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## **Analysis of Growth and Prevalence of Malnutrition during Total Parenteral Nutrition Weaning: A Methodological Demonstration**

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Analysis of Growth and Prevalence of Malnutrition during Total Parenteral Nutrition Weaning:  
A Methodological Demonstration

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GRAND VALLEY STATE UNIVERSITY

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## Abstract

**Background** Total Parenteral Nutrition (TPN) is a life-saving intervention which provides nutrition to premature infants with immature gut functioning. Though essential for nutrition provision in the first days of life, TPN is not without risk. Therefore, it is important to introduce feedings into the gut and to wean off TPN when able. During this weaning phase, calorie and protein deficits have been observed to occur. Very few studies have investigated TPN weaning periods, and there are no studies on malnutrition associated with the TPN weaning period in premature infants.

**Methods** This study employed a retrospective chart review, with medical records from a Level IV Midwest Neonatal Intensive Care Unit (NICU). Subjects were premature infants born between November 1, 2017 and June 30, 2018, weighing less than 1500 grams at birth, who received TPN for greater than two days during their hospital stay. Z-scores for weight, length, and head circumference were calculated and the change in weight z-score was used to assign malnutrition categories based on recommendations from the proposed methodology. Pearson's Chi-Square for association and Kendall's tau correlation tests were conducted to assign significance between differences and to understand relationships between variables.

**Results** There was a significant positive correlation between TPN wean length and overall malnutrition, indicating that malnutrition incidence increased as TPN wean length increased. Analysis of change in weight z-score indicated a 50% prevalence of any form of malnutrition at two weeks of age. Upon further investigation, there was a significant difference in means of TPN wean length between each form of malnutrition (mild, moderate, and severe).

**Conclusion** The results of this study support the emerging concept that the TPN weaning period is a phase when malnutrition can start to develop in premature infants. This study demonstrates

how the proposed malnutrition criteria can be combined with TPN weaning data to add to an overall picture of growth during the NICU stay. Future research is warranted to confirm these findings with a larger sample and to establish TPN weaning protocol standards.

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## **Definitions and Abbreviations**

*Premature Birth:* Birth that occurs before 37 weeks gestational age.<sup>1</sup>

*LBW:* Low Birth Weight. Infant born with weight below 2500 grams (5 pounds, 8 ounces).<sup>1</sup>

*VLBW:* Very Low Birth Weight. Infant born with weight below 1500 grams (3 pounds, 4 ounces).<sup>1</sup>

*TPN:* Total Parenteral Nutrition. Refers to nutrition provided intravenously.<sup>1</sup>

*EN:* Enteral Nutrition. Refers to nutrition provided directly to the gastric or jejunal region.<sup>1</sup>

*Growth z-score:* Standardized measure that represents the anthropometric value as a number of standard deviations below or above the reference mean or median value.<sup>2</sup>

## Introduction

Evidence over the past three decades points to widespread cumulative nutritional deficits and growth failure occurring within the first weeks of life in premature infants.<sup>3-5</sup> These deficits are more likely to occur during the time period of weaning total parenteral nutrition (TPN) to enteral nutrition.<sup>5,6</sup> Despite this knowledge, limited studies have investigated the TPN weaning period specifically related to malnutrition, and there is a lack of knowledge about prevalence of neonatal malnutrition during this high-risk transition.

When infants are born prematurely (less than 37 weeks gestation age)<sup>1</sup>, they may require total parenteral nutrition (TPN) until their gastrointestinal tract anatomy is developed enough to tolerate feedings.<sup>7-12</sup> During the first few weeks of life, premature infants are at risk for fluid, protein and caloric deficits.<sup>10,13-15</sup> Data suggest that early, aggressive TPN not only provides the macronutrients required to thrive outside the womb, but supports optimal neurodevelopmental outcomes.<sup>13,16-22</sup> There is evidence of a significant link between energy intake and neurodevelopmental outcomes at 18 months gestational age for premature infants born weighing less than 1000 grams.<sup>16</sup> For example, for every gram increase in weight, an infant's score on the Bayley Mental Developmental index (MDI) is increased.<sup>16</sup> The ultimate goal of TPN and enteral feedings in the premature infant is to achieve a postnatal growth velocity that is similar to intrauterine growth in infants with the same gestational age.<sup>18,21,23,24</sup> When this goal is not met and an infant experiences growth failure, there is a well-developed association with long-term neurologic and cognitive impairments.<sup>6,17,18,23,25</sup>

Prior to discharging home, an infant who was receiving TPN in the hospital must be weaned to enteral nutrition. During TPN weaning, calorie and protein goals are not always met, indicating that this may be a time period in the Neonatal Intensive Care Unit (NICU) stay that

places the neonate at increased malnutrition risk.<sup>6</sup> In fact, 80% of very low birthweight premature infants that were included within a study conducted by the National Institutes of Health Neonatal Research Network from 2008-2010 had documented growth failure upon discharge.<sup>6</sup> Additionally, in the year 2013, 50.3% of infants who discharged from hospitals within the Vermont Oxford Network were classified as growth restricted upon their date of discharge.<sup>6</sup> Despite these findings, the effect of TPN weaning duration on the development of neonatal malnutrition is not known.

