there was no maternal infection diagnosed and the preterm delivery was for maternal factors. The infant required PRBC transfusions secondary to anemia of prematurity. The infant later developed anemia past the neonatal period, for

which iron was prescribed. Per the EMR, this infant had an uneventful hospitalization. Table 5.17 includes the descriptive statistics of variables for case 11. Figure 5.20 is the visual plot for variables for case 11.

Table 5.17 Physiological variables for case 11

Variable	Pre Mean (SD) Range	During Mean (SD) Range	Post Mean (SD) Range
ABT °C	36.34 (SD 0.025) 34.56 to 37.05	36.26 (SD 0.00) 35.92 to 36.47	36.5 (SD 0.02) 34.39 to 37.07
CPTd °C	0.7 (SD 0.04) -0.61 to 1.91	1.2(SD 0.07) -0.3 to 3.04	0.3 (SD 0.04) -0.13 to 3.06
HR bpm (130 to 177)	150 (SD 0.5) 132 to 178	141 (SD 0.6) 131 to 167	145 (SD 0.4) 127 to 167
SP02%	98 (SD 0.3) 48 to 100	98 (SD 0.12) 92 to 100	95 (SD 0.7) 0 to 100

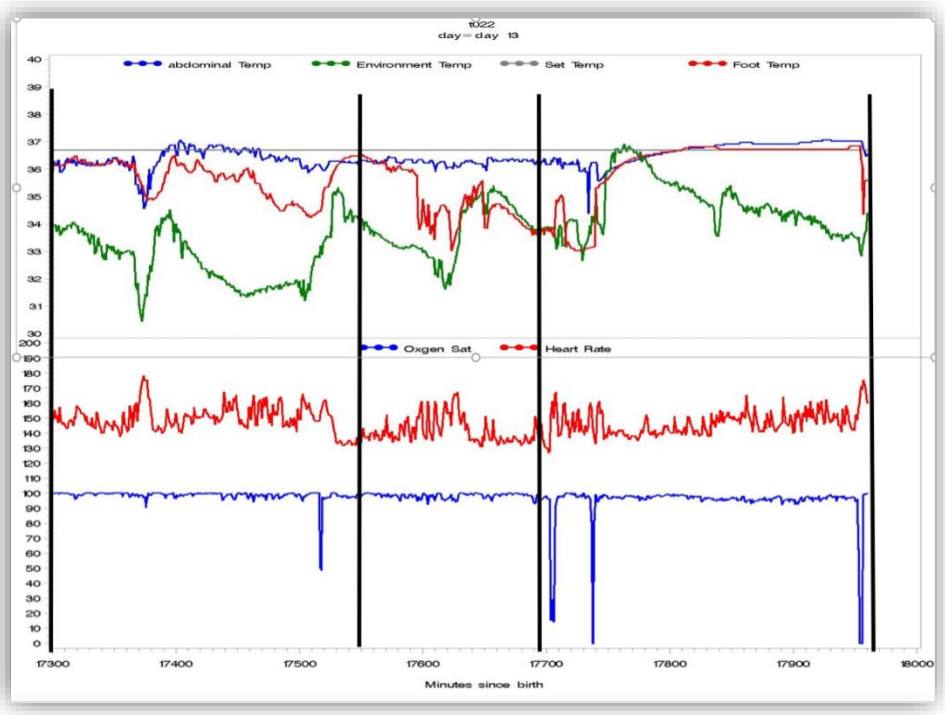


Figure 5.20 Variable plots for case 11

SUMMARY ANALYSIS FOR CASE 11

ABT: The ABT is hypothermic during the pretransfusion (mean 36.34 °C, range of 34.56 °C to 37.05 °C) and transfusion period (mean of 36.26 °C and range of 35.92 °C to 36.47 °C). Although the mean is normal after the transfusion, 36.5°C, the range still contains hypothermic temperatures (34.39 °C to 37.07 °C).

Cptd: Before the transfusion, there are abnormally low CPTd intermittently (-0.61 °C to 1.91 °C, although there is a normal mean CPTd (0.7 °C). During the transfusion, plot inspection reveals increased CPTd values and data reveal abnormally increased thermal gradients (mean of 1.2 °C, range of -0.3 °C to 3.04 °C. This condition stays the same after the transfusion with a mean of 0.3 °C, and a range of -0.13 °C to 3.06 °C. Large CPTd values have been associated with infection (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017).

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some lower values noted in the range of measures, however this is not reflective of the case.

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case (American Academy of Pediatrics, 2007). There are some lower values noted in the range of measures, however this is not reflective of the case.

Conclusion: This infant had slight thermal instability over the transfusion case and abnormally large intermittent CPTd values during and post transfusion. Clinical data revealed blood cultures remained negative and the infant never had the need for antibiotics after the admission. The infants HR and SPO2 values remained normal. The

transfusion did not seem to alter this infant's condition and there were no subsequent sign of NEC or other infection.

CASE 12

This case was linked to infant 10, born at 27 3/4 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 13. This transfusion was infused through an upper extremity PIV. This PRBC transfusion infused approximately 3 hours and 30 minutes.

This infant was born to a mother with severe preeclampsia. The mother was being treated with antibiotics during delivery; however, she had not been diagnosed with Chorioamnionitis. This mother also had a positive urine drug screen for marijuana during the pregnancy of this infant.

This infant was on Vancomycin during this case for *coagulase negative staphylococcus* (CONS) sepsis. The infant was not eating during this case and per the EMR data, there was never any indication of feeding intolerance post transfusion. Table 5.18 includes the descriptive statistics of variables for case 12. Figure 5.21 is the visual plot for variables for case 12.

Table 5.18 Physiological variables for case 12

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT °C	36.57 (SD 0.01) 34.52 to 36.93	35.26 (SD 0.05) 33.14 to 36.22	34.27 (SD 0.03) 33.06 to 36.53
CPTd °C	0.57 (SD 0.02) - 1.32 to 1.47	-1.05 (SD 0.04) - 2.25 to 2.06	-0.06 (SD 0.05) - 2.25 to 2.06
HR bpm (130 to 177)	140 (SD 0.6) 110 to 198	156 (SD 0.9) 137 to 210	141 (SD 0.4) 130 to 170
SP02 %	98 (SD 0.18) 78 to 100	96 (SD 0.2) 81 to 100	99 (SD 0.1) 91 to 100