New guidelines to assess malnutrition in premature infants have been proposed by a group of expert NICU registered dietitian nutritionists and published in the Journal of the Academy of Nutrition and Dietetics (JAND).<sup>25</sup> This new methodology attempts to standardize and define premature and neonatal malnutrition, and relies on quantitative data such as weight for age z-scores, and number of days to regain birthweight.<sup>25</sup> With these diagnostic criteria in place, the risk of developing malnutrition during and after TPN weaning, along with the prevalence of malnutrition during the TPN weaning phase, can now be quantified using a standardized tool. This study will add to the body of knowledge about the increased risk of the TPN weaning period, and results may be used in the development of TPN weaning protocols for optimal growth outcomes and the prevention of malnutrition for premature infants.

### ***Purpose***

This study aims to demonstrate the implementation of a recently proposed methodology for assessing malnutrition in premature infants, and to apply that criteria to infants during the weaning period from TPN to enteral nutrition. The objective is to understand the prevalence of neonatal malnutrition during the TPN weaning period.

### ***Research Questions***

1. What is the prevalence of neonatal malnutrition in infants born prematurely, after hospitalization that includes TPN weaning?
2. What is the relationship between malnutrition z-score and TPN wean length?
3. What is the association between TPN wean length and neonatal malnutrition category?

### ***Significance***

In addition to demonstrating the use of proposed malnutrition diagnosis criteria with premature infants, this study adds an examination of the relationship between attributes of the TPN weaning period and development of malnutrition in very low birthweight infants born prematurely. This work will add to the current knowledge by providing a method of quantifying, and specifying, nutrition risk during the TPN weaning period. Through analysis of secondary data and use of the neonatal malnutrition diagnostic criteria, this study will add to the current literature by determining (1) the prevalence of neonatal malnutrition in premature infants after hospitalization with TPN weaning; (2) the relationship between neonatal malnutrition diagnosis and TPN weaning length; and (3) the association between categories of neonatal malnutrition and TPN weaning length.

## **Review of Literature**

Premature infants often rely on TPN to provide nutrients they otherwise would be receiving in utero. No study to date has defined the optimal gestational age or weight cut off for determining which infants receive TPN; however, neonatal intensive care units have been documented to commonly use less than 30 weeks gestational age and/or less than 1,250 grams birth weight as criteria.<sup>13</sup> Many extend this criteria for TPN initiation to less than 32 weeks gestational age at birth and/or less than 1,500 grams birthweight, although the risks of TPN within these older premature infants are not proven to outweigh the benefits.<sup>9,12</sup>

Despite the multitude of studies available on premature infants receiving TPN, it is unclear which cut-offs should be used to balance the benefits against the known risks of use of TPN in infants.<sup>4,23</sup> Short term risks identified in TPN use include sepsis, line-misplacement, catheter related blood stream infection, and parenteral nutrition-associated liver disease (PNALD).<sup>4,18</sup> TPN-induced amino acid imbalances from cysteine and taurine deficiencies and excessive methionine have been found to lead to hepatic dysfunction.<sup>8</sup> Long term risks for infants on prolonged TPN infusion are still being studied; however, research has found an association between the aluminum contamination of TPN solutions and decreased bone mass of preterm infants during adolescence.<sup>4</sup>

### ***TPN Weaning in the Premature Infant***

TPN weaning occurs early in many practices to limit the use of indwelling catheters and prevent infection risk, with initiation and advancement of enteral feedings often stopped due to high gastric residuals, abdominal distention, blood transfusions, and changes in medical status.<sup>23,26</sup> Any of these interruptions in nutrient provision can be detrimental to the growth of infants during this vulnerable phase of TPN weaning.<sup>6,23,26</sup>

Currently, there are not clear, evidence-based guidelines established for the best practices for TPN weaning for premature infants. Instead, preliminary TPN weaning protocols in published literature have been designed to reduce the risks described above, not specifically to address growth velocity.<sup>4,18,23,27,28</sup> For example, according to the American Society for Parenteral and Enteral Nutrition (ASPEN) Parenteral Nutrition Safety Consensus Recommendations, pediatric patients should receive a gradual taper-down period when weaning TPN to prevent rebound hypoglycemia.<sup>28</sup> Evidence suggests that prolonged or recurrent hypoglycemia has been linked to neurodevelopmental impairment in pediatric patients, including intractable epilepsy, cerebral palsy, mental motor retardation, and visual disturbances.<sup>28</sup> Severe hypoglycemia and wide glycaemic fluctuations in neonates have been associated with neuronal cell death. Furthermore, hypoglycemia in infants is independently associated with mortality.<sup>28</sup>

### ***Lack of Pediatric TPN Weaning Evidence***

Diversity of practice regarding nutrition support contributes greatly to underfeeding in neonates; however, there is a documented lack of evidence-based guidelines for pediatric TPN, which explains the variation in prescribing and weaning.<sup>15,29</sup> Although there are guidelines on estimated nutritive needs while a premature infant is on TPN, there are no standardized guidelines for the weaning period during which TPN and enteral feedings are being used simultaneously.<sup>30,31</sup> This leaves hospitals to derive their own weaning methods.<sup>30,31</sup>

Previous studies have suggested that, by standardizing prescribing practices for TPN and enteral feedings, nutrition provision was improved by increasing caloric and protein intake and promoting weight gain.<sup>10,16,32</sup> A protocol, however, is only useful when it is adhered to. A recent study indicated frequent discrepancies in what physicians intended to prescribe and what was actually provided to preterm infants.<sup>5</sup> These differences were ultimately found to be physicians

deviating from the recommendations of their hospital protocols for initiation and dose of TPN macronutrients.<sup>5</sup> Additionally, the length of the TPN wean period has not been well examined. With previous evidence pointing to the nutrition risk of this time period, the length of time an infant is placed at increased risk should be explored.

### ***Transition to Enteral Feedings***

Enteral feeding has been found to preserve gut integrity, prevent bacterial translocation, and protect the neonate against parenteral nutrition associated liver disease.<sup>30</sup> Therefore, published recommendations encourage the introduction of feedings into the gut as early as anatomically possible, usually by day one or two in small amounts.<sup>6,25,30</sup> These small trophic enteral feedings have demonstrated the ability to stimulate the immature intestinal tract to undergo maturation.<sup>25</sup> Until complete maturation, the immature gut is unable to digest and absorb the needed amounts of nutrients to sustain itself.<sup>25</sup> Thus, TPN is needed until substantial amounts of enteral feedings are tolerated.<sup>28</sup> With regular stimulation of the gut, maturation is estimated to occur within two weeks of the initiation of trophic feedings.<sup>10,25,29-30</sup>

Evidence shows that during this transitional phase in nutrition provision, where TPN is being weaned and enteral feedings are advanced, the premature infant is frequently being underfed.<sup>26,32-34</sup> One particular study was able to define a net deficit of protein at 0.6g/kg/day during the weaning phase, and a maximum intake of 108 kcal/kg/day when compared to a recommended 120 kcal/kg/day goal during the weaning phase.<sup>26</sup> Reasons for this have been attributed to parenteral nutrition being weaned or terminated too early, delayed initiation of enteral feedings, inadequate nutrition prescriptions for TPN, inadequate fortification of breastmilk, and withholding feedings as a reflex to unusual behaviors in hospitalized infants.<sup>32-34</sup>

### ***Assessing Growth in the Premature Infant***

After they are delivered, all infants will lose weight.<sup>35</sup> This postnatal diuresis is expected and demonstrated in both term infants and premature infants.<sup>35</sup> Ideally, newborns will regain their birthweight within two weeks. However, most premature infants will demonstrate poor growth in weight gain, length, and head circumference within the first two weeks of life.<sup>35</sup> Therefore, when assessing the growth status of premature infants, it is imperative to use the correct growth charts to plot weight, length, and head circumference. The 2013 Fenton preterm growth chart or the 2010 Olsen intrauterine growth chart should be exclusively used for infants born at a gestational ages of 36 6/7 weeks and younger.<sup>1,23</sup> Other growth charts do not account for postnatal diuresis, and therefore are not appropriate for use in the premature infant population.<sup>23</sup>

Growth velocity in premature infants has most commonly been assessed with calculations for increases in grams/kilogram/day of weight.<sup>23,25,36</sup> Growth failure had been generally associated with growth velocity rates less than 15 g/kg/day and less than 0.5-1.0 cm increases in both length and head circumference.<sup>1,25</sup> However, the overall goal of 15 g/kg/day does not consider the necessary changes in rate of weight gain as birth gestational age and postnatal age increase.<sup>23,25</sup> Alternatively, change in z-scores, which are standard deviation scores, are currently the preferred method for diagnosing malnutrition.<sup>2,25</sup>