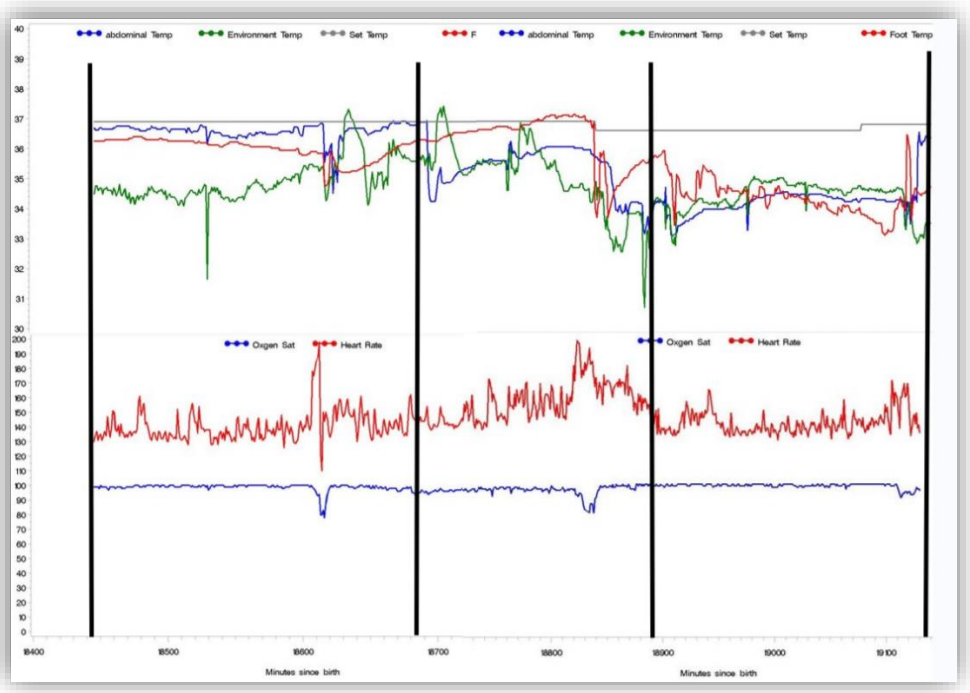


Figure 5.21 Visual plots for case 12

SUMMARY ANALYSIS FOR CASE 12

ABT: The infant was mostly thermally stable during the pretransfusion period, with a normal mean of 36.57 °*C*, however, there were some hypothermic temperatures (range of 34.52 °*C* - 36.93 °*C*). During the transfusion, the infant develops hypothermia, with a decreased mean of 35.26 °C, and a range of 33.14 °C to 36.22 °C containing no normothermic temperatures. After the transfusion, the infant is more hypothermic with a mean of 34.27 °C, and range of 33.06 °C to 36.53 °C. Plot visualization shows that at the very end of the case observation, the ABT reaches a normal temperature for 1-2 measures.

CPTd: Prior to the transfusion, the ABT is seen above the FT by plot inspection and the mean is within normal limits (0.57 °C) with a range of -1.32 °C to 1.47 °C. During the transfusion, the abnormal thermal gradients happen synchronously with the

extreme hypothermia, with the FT greater than the ABT. The mean is -1.05 °C (SD 0.04), with a range of -2.25 °C to 2.06 °C. After the transfusion, the FT becomes less than the ABT about halfway through the interval, affecting the CPTd values (mean -0.06 °C (SD 0.05), range of -2.25 °C to 2.06 °C). These data showed the infant did not remain stable during the transfusion and as the transfusion ends, begins to approach more normal values; however, remains unstable.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some abnormal values noted in the range of measures, however this is not reflective of the case. The infant has a higher mean HR during the transfusion period than pre or post transfusion. Also, the infant's range during the pretransfusion and transfusion period is well above the higher 95th percentile for this infant's GA (infant had HR 198 bpm – 210 bpm). Post transfusion, the infant displays a much more normal mean and range of HR. Could this be a result of the degree of anemia this infant had, and HR decreased to a normal range as a result of the transfusion?

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case; however, there were desaturation events prior to the transfusion and during the transfusion (American Academy of Pediatrics, 2007).

Conclusion: There is hypothermia during transfusion, which is to a lower level than the pretransfusion period. This hypothermia does not recover but gets worse for the remainder of the transfusion case. The thermal gradient becomes abnormal with the periphery warmer than the infant's central body simultaneously with this severe

hypothermia and remains that way into the post transfusion period as well. This infant was infected with CONS sepsis during this case.

Although there were not abnormally large CPTd values that indicate infection, the abundance of abnormal thermal gradients could be indicative of this infant being very stressed due to extreme hypothermia, which may confound the analysis of this variable and complicating the case further. This infant was transfused secondary to anemia of prematurity per EMR. There are no lab values available for this transfusion case; however, this instability and stress could be the result of the degree of anemia in this infant.

CASE 13

This case was linked to infant 11, born at 28 1/7 weeks GA (see Table 5.5). The transfusion occurred on the infant's DOL 20, at over 2 weeks of age. There were some infant subjects in the parent study who remained in data collection longer than 14 days to examine data trends for a longer timeline and this infant was one of those longer enrolled subjects. This transfusion was infused through an upper extremity PIV over 3 hours and 15 minutes.

Per EMR data, there was maternal polysubstance abuse as infant's urine drug screen was positive for barbiturates and the meconium drug screen were positive for cocaine and opiates. The mother was also diagnosed with Chorioamnionitis and on antibiotic therapy at the time of delivery and preterm rupture of membranes. This infant did receive 7-days of antibiotic therapy (Ampicillin and Gentamicin) due to maternal factors after admission to the NICU. The infant was not on antibiotics at time of this transfusion case.

After the transfusion case, the infant required antibiotic therapy (48-hour Ampicillin and Gentamicin) to rule out infection due to evidence of blood in the infant's stool. In another three weeks, the infant underwent testing for infection again because of increased bradycardia and apnea. At that time, it was found the infant had a positive urine culture for *Enterococcus*. The infant received 48-hours of Ampicillin and Gentamicin. Table 5.19 includes the descriptive statistics of variables for case 13. Figure 5.22 is the visual plot for variables for case 13.

Table 5.19 Physiological variables for case 13

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT °C	36. 11 (SD 0.00) 35.5 to 36.6	36. 5 (SD 0.01) 36.05 to 36.96	37.15 (SD 0.02) 35.6 3 to 37.67
CPTd °C	1.65 (SD 0.06) 0.2 to 3.41	1.99 (SD 0.05) 0.83 to 3.16	1 (SD 0.05) 0 to 3.82
HR bpm (123 to 176)	174 (SD 0.48) 106 to 189	171 (SD 0.55) 131 to 188	175 (SD 0.5) 159 to 203
SP02 (not available)			