The Z-score expresses the weight, length or head circumference as a number of standard deviations below or above the reference median or mean value.<sup>2,36</sup> Advantages of interpreting z-scores are that they are generalizable to all genders, ages, and racial/ethnic groups.<sup>2</sup> Additionally, trended z-scores are more sensitive to minor, but cumulative, changes in anthropometric values when compared to trended percentiles.<sup>2</sup> When calculated regularly, z-scores allow the

practitioner to analyze whether an infant is maintaining growth or gaining above or below the intrauterine standards.<sup>36</sup>

Additionally, previous research has demonstrated that declining trends of weight-based z-scores are significantly associated with extrauterine growth restriction in premature infants, as a result of undernutrition.<sup>36</sup> This lends support to the idea that using z-scores, specifically the weight based z-scores, may assist with early prediction of malnutrition in premature infants.<sup>36</sup>

### ***Malnutrition in the Premature Infant***

Malnutrition in the premature infant has been investigated; however, there has been considerable variation in terminology and criteria used to define it. In 2012, a journal article published within the Turkish Journal of Pediatrics investigated fetal malnutrition, calling it “morphological change” and using a clinical nutrition status score based on physical parameters alone.<sup>37</sup> A 2012 article published within the Journal of Parenteral and Enteral Nutrition interchangeably used the terms “severe acute malnutrition” and “kwashiorkor” when referring to premature very low birthweight infants.<sup>38</sup> Many published papers have used the terminology “growth failure” when referring to undernutrition.<sup>39</sup> The lack of standardization of terms and methods to describe malnutrition has made it difficult to track prevalence rates, or to determine which methods of diagnosis and monitoring are reliable and consistent.

In September 2018, the Academy of Nutrition and Dietetics (AND) published newly proposed diagnostic criteria to identify malnutrition in the preterm and neonatal populations.<sup>25</sup> The primary indicators for malnutrition include: weight-for-age z-score, weight gain velocity, nutrient intake, days to regain birthweight, linear growth velocity, and decline in length-for-age z-score. Diagnoses are further classified into mild, moderate, and severe malnutrition.<sup>25</sup> By using a weight-for-length z-score change between birth and two weeks of age, the proposed

malnutrition criteria account for both postnatal diuresis and time to regain birthweight. These guidelines were developed by a committee comprised of experienced NICU registered dietitian nutritionists. The committee utilized literature review and group consensus, and used a methodology similar to the consensus statement of the AND and ASPEN on pediatric malnutrition.<sup>25</sup>

Multiple factors can influence the development of malnutrition in premature infants. The risk for premature infants originates within their reduced nutrient stores at birth and inadequate nutrient absorption, and often increases with delayed parenteral and enteral nutrition advancement.<sup>25,36</sup> Malnutrition in the neonatal period should not be taken lightly; in the NICU, undernutrition has been associated with unfavorable clinical outcomes including sepsis, chronic lung disease, and prolonged mechanical ventilation.<sup>34</sup> And the effects of malnutrition are far-reaching; research indicates a clear link between poor growth in premature infants and poor neurocognitive development later in adolescence.<sup>16,36,38,39</sup> All of these factors make it important that malnutrition in premature neonates be studied and understood, so that preventable causes of malnutrition that can be addressed in this vulnerable population.

## **Materials and Methods**

### ***Design***

This study used a retrospective chart review design, with data abstracted from electronic medical records from the time period November 1, 2017- June 30, 2018 in a Level IV Midwest NICU.

### ***Subject Selection***

#### *Inclusion criteria*

Infants with the following ICD 10 codes for premature birth (P07.2-P07.39) and for birthweight of 1500 grams or less (P07.1-P07.16) were included in this study. Subjects must also have received TPN within their hospital stay for at least two continuous days or longer.

#### *Exclusion criteria*

Infants with any of the following ICD 10 code diagnoses during the hospital admission were excluded from the study: P76-P78, digestive system disorders of newborn including short gut syndrome and necrotizing enterocolitis; P 29.0-P29.9, cardiovascular disorders originating in the perinatal period; Q20-Q28, congenital malformations of the circulatory system; Q90-Q91, Trisomy 18 and Trisomy 21; Q05, spina bifida; Q87.1, Prader-Willi syndrome, and G80.1-80.9, cerebral palsy. These diagnoses have been found to have associated feeding intolerances and anecdotally may take longer to wean from TPN or may have disease-associated altered growth patterns.<sup>11-13</sup>

### ***Data Description***

The following data elements were requested from the electronic medical records of the selected premature infants for this study: birth gestational age, birth date, date of admission, daily weight (in grams), weekly length (in centimeters), weekly head circumference (in centimeters), date of TPN administration, date of enteral breastmilk administration, and diagnoses from initial birth encounter.

### ***Sample Size Determination***

After data abstraction by a biostatistician, based on inclusion and exclusion diagnostic criteria, there were 65 case records returned of infants who received TPN for at least two days during the study period. Of these, 26 infants were born with very low birthweight. One of these infants expired and was removed from the study, and an additional infant was not able to be successfully weaned from TPN and was removed from the study.

### ***Calculated Variables***

The full TPN time period included the initiation of TPN to the last day of solely provided TPN. The TPN weaning period was defined as the number of days from the day peak volume of TPN was decreased until full enteral feedings were in place and TPN was stopped. The full enteral time period was defined as the first day that TPN was not written for and enteral feedings were the sole source of nutrition.

Growth velocity using z-scores were assessed on each of three measures (weight, length, and head circumference), then averaged over the full TPN period, the TPN weaning period, and the full enteral nutrition period. Additionally, the z-score change within these three time periods was also calculated.

Z-scores were calculated from weight, length, and frontal occipital circumference using PediTools, which compares growth measures with growth standards from the Fenton 2013 Growth Charts.<sup>40</sup> This website tool allows the user to utilize the Fenton, Olsen, and WHO growth charts for interpretation of weights, lengths, and head circumferences.<sup>40</sup>

For each infant included in the sample, a malnutrition z-score was calculated according to the proposed criteria from the Academy of Nutrition and Dietetics, by calculating the change in weight-for-age z-score from birth to 2 weeks of life.<sup>25</sup>

From this malnutrition z-score, categories of malnutrition are as follows<sup>25</sup>:

- Z-score of  $-0.8$ - $1.2$  standard deviations denotes mild malnutrition.
- Z-score of  $>-1.2$ - $2$  standard deviations denotes moderate malnutrition.
- Z-score of  $>-2$  standard denotes severe malnutrition.

### ***Data Management***

Data were transmitted to the researcher's password protected computer and kept in a locked office on-site at the hospital where the medical records originated. These data will be stored on the password-protected computer for six years following completion of the study.

### ***Statistical Analyses***

As part of data exploration, we tested the assumptions of skewness and kurtosis using Kolmogorov-Smirnov tests.<sup>41</sup> Results revealed violations of these assumptions of normality for TPN wean length. Based on this finding, nonparametric tests Pearson's chi-square and Kendall's tau for correlation were chosen for the data analyses.<sup>41</sup> Based on correlation coefficient  $r$  effect size power analysis, a power of .90 for  $p$  value of .10, was achieved with a minimum of 24 subjects in the Kendall's tau correlation test.

Following basic descriptive analyses of the research subjects, statistical analyses utilizing SPSS v. 22<sup>42</sup> were performed to answer the research questions. See Table 1 for the research questions matched to variables and statistical tests. Anthropometric z-scores (weight, length and head circumference) were compared across time periods (TPN full-strength, TPN weaning period, and full enteral feeding). The change in z-score was analyzed during these periods. Change in weight z-scores were analyzed for association with length of TPN weaning period. Finally, malnutrition categories were assigned for infants based on the weight for age z-score criteria proposed by the Academy of Nutrition and Dietetics when the infants are at least 2 weeks of age.<sup>25</sup>

Table 1. Research questions aligned with data variables and statistical analyses performed.

<b>Research Question</b>	<b>Data Variables</b>	<b>Statistical Analyses</b>
1. What is the prevalence of neonatal malnutrition in infants born prematurely, after hospitalization including TPN weaning?	Change in z-score for weight from birth to 2 weeks, (Malnutrition z score)	<ul style="list-style-type: none"> <li>• Percent and n by all malnutrition and by malnutrition category.</li> </ul>
2. What is the relationship between malnutrition z-score and TPN wean length?	Birthweight/age z score; 2 wk/age z score; TPN wean length (days)	<ul style="list-style-type: none"> <li>• Kendall's tau correlation</li> </ul>
3. Is there an association between TPN wean length and neonatal malnutrition category?	Malnutrition category, TPN wean length	<ul style="list-style-type: none"> <li>• Average wean length of each group (no, mild, mod, severe)</li> <li>• Pearson's Chi-square</li> </ul>

## Results

The mean birth gestational age for the infants in this study was 29 weeks with an average birthweight of 1148 grams. The TPN wean lengths ranged from three to 42 days, with a mean average wean length of 8.29 days. Complete results of the descriptive statistics are shown in Table 2.

Table 2. Descriptive statistics of study sample, by measurement type and time period, low-birthweight infants in a Level III NICU Michigan, 2017-18.