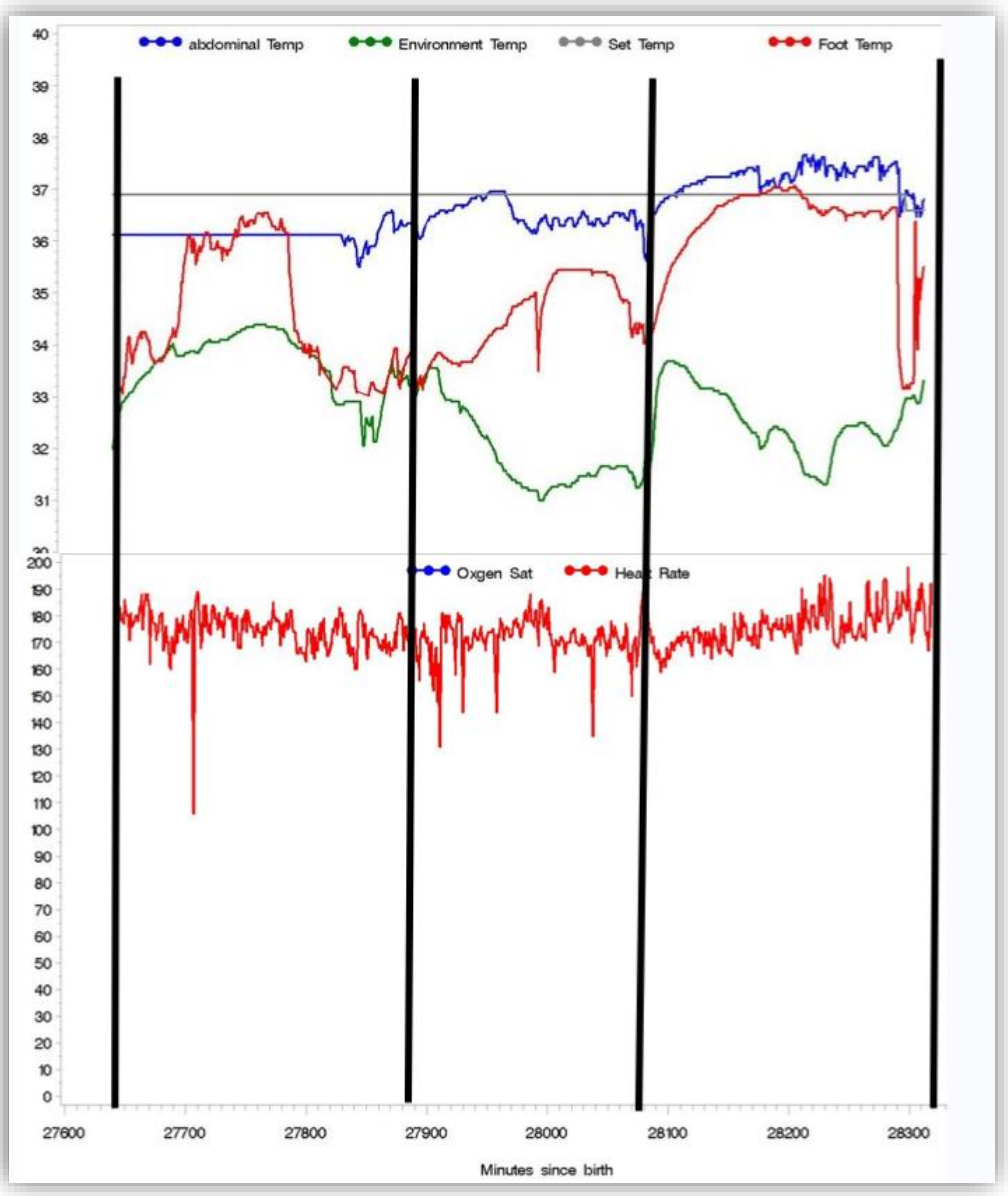


Figure 5.22 Variable plots for case 13

SUMMARY ANALYSIS FOR CASE 13

ABT: During the pretransfusion period, the infant is hypothermic with a mean abdominal temperature of 36.11°C. Data plots reveal a straight line, so it is unclear in the beginning of the interval if the measures are accurate. As the transfusion begins, the infant's ABT begins to increase and reaches normothermia as the PRBCs are infusing

(mean ABT 36.5°C, range 36.05 °C to 36.96 °C). The infant continues to improve thermally post transfusion (37.15°C). The ranges of abdominal temperatures across the case are vast however, the mean abdominal temperatures are reflective of improvement.

CPTd: Visualization of the plots show abnormally large CPTd values across all intervals that are largest during the transfusion. During the transfusion there is a mean of 1.99 °C (SD 0.05), with a range of 0.83 °C to 3.16 °C. All mean data are within normal limits; however, data and visual inspection of plots show many large CPTd values with resolution during the post transfusion interval.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are instances of tachycardic measures in all of the case periods. During the pretransfusion period, 43% of the measures fell outside of the upper 95th percentile for this infant and is classified tachycardia. During the transfusion, the infant only displayed 18% of tachycardic measures and after the completion of the transfusion, the infant has 39% of HR measures that are classified tachycardic for its GA (Alonzo et al., 2018). In terms of the HR variable, the period of time where the infant had less abnormal measures was during the transfusion and therefore can be concluded that this transfusion brought this physiologic variable closer to the infant's acceptable range.

SP02: There were no SP02 measures available for this case.

Conclusion: This infant is hypothermic during the pre-transfusion period and remains hypothermic until right before the transfusion starts then begins to improve into the transfusion and is normothermic after the transfusion. Thermal gradients remained abnormally large through pre-transfusion interval and during the transfusion. These large

CPTd are associated with infection (Leante-Castellanos et al., 2012; Knobel-Dail et al., 2017). Knowing from clinical data that this infant was later diagnosed with infection, suggests that the abnormally large CPTd found during this transfusion case study may have been predictive of this infection. It is unclear whether the infant did not tolerate the PRBC transfusion or if the transfusion helped the infant stabilize and mask the symptoms of the impending infection.

CASE 14

This case was linked to infant 12, born at 25 6/7 weeks GA (see Table 5.5). This transfusion case occurred on DOL 4 for this infant. This transfusion was infused through a central UAC over approximately 3 hours and 30 minutes.

This infant was born to a mother who was diagnosed with Chorioamnionitis and on antibiotic therapy at delivery. On admission, this infant had a white blood cell (WBC) count of 44 and 18 bands which is indicative of infection. The infant was also hypotensive. The infant was on antibiotics (Ampicillin and Gentamicin) during this case. A few days after the transfusion, the infant still had an increased white blood cell count and new onset of metabolic acidosis, but blood cultures remained negative. The infant was not fed since birth and prior to this case, remaining NPO (nothing by mouth) until 3 days after the case (DOL 7). Per electronic medical record (EMR) data, there was never concern for feeding intolerance following this transfusion case. Table 5.20 includes the descriptive statistics of variables for case 14. Figure 5.23 is the visual plot for variables for case 14.

Table 5.20 Physiological variables for case 14

Variable	Pre Mean (SD) Range	During Mean (SD) Range	Post Mean (SD) Range
ABT °C	36.93 (SD 0.01) 36.64 to 37.07	37.17 (SD 0.01) 36.69 to 37.4	37.2 (SD 0.01) 37.02 to 37.35
CPTd °C	0.6 (SD 0.01) 0.13 to 0.93	0.6 (SD 0.02) 0.43 to 0.83	0.2 (SD 0.02) -0.97 to 1.13
HR bpm (134 to 176)	163 (SD 0.38) 154 to 187	161 (SD 0.27) 129 to 174	166 (SD 0.32) 154 to 181
SP02 %	86 (SD 1.5) 0 to 99	94 (SD 0.36) 31 to 100	94 (SD 0.04) 16 to 98