Measurement	N	Mean	Standard Deviation
Birthweight (grams)	24	1147.88	270.86
Weight (Average Z-score)			
Full TPN	23	0.34	0.86
Wean	24	0.88	0.69
Full Enteral	23	-1.00	0.76
Linear growth (Average Z-score)			
Full TPN	23	-0.25	0.85
Wean	21	-0.63	0.96
Full Enteral	24	-0.89	0.89
FOC <sup>a</sup> (Average Z-score)			
Full TPN	23	0.36	1.09
Wean	21	-1.26	0.94
Full Enteral	24	-1.12	1.26
Change in Z-score			
Weight	22	-0.64	0.64
Length	23	-0.71	0.77
FOC	23	-0.73	1.27
Gestational Age at Birth (weeks)	24	29.04	3.13
TPN Wean Length (days)	24	8.29	8.08

<sup>a</sup>Frontal occipital circumference

By two weeks of age, 50% of the infants in this study (n=12) met the criteria for any form of malnutrition; 29% (n=7) developed mild malnutrition, 17% (n=4) developed moderate malnutrition, and 4% (n=1) met criteria for severe malnutrition.

### ***Correlation and Chi-Square Analyses***

The Kendall's tau correlation test was used to examine the relationship between length of the TPN wean and the malnutrition z-score (change in z-score from birth to two weeks of age). Results indicated a significant negative correlation,  $\tau = -.408$ ,  $p = .008$ , such that as the length of the TPN weaning period increased, the z-score indicating malnutrition became more negative. This indicates that infants with a longer TPN wean were more likely to meet the malnutrition z-score threshold for a diagnosis of any category of malnutrition.

A Pearson's chi-square test was performed to ascertain the significance of the difference in TPN weaning length by malnutrition category (mild, moderate, or severe). There was a significant association,  $\chi^2(2) = 48.36$ ,  $p = .007$ , between average length of TPN wean and malnutrition category, with longer wean lengths associated with greater severity of malnutrition. The single case of severe malnutrition resulted from a TPN wean of almost double the mean duration of the sample, at 16 days.

## Discussion

This study found that the proposed criteria recently published by the Academy of Nutrition and Dietetics are an easily implemented methodology for assessing growth in preterm infants. Use of this criteria lent additional support to previously published findings that indicate very low birthweight infants on TPN may be at risk for developing growth deficits. The results of this study add to the proposed methodology for establishing a malnutrition diagnosis by specifying the relationship between TPN wean length and the occurrence of neonatal malnutrition. Contributing to the knowledge on this subject, this study found that longer TPN wean lengths are correlated with a diagnosis of malnutrition. Additionally, these results suggest that, once weaning has begun, the longer an infant remains on TPN the greater the degree of malnutrition that may be diagnosed. These findings further endorse the need for standardized nutrition strategies and recommendations to be developed for TPN weaning in this specific population.

In our demonstration using retrospectively collected NICU records, the proposed criteria for neonatal malnutrition were easy to implement with available clinical data. Because clinicians employed in the field of neonatology already have access to the information needed to diagnose premature infants and neonates with malnutrition, employing this methodology for diagnosing malnutrition, in many cases, can be initiated without additional calculations or effort on the practitioner's side. Considering that some electronic medical records automatically calculate the z-scores when displayed on a growth chart, change in weight z-score would be simple and easy to compute when assessing these infants. This method is supported by recent literature; the difference in weight-for-age z-score at birth and two weeks of life has been highlighted by two 2018 studies as a more rational way to analyze growth than assessing the weight z-score alone,

as it depicts growth faltering rather than poor initial weight z-score and trend.<sup>44,45</sup> Additionally, z-scores have been found to have a high sensitivity and specificity at their respective time points, and are statistically significant in predicting growth faltering.<sup>43</sup> Therefore, they are instrumental in the monitoring and development of malnutrition within premature infants, and their use should be encouraged when assessing growth in this specific population.<sup>25</sup>

We found a 50% overall malnutrition rate within our sample, which does not deviate from previous findings. In an article published in 1994, the rate of fetal malnutrition was found to be 54.0%.<sup>46</sup> A 1999 study on fetal malnutrition boasted a malnutrition prevalence rate of 19.6%.<sup>47</sup> Two separate studies in 2008 and 2011 relied on a tool that analyzed the physical signs of malnutrition and reported a 29.97% incidence of overall malnutrition, and a 54.8% of malnutrition for their SGA infants, respectively.<sup>37,48</sup> In 2015, the Von Network released a 50.3% growth failure figure, and most recently, a 2018 study predicting growth failure among very low birthweight infants reported a similar rate of 45.5%.<sup>39</sup> The lack of standardization to interpret growth velocity and determine malnutrition in this population makes comparisons between studies difficult; however, similar incidences of undernutrition have been documented in this population, leading us to believe that the tool developed by the Academy to diagnose malnutrition is sound.

One of the strengths of our study was the ability to derive important information regarding malnutrition from research data, including the identification of a trend occurring within the TPN weaning period. With hospital tools being utilized for anthropometrics, the weights were likely to be precise and reliable. Due to the use of the standardized measure of z-scores for diagnosis, different criteria for gender were not necessary for the malnutrition diagnosis.

Limitations of this study include the possibility of data entry error in the medical records and missing data. Specifically, weights and gestational age were unavailable from some potential participants and led to several potential candidates being ineligible for the study. The small sample size left for analysis limited the statistical power of the results and required the use of nonparametric tests. Because this study was focused on TPN weaning specifically at a time period where growth and nutrition is compromised, the findings may not be generalized to infants solely on enteral nutrition. Due to the specificity of inclusion criteria and specific neonatal malnutrition criteria, the findings from this study will benefit prematurely born neonates, and may not be generalizable to term infants, older children and adults. Finally, the association of TPN wean length and malnutrition risk was revealed during this study; however, due to the retrospective design of this study, cause-and-effect relationships cannot be established.

Future research is warranted on standardized methods for TPN weaning for premature infants, to reduce malnutrition in this vulnerable population. Current strategies include volume-based weaning and percentage-based weaning. Volume-based suggestions exist from researchers in the neonatal field such as Embleton and Simmer<sup>11</sup>, who recommend decreasing parenteral nutrition as enteral volumes increase, with special attention to total volume staying in the 150-175 mL/kg/day range. They recommend ceasing TPN once enteral feedings are providing 125-150 ml/kg/day. However, they do not recommended specific target ranges for macronutrients. Percentage-based weaning suggestions for TPN weaning in children recommend weaning by a small percentage every week, but do not offer further guidance, such as the duration of the wean for neonates.<sup>8</sup>

The findings of this study may be useful for NICUs that are developing their own TPN weaning practices, and may deter practitioners from excessive prolongation of TPN weaning in

this population. If larger studies continue to prove that TPN wean duration is associated with diagnoses of neonatal malnutrition, this may encourage more aggressive initiation of enteral nutrition, and quicker TPN weaning. With more attentiveness to growth parameters during this time frame, and established TPN weaning protocols in institutions, malnutrition in premature infants may eventually be reduced.

### **Conclusion**

In response to previously published evidence suggesting that the TPN weaning period may place infants at risk for inadequate nutrition provision, our study provides preliminary evidence that the TPN weaning period may also be associated with neonatal malnutrition. We have demonstrated how to apply the diagnostic criteria proposed for neonatal malnutrition, with the addition of data on the TPN weaning duration, to complete a picture of growth using available clinical data for premature infants receiving nutrition support in the first two weeks of life.

Approximately fifty percent of the infants in this study met the criteria for a neonatal malnutrition diagnosis. Additionally, we found a significant positive association between the length of the TPN weaning period and malnutrition diagnosis. We recommend that future studies investigate the composition of the TPN being used and the necessity behind prolonged TPN weans. Without clear, evidence-based guidelines for TPN weaning in premature infants, this period is likely to continue to be a critical area for adequate nutrition provision and a risk for the development of malnutrition.

Considering that malnutrition has been associated with unfavorable clinical outcomes including sepsis, chronic lung disease, prolonged mechanical ventilation, and poor neurodevelopmental outcomes, early diagnosis of malnutrition is crucial.<sup>34, 51</sup> With the proposed

guidelines for diagnosing and staging malnutrition in the neonatal population, practitioners can correct malnutrition as it is developing, and ensure that their protocols for TPN weaning, including duration, promote adequate nutrition for optimal growth outcomes.

## Appendix



DATE: May 10, 2018

TO: Elizabeth MacQuillan  
FROM: HRRC (Human Research Review Committee)  
STUDY TITLE: Analysis of Protein Adequacy During Total Parenteral Nutrition Weaning in Premature Infants and the Subsequent Effects on Growth.  
REFERENCE #: 18-271-H  
SUBMISSION TYPE: HRRC Initial Submission

ACTION: Agreement to rely on an external IRB  
EXTERNAL IRB: Spectrum Health IRB  
EFFECTIVE DATE: May 10, 2018  
REVIEW TYPE: Confirmation of reliance

Thank you for your submission of materials for this research study. This letter confirms that the GVSU HRRC has agreed to rely upon the organization identified above for continuing oversight of this research. All study modifications, requests for continuing review, and the study completion notification should be sent to the reviewing (external) IRB listed above. However, records pertaining to this protocol must remain accessible to the GVSU HRRC and the GVSU Office of Research Compliance and Integrity (ORCI) for compliance monitoring. Please note that the GVSU HRRC reserves the right to withdraw its acceptance to rely on the reviewing IRB at any time.