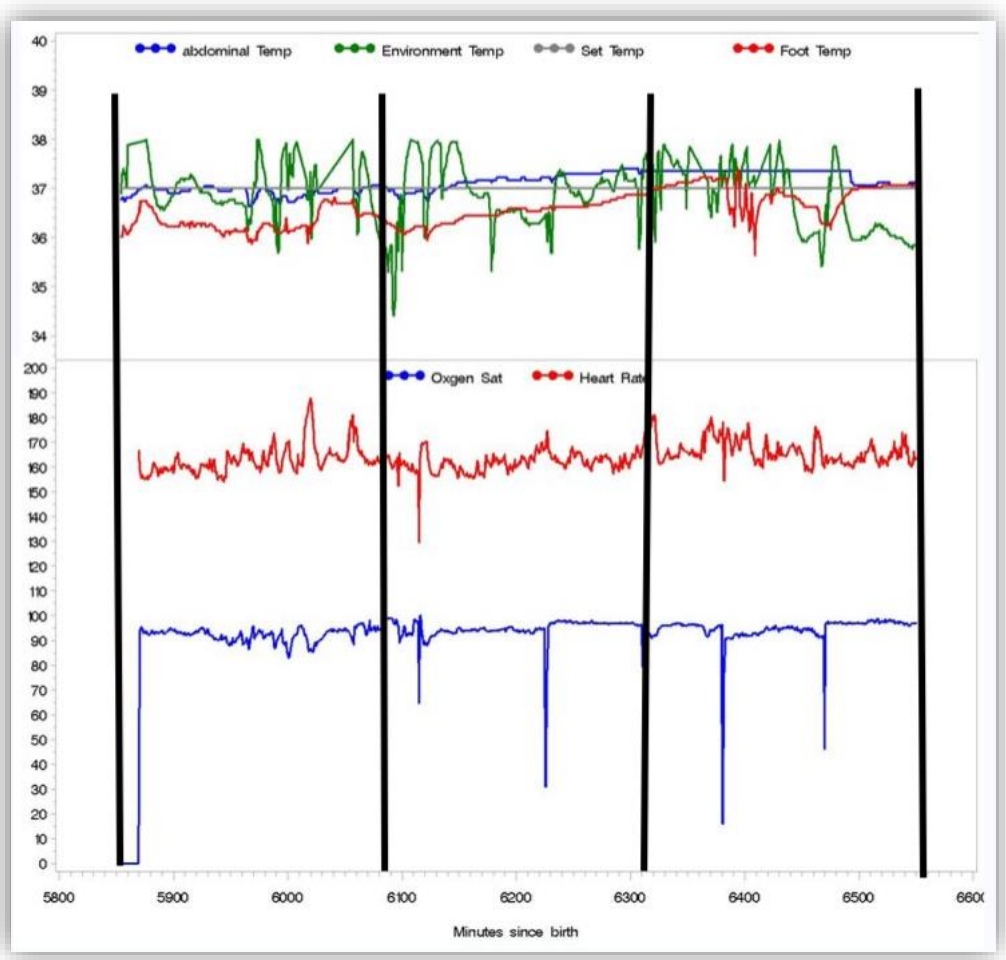


Figure 5.23 Variable plots for case 14

SUMMARY ANALYSIS FOR CASE 14

ABT: During the entire transfusion case, the infant is normothermic as seen through all means (36.93 °C, 37.17 °C, 37.2 °C) and ranges. The infant's ABT increases as the transfusion progresses. There are no instances of hypothermia during this case.

CPTd: Overall, the infant displays no abnormal thermal gradients with means remaining normal (0.6 °C, 0.6 °C, 0.2 °C) and all ranges within normal limits.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some lower values noted in the range of measures, however this is not reflective of the case.

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case. There are some lower values noted in the range of measures, however this is not reflective of the case (American Academy of Pediatrics, 2007).

Conclusion: This was a very normal transfusion case, and overall, this infant tolerated this transfusion. Interestingly, this infant was transfused via central UAC, with blood that was not warmed as in all other case and even though of a very low GA, maintained normothermia. Because the infant was on antibiotic treatment, perhaps this coverage for infection also helped to stabilize the infant. Another possible reason for stability is that the servo set temperature was higher, due to the GA and a temperature of 37 °C was enough to maintain the infant's temperature?

CASE 15

This case was linked to infant 12, the infant in case 14 who was 25 2/7 weeks GA (see Table 5.5). This second transfusion occurred on DOL 10 for this infant. This

transfusion was infused through a lower extremity PIV over approximately 3 hours and 30 minutes.

During this case, the infant was on Dopamine treatment for renal perfusion related to decreased urine output, not hypotension. Feedings were stopped 4-hours prior to this transfusion. Feedings of breast milk were resumed the day following this case without issue. Four days after this transfusion case, the infant was noted to have developed a *Candida* urinary tract infection and an antifungal medication was started. Table 5.21 includes the descriptive statistics of variables for case 15. Figure 5.23 is the visual plot for variables for case 15.

Table 5.21 Physiological variables for case 15

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT °C	36.5 (SD 0.03) 34.83 to 37.17	36.67 (SD 0.02) 35.22 to 37.3	35.6 (SD 0.11) 33.01 to 37.3
CPTd °C	1.17 (SD 0.04) 0 to 2.3	0.66 (SD 0.02) -0.92 to 1.86	-0.5 (SD 0.1) -4.5 to 1.48
HR bpm (134 to 178)	179 (SD 1.03) 37 to 202	171 (SD 0.6) 93 to 188	178 (SD 0.5) 133 to 206
SP02 %	86 (SD 1.1) 0 to 99	90 (SD 0.5) 0 to 99	89 (SD 0.2) 67 to 97

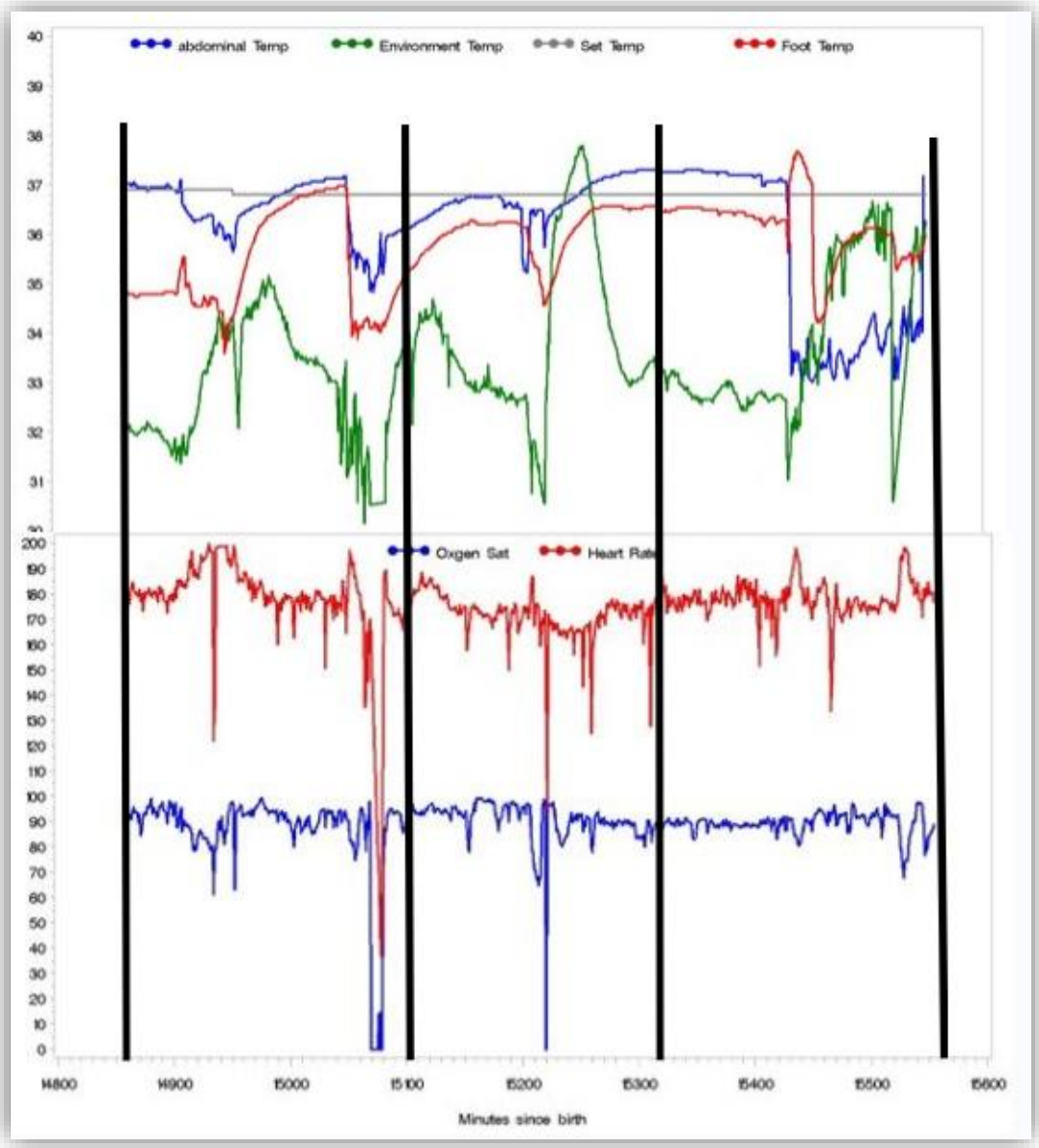


Figure 5.24 Variable plots for case 15

SUMMARY ANALYSIS FOR CASE 15

ABT: The infant was not as thermally stable through this transfusion as it was in case 14. Pre-transfusion and during the transfusion, the mean ABT values are within normal limits; however, both ranges contain hypothermic values. During the post

transfusion period, the infant's mean ABT is hypothermic (35.6 °C) with a range of 33.01 °C to 37.3 °C.

CPTd: In the pre-transfusion interval, the CPTd values had a mean of 1.17 °C (SD 0.04) 0 °C to 2.3 °C, which is mostly normal. Inspection of plots revealed the large values were minimal and in the beginning of the interval. During the transfusion, the values became more abnormal, with a normal mean of 0.66 °C, and abnormal values within the range of -0.92 °C to 1.86 °C. Visual inspection of the plots shows a normal pattern. Post transfusion, visual inspection shows approximately 50% of the measures with FT greater than ABT, meaning the periphery was warmer than the central body. Data revealed an anormal mean (-0.5) and a very abnormal range of -4.5 °C to 1.48 °C. The thermal gradients became more unstable over the transfusion case.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. Although mean HR was normal throughout the case, the range of HR display abnormal values for this infant's GA throughout. During the pretransfusion period, 82% of the HR measures fell outside of the upper 95th percentile for this infant and thus classified tachycardia. During the transfusion, the infant displayed a lower amount (36%) of tachycardic measures and after the completion of the transfusion, the infant's abnormal measures increased to 79%. (Alonzo et al., 2018). The period of time where the infant had less abnormal HR measures was during the transfusion and therefore can be concluded that this transfusion brought this physiologic variable closer to the infant's acceptable range. With a large rebound of abnormal HR measures post transfusion, would this indicate a need for another transfusion?

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case. There are some lower values noted in the range of measures, however this is not reflective of the case (American Academy of Pediatrics, 2007).

Conclusion: Overall, this infant became more centrally hypothermic through the transfusion case and had worsening thermal gradients as indicated by worsening CPTd values. From the available data, it was found the infant required a septic workup and antifungal treatment a few days after the blood transfusion case. The abnormal thermal gradients seen through and after the blood transfusion may have been more related to the infant's impending infection and not directly related to the blood transfusion. The physiologic measures during this case were variable throughout. The infant's HR remains in the upper 95th percentile (179bpm, 171bpm, 178bpm) during the entire case and the SP02 are on the lower end of the acceptable range (85-100%) with means of (86%, 90%, 89%). There are instances of desaturations throughout the case.

CASE 16

This case was linked to infant 13, born at 27 1/7 weeks (see Table 5.5). This transfusion case occurred on DOL 11 for this infant. This transfusion was infused through an upper extremity PIV over 3 hours and 30 minutes.

The infant in this case was presented with no effort at birth. The infant was intubated which stabilized the respiratory effort. The mother of this infant had severe preeclampsia and Hemolysis Syndrome. This preterm delivery was due to maternal factors.

During this case, the infant was not feeding and had a Replogle suction tube in place to decompress the GI tract as a result of feeding intolerance which was determined

from abdominal distension, an abnormal abdominal radiograph, and increased apnea (stop breathing for 20 seconds). This infant underwent laboratory testing to rule out infection at this time and antibiotics were started (48-hours Ampicillin and Gentamicin). The infant again required a septic workup 4 days after the transfusion due to increased apnea and low urine output. The infant was placed back on a ventilator at that time and given 48 more hours days of antibiotics (same course). All cultures remained negative. Per electronic medical record (EMR) data, all PRBC transfusions were secondary to anemia of prematurity. Table 5.22 includes the descriptive statistics of variables for case 16. Figure 5.25 is the visual plot for variables for case 16.

Table 5.22 Physiological variables for case 16

Variable	**Pre** **Mean (SD) Range**	**During** **Mean (SD) Range**	**Post** **Mean (SD) Range**
ABT °C	36.79 (SD 0.01) 35.33 to 37.29	36.92 (SD 0.02) 35.21 to 37.21	36.87 (SD 0.01) 36.65 to 37.08
CPTd °C	1.2 (SD 0.04) 0.18 to 3.41	0.75 (SD 0.03) -0.92 to 3.02	0.64 (SD 0.01) 0.28 to 0.87
HR bpm (131 to 176)	157 (SD 0.84) 94 to 184	153 (SD 0.46) 119 to 169	151 (SD 0.33) 134 to 164
SP02 %	94 (SD 0.3) 62 to 100	86 (SD 1.5) 0 to 98	94 (SD 0.1) 84 to 97

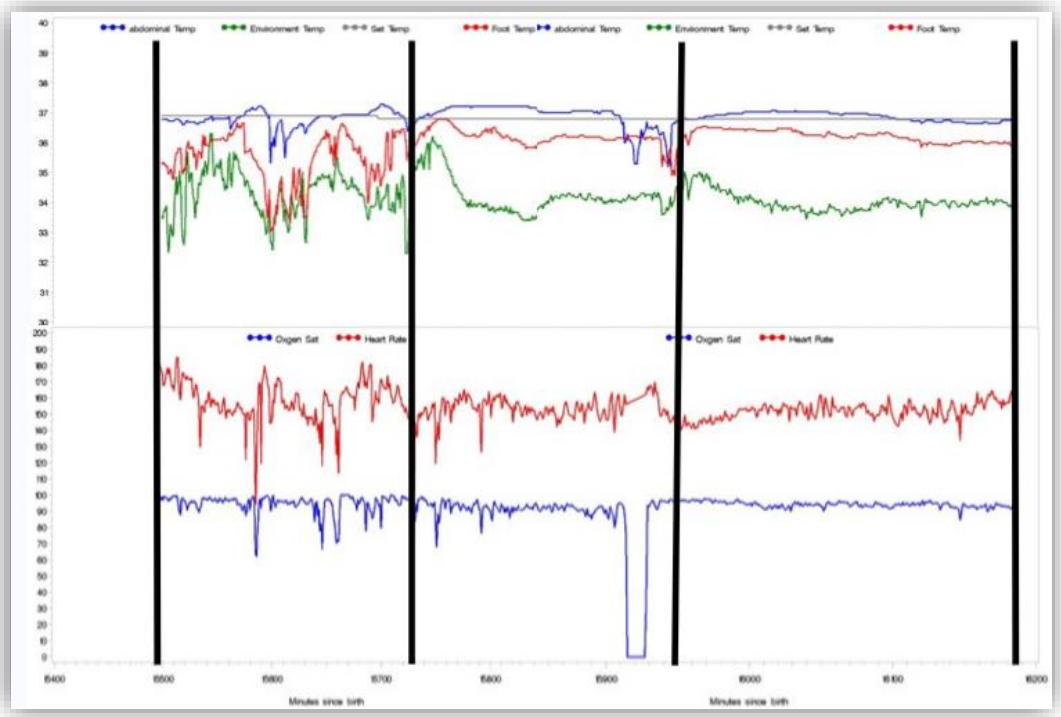


Figure 5.25 Variable plots for case 16

SUMMARY ANALYSIS FOR CASE 16

ABT: ABT values had means that were normothermic (36.76 °C, 36.92 °C, 36.87 °C); however, the range of temperatures during within the intervals included hypothermic temperatures.

CPTd: Pretransfusion, the CPTd values had a normal mean (1.2 °C) but the range had abnormally large values within (0.18 °C to 3.41 °C). Plot inspection revealed the gap between the ABT, and FT was widest prior to the blood transfusion. During the transfusion, the mean remains normal (0.75 °C) and the ABT is closer to the FT (-0.92 °C to 3.02 °C). After the transfusion, the mean and range remain normal. Because there are values over this case that are very large, it may be indicative of infection, but overall, the infant appears to tolerate the infection.

HR: All HR means were within acceptable range for this infant based upon GA (Alonzo et al., 2018) throughout this case. There are some lower values noted in the pre-transfusion interval, but these abnormal values are not present during or after the transfusion.

SP02: All SP02 means were within acceptable range (85-100%) for this infant during this case. There are some lower values noted in the range of measures, however this is not reflective of the case (American Academy of Pediatrics, 2007).

Conclusion: Overall, it appears this infant tolerated this PRBC transfusion and showed thermal and physiological improvement as the case progressed. The increased thermal gradients may have been indicative of infection; however, this infant had antibiotic coverage already.

Between case analysis The cases were grouped by age sex, and race, to examine case summaries to expose commonalities and themes. Table 5.23 displays between case analysis infant demographics (reported by case number) for GA at birth.

Table 5.23 Between Case Analysis of Infant Demographics for GA at Birth

GA at birth	Case
24-25 weeks	5, 6, 14, 15
26-28 weeks	1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 16

GESTATIONAL AGE

Examining summaries across these cases, it was found that three out of four infants in the 24-26 weeks GA group became more hypothermic and became less stable thermally as the case progressed (case 5,6,15). In these infants, the PRBC transfusion

appeared to make them colder than before the transfusion. The exception in this age group is case 14 in which the infant was normothermic and without abnormal thermal gradients the entirety of the case. This case data did not follow our hypothesis that when preterm infants are transfused centrally, they would experience hypothermia. The reason why this infant did not show hypothermia may be related to the incubator temperature being set at a higher temperature (37 ℃). As the outlier in the group, this could be a logical explanation and potential intervention to combat hypothermia during PRBC transfusions in preterm infants. The majority of the other cases in this study were born 26-28 weeks GA The between case analysis found 7 of 11 cases showed data indicative of a stable infant or an infant who showed thermal improvement throughout the transfusion. Four of the 11 cases data showed infants that did not tolerate or became more hypothermic throughout the transfusion. There are other confounding variables to account for this spread of results such as current antibiotic therapy or older GA.

SEX

The infants in the study were either male (M) or female (F), there were no reports of sexual ambiguity in this study. The between case analysis of infant sex was performed. Table 5.24 displays between case analysis infant demographics (reported by case number) for sex.

Table 5.24 Between case analysis infant demographics for sex

Sex	**Case**
M	3, 4, 7, 8, 10, 11, 13, 16
F	1, 2, 5, 6, 9, 12, 14, 15

There was equal representation of sexes in this study (8 M and 8 F). Through between case analysis, it was determined that the female infants in this study fared worse than the males. Of the 8 male infants in this study, 5 remained stable or showed improvement thought the transfusion were only 3 became more unstable. Of the 8 female infants in this study, only 3 remained stable or showed improvement thought the transfusion and 5 became more unstable. This is contradictory of what research shows in males having worse outcomes than females (O'Driscoll et al, 2018). These results based upon sex opens more opportunity for research in this area with a larger sample.

RACE

The cases in this study included only Black (B) and White (W) subjects. There were other racial categories in the parent study; however, the 13 out of 30 infants that received PRBC transfusions with valid data, were B and W. Table 5.25 displays between case analysis infant demographics (reported by case number) for race.

Table 5.25 Between case analysis infant demographics for Race

Race	**Case**
B	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 14, 15
W	8, 12,13, 16

Overwhelmingly, there were more B than W in this study sample. Of the 4 W infants in this study, there was an even split of stable versus unstable. Infants 8 and 16 remained stable throughout the transfusion case whereas infants 12 and 13 did not tolerate the transfusion. Of the 12 AA infants, there was even divide of results. Six of the

cases remained stable or improved as the transfusion progressed (cases 2, 3, 7, 9, 11, 14) and the remaining 6 cases (cases 1, 4, 5, 6, 10, 16) did not tolerate the transfusion. Research has shown a connection between a racial disparity in the NICU (Profit et al., 2017). Profit et al (2017) performed a study which showed non-Hispanic white infants scored higher on measures of processes compared to African Americans and Hispanics. Compared with White infants, African Americans scored higher on outcomes. These results, along with current research findings supports the need for more research between racial outcomes in NICUs a larger sample.

DISCUSSION

The purpose of this study was to examine the relationship between body temperature, feeding practices, and blood transfusions as well as morbid conditions such as hypothermia, feeding intolerance and NEC in preterm infants to inform science and lead to interventions to improve infant outcomes.

Of the 13 infants that received PRBC transfusions in the parent study, there were a total of 16 analyzable transfusion cases produced. Each case was analyzed using a multi-case (Zainal, 2007), within and between case analyses mixed methods approach (Polit & Beck, 2017).

A within case study approach is valuable to current research as it proves beneficial when there is a vital need to gain perspective of an issue, experience, or a related phenomenon of interest, from a natural, unbiased, and authentic standpoint (Crowe et al., 2011). Employing mixed methods into within case study analysis provides a rich representation of a phenomenon. This intensive analysis allows for the quantitative and qualitative data to be intertwined to "paint" a picture of the entire case within the

study. In this study, the analysis went further than just analyzing the numbers of the infant, but rather built the case on the clinical context of each infant. Overall, the 16 cases within this study were found to be mixed with 8 stable cases and 8 unstable cases. Although a small sample, saturation was achieved using mixed methods and provides a basis for future studies.

The study results show that preterms can experience hypothermia during a PRBC transfusion. Infants with a lower gestation at birth (24-25 weeks) became more hypothermic and some less stable thermally throughout the case with one exception to this finding (Case 14). Case 14 remained normothermic and without abnormal thermal gradients the entirety of the case. However, Case 14 was found to have a higher incubator servo control (ISC) temperature throughout the case, which could account for the stable temperature. This finding provides a basis for further research in this area. Researchers have previously made this recommendation (Knobel et al., 2010); however, it is not a standard across NICUs.

Some cases in this study were found to have abnormal physiological measures such as heart rate and oxygen saturation. The laboratory values indicating an infant's Hgb and Hct could provide more insight into the clinical context of the cases. It is plausible that these cases have been tachycardic as a means of compensation for hypovolemia and experiencing low oxygen level due less available oxygen carrying cells (Polin et al., 2017). A 2016 secondary, prospective, multicenter study investigated the relationship of PRBCs, anemia, and NEC in preterm infants (Patel et al., 2016). The researchers found severe anemia and not the PRBC transfusion itself resulted in NEC in a sample of nearly 600 preterm infants (Patel et al., 2016). If the level of anemia to which the preterm

infant can remain a potential precursor to the pathogenesis of NEC, further research is vital to this population.

A major contributor to preterm infant morbidity and mortality is infection. As seen in this study, infection can be overlooked by the healthcare team. Some cases in this study were presumed to be free from infection during the transfusion, but later required a septic workup due to abnormal vital signs and changes in clinical presentation. Previous research has shown that abnormal physiological measures can be indicative of infection (Knobel-Dail et al., 2017). If there was a visual representation of the CPTd of a preterm infant in real time, there could potentially be better odds at early diagnosis and treatment of infection. Currently, a National Institute of Health funded, multi-site study in underway to examine abnormal thermal gradients in 440 preterm infants to predict infection (Dail et al., 2021). This research effort is promising for the future of neonatal medicine and research as it could aide in earlier detection of infection by use the preterm infant's temperature as a predictive tool.

Researchers posit an association between PRBC and NEC in preterm infants (Santos et al., 2011). However, there are still conflicting results due to bias (Cunningham et al., 2017) and those who report no association at all (Garg et al., 2016). With the continuing ambiguity in research claims around a medically necessary corrective intervention such as a PRBC transfusion and a potentially fatal neonatal complication, as NEC, the need for more research is endless.

FUTURE RESEARCH

Overall, the 16 cases within this study were found 8 stable cases and 8 unstable cases. Although a small sample, the saturation provided by using mixed methods, within and between case analysis proved thought provoking for future studies.

In a current study (NIH/NINR:1R01NR017872), data similar this dissertation study will be available for over 300 preterm infants. With these data an analysis to examine blood transfusions, feeding practices, and morbid outcomes in a large cohort can be done. This larger sample will allow for a more powerful analysis within and between cases, and accounting for the biologic factors of GA, sex, and race.

In another study, the hypothesis of infusing cold PRBC versus warmed PRBC can be tested. This study will be a pilot to test a commercial PRBC warming product on preterm infant PRBC transfusions with a level III NICU which care for some of the most critical preterm infants within the state of South Carolina.

A study to focus on feeding practices in the context of body temperature, and blood transfusions to assess morbid conditions such as hypothermia, feeding intolerance and NEC in preterm infants is needed. Feedings into a GI system that is hypothermic and possibly ischemic may further contribute to signs and symptoms of feeding intolerance and/or NEC. There is instability, poor vasomotor tone and/or stress during the entirety of the transfusion. It is difficult to rule out which condition comes first and any inference of causation between illness severity, hypothermia, GI ischemia and feeding intolerance or a NEC diagnosis. There has been heightened interest in what preterm infants are fed and when preterm infants are fed around the time of a PRBC transfusion. The WHEAT trial, Withholding Enteral feeds Around packed red cell Transfusion is currently

examining the effects of withholding feedings in a large sample of preterm infants around PRBC transfusions to assess outcomes. Although it is known that human milk is best for preterm infants (Gephart et al., 2018), not all preterm infants receive human milk. A future study could compare the feeding contents of preterm infants and the incidence of feeding intolerance and NEC.

Lastly, a study examining body temperature, feeding practices, and blood transfusions as well as morbid conditions such as hypothermia, feeding intolerance and NEC in preterm infants and length of stay in the NICU would be beneficial to the science and the medical community.

CONCLUSION

NEC has been researched for decades without a clear causality (Thompson-Branch & Hanranek, 2018). The only known and agreed upon precursor to this potentially fatal complication is prematurity. With 1 of every 10 births in the US being preterm, preterm births remain a national health concern (CDC, 2020). Although the results of this study were from a small sample and revealed a definitive conclusion, more studies are needed test our working hypothesis that central hypothermia, combined with feedings and PRBC transfusion could be an etiological factor to the pathogenesis of NEC. This research is invaluable to the neonatal community to combat morbid conditions in preterm infants.

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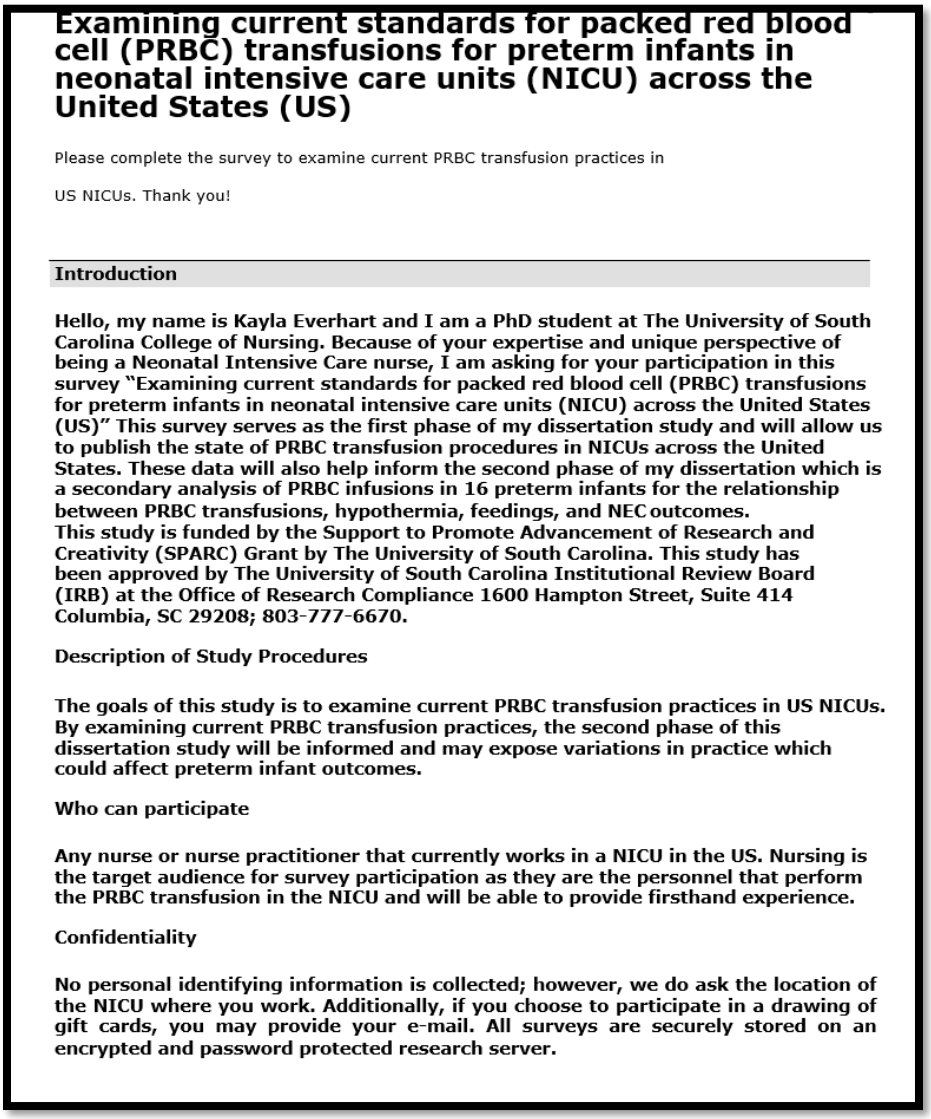
APPENDIX A

SURVEY QUESTIONS



Examining current standards for packed red blood cell (PRBC) transfusions for preterm infants in neonatal intensive care units (NICU) across the United States (US)

Please complete the survey to examine current PRBC transfusion practices in

US NICUs. Thank you!

Introduction

Hello, my name is Kayla Everhart and I am a PhD student at The University of South Carolina College of Nursing. Because of your expertise and unique perspective of being a Neonatal Intensive Care nurse, I am asking for your participation in this survey "Examining current standards for packed red blood cell (PRBC) transfusions for preterm infants in neonatal intensive care units (NICU) across the United States (US)" This survey serves as the first phase of my dissertation study and will allow us to publish the state of PRBC transfusion procedures in NICUs across the United States. These data will also help inform the second phase of my dissertation which is a secondary analysis of PRBC infusions in 16 preterm infants for the relationship between PRBC transfusions, hypothermia, feedings, and NEC outcomes.
This study is funded by the Support to Promote Advancement of Research and Creativity (SPARC) Grant by The University of South Carolina. This study has been approved by The University of South Carolina Institutional Review Board (IRB) at the Office of Research Compliance 1600 Hampton Street, Suite 414 Columbia, SC 29208; 803-777-6670.

Description of Study Procedures

The goals of this study is to examine current PRBC transfusion practices in US NICUs. By examining current PRBC transfusion practices, the second phase of this dissertation study will be informed and may expose variations in practice which could affect preterm infant outcomes.

Who can participate

Any nurse or nurse practitioner that currently works in a NICU in the US. Nursing is the target audience for survey participation as they are the personnel that perform the PRBC transfusion in the NICU and will be able to provide firsthand experience.

Confidentiality

No personal identifying information is collected; however, we do ask the location of the NICU where you work. Additionally, if you choose to participate in a drawing of gift cards, you may provide your e-mail. All surveys are securely stored on an encrypted and password protected research server.

Payment

Research incentives for survey participation will include one random drawing each week of the survey period (1 month) from survey responses received during that week, for one VISA gift card valued at 50 US Dollars. To be eligible for the drawing, you must specify an email. Only one survey should be submitted per respondent. To receive the gift card, you must reply to an email from the researcher and give you name and address.

Voluntary Participation

You are not obligated to complete the survey and may withdraw from the survey at any time. There is no penalty for withdrawing from the survey.

Questions

If you have any questions regarding this survey please contact the PI, Kayla Everhart at: everhakc@email.sc.edu or committee member Dr. Sara Donevant at: donevant@mailbox.sc.edu

Instructions for completing the survey:

This survey is distributed through the RedCap database. A link will be provided to you and once the link is activated, you can begin the survey. The survey does not need to be filled out in one sitting and should take approximately 10-15 minutes to complete.

Survey Consent By answering 'yes', you voluntarily give your consent to participate in this survey on current standards for PRBCs in preterm infants. You may leave the survey at any time.	◯ Yes ◯ No

Demographics

Please provide your age	_____
Please provide the length of time you have been a nurse (years)	_____
Please provide the length of time you have been a NICU nurse (years)	_____
Please provide your highest nursing education level	◯ ADN ◯ BSN ◯ MSN ◯ PhD ◯ Prefer not to answer
Where is the NICU where you work as a registered nurse or nurse practitioner located?	_____ (Please provide City and State)
What level is the NICU in which you currently practice?	◯ I ◯ II ◯ III ◯ IV

Clinical Indicators

What are the clinical indicators in which an infant would receive a PRBC transfusion in the NICU your current practice?

- ☐ Apnea/Bradycardia
- ☐ Low hematocrit
- ☐ Abnormal vital signs
- ☐ Hypotension
- ☐ Hypovolemia
- ☐ Other

(Please check all that apply)

Please provide other clinical indications for PRBC transfusion in your NICU

_____

Please check all access sites that a PRBC can be infused per your NICU protocol:

- ☐ Peripheral IV
- ☐ PICC
- ☐ Umbilical arterial catheter
- ☐ Umbilical venous catheter
- ☐ Broviac/Central venous line
- ☐ Do not know

(Select all that apply)

Are PRBC transfusions allowed to warm prior or during transfusion?

- ○ Yes
- ○ No
- ○ Do not know

If yes, how is warming accomplished?

_____

Are blood warmers used in the NICU where you work for

s routine PRBC transfusions? (other than exchange transfusions)

- ○ Ye
- ○ No
- ○ Do not know

If yes, what is the brand of blood warmer?

_____

Feeding and PRBC transfusions

Do you have a policy or procedure to determine how infants are fed before, during and after PRBC transfusions?	◯ Yes ◯ No ◯ Do not know
Are feeding protocols altered or changed when administering PRBC transfusions to an infant in your NICU?	◯ Yes ◯ No ◯ Do not know
Are infants NPO during any time of a PRBC transfusion?	☐ Before PRBC transfusion ☐ During PRBC transfusion ☐ After PRBC transfusion ☐ Do not know (Select all that apply)
How many hours will the infant be NPO BEFORE the PRBC transfusion?	_____
How many hours will the infant be NPO DURING the PRBC transfusion?	_____
How many hours will the infant be NPO AFTER the PRBC transfusion?	_____
If not made NPO, are feeding amounts altered before, during, or after PRBC transfusions?	☐ Before the PRBC transfusion ☐ During the PRBC transfusion ☐ After the PRBC transfusion ☐ Do not know (Select all that apply)
Please indicate how feedings are altered BEFORE the PRBC transfusion	_____
Please indicate how feedings are altered DURING the PRBC transfusion	_____
Please indicate how feedings are altered AFTER the PRBC transfusion	_____
Are feeding practices before, during and after a PRBC transfusion determined by the ordering physician, practitioner, or physician's assistant?	◯ Yes ◯ No ◯ Do not know
Do the clinicians in your unit use different feeding practices around administering PRBC transfusions?	◯ Yes ◯ No ◯ Do not know

Infant Assessment

Do you have a policy or procedure on frequency of vital signs in your NICU on infants NOT receiving PRBC transfusion?	○ Yes ○ No ○ Do not know
How often do nurses record a complete set of vital signs (HR, RR, O2 sat, BP, temp) on 23-27 weeks gestational age infants NOT receiving a PRBC transfusion in your NICU?	☐ every 1-2 hours ☐ every 2-4 hours ☐ every 4-6 hours ☐ every 6-8 hours ☐ every 8-10 hours ☐ every 10-12 hours (Select all that apply)
How often do nurses record a complete set of vital signs (HR, RR, O2 sat, BP, temp) on 28-32 weeks gestational age infants NOT receiving a PRBC transfusion in your NICU?	☐ every 1-2 hours ☐ every 2-4 hours ☐ every 4-6 hours ☐ every 6-8 hours ☐ every 8-10 hours ☐ every 10-12 hours (Select all that apply)
Do you have a policy or procedure on frequency of vital signs DURING a PRBC transfusion in your NICU?	○ Yes ○ No ○ Do not know
Please explain the policy and procedure on frequency of vital signs DURING a PRBC transfusion in your unit	_____
How are infants assessed physiologically DURING a PRBC transfusion in your NICU?	☐ Body temperature ☐ HR ☐ RR ☐ BP ☐ O2 ☐ Visualize the PRBC infusion site (Select all that apply)

Body temperature? How often?
HR? How often?
RR? How often?
BP? How often?
O2 saturation? How often?
visualize the PRBC infusion site? How often?

What other information would you like to share about PRBC transfusions given to preterm infants in your NICU? _____

What is your return email address? (This information will ONLY be used for the gift card drawing for participation if you wish to participate in a chance of winning weekly gift card) _____