It is your responsibility to:

1. Comply with all requirements, policies and procedures of the reviewing IRB and the GVSU HRRC.
2. Inform the GVSU HRRC of any actions by the external IRB affecting their approval to conduct the study, including suspension or termination of approval.
3. Submit a Change in Approved Protocol Form to the GVSU HRRC if the study is modified in such a way that additional institutional approvals are required (e.g., radiation safety, biosafety).
4. Provide a copy of any modification/amendment, continuing review, and/or unanticipated problem/serious adverse event notification approved by the external IRB. If GVSU personnel are added to the protocol after the initial approval, a Conflict of Interest Disclosure and Certification Form must be submitted and approved for each new participant prior to them beginning the research.
5. Any research-related problem or event resulting in a fatality or hospitalization requires immediate notification to the ORCI ([rci@gvsu.edu](mailto:rci@gvsu.edu) or 616-331-3197) **and** the Research Integrity Officer, Dr. Jeffrey Potteiger at (616) 331-7207. See *HRRC policy 1020, Unanticipated problems and adverse events*.
6. Submit the GVSU HRRC Closure Form at the completion of the research.

Studies covered under reliance agreements are eligible for audits.

If you have any questions, please contact the Office of Research Compliance and Integrity at (616) 331-3197 or [rci@gvsu.edu](mailto:rci@gvsu.edu). The office observes all university holidays. Please include your study title and reference number in all correspondence with our office.



APPROVAL OF RESEARCH

May 4, 2018

Lauren W Kane, BS RD  
Spectrum Health Helen DeVos Childrens  
100 Michigan St. NE  
Grand Rapids, MI 49503

TYPE OF REVIEW: **Initial, Non-Committee Review**

IRB#: **2018-084** (*please reference this number in all correspondence with the IRB*)

PROTOCOL NAME: **Analysis of Protein Adequacy During Total Parenteral Nutrition Weaning in Premature Infants and the Subsequent Effects on Growth.**

SPONSOR: **Investigator**

Dear Ms. Kane:

The above referenced protocol and associated materials were reviewed and approved by the IRB via expedited review on May 3, 2018 under category 5 as described in [45 CFR 46.110](#).

The approval period for this research is from **May 3, 2018 to May 2, 2019**.

The IRB reviewed the following documents related to the approval of the research proposal:

- Initial application signed 03/26/18
- Intake Form signed 02/17/18
- Study protocol dated 12/2017
- Data collection sheet undated

The IRB made the following determinations:

1. **WAIVER OF CONSENT/HIPAA AUTHORIZATION:** A waiver of consent has been approved per 45 CFR 46.116(d) and a waiver of HIPAA authorization has been approved per 45 CFR 164.512(i)(2)(ii).
2. **RESEARCH INVOLVING CHILDREN:** The inclusion of children has been approved per 45 CFR 46.404 / 21 CFR 50.51.
3. **WAIVER OF PARENTAL PERMISSION:** A waiver of parental permission has been approved per 45 CFR 46.116(d).
4. **WAIVER OF ASSENT:** A waiver of assent has been approved per 45 CFR 46.116(d) / 21 CFR 50.55(d).

5. **RESEARCH INVOLVING NEONATES OF UNCERTAIN VIABILITY:** The inclusion of neonates of uncertain viability has been approved per 45 CFR 46.205.

Any changes made to the study following this approval, including informed consent changes, require submission in writing to the IRB and approval by the committee. Changes may not be implemented until approved by the IRB except when necessary to eliminate apparent immediate hazards to the subject. Approval of your research means you are responsible for complying with all applicable policies and procedures of the FDA, OHRP, HIPAA, Spectrum Health, and the Spectrum Health IRB. Also, please be advised that unanticipated problems involving risk to subjects or others must be *promptly* reported to the IRB. You may reference the [Investigator Manual](#) for guidance on expectations of the IRB after approval.

Please be advised, this approval letter is limited to IRB review. It is your responsibility to ensure all necessary institutional permissions are obtained prior to beginning this research. This includes, but is not limited to, ensuring all contracts have been executed, any necessary Data Use Agreements and Material Transfer Agreements have been signed, documentation of support from the Department Chief has been obtained, and any other outstanding items are completed (i.e. CMS device coverage approval letters, material shipment arrangements, etc.).

The IRB requires submission of the Continuing Review Progress Report or Study Completion Notification to the committee prior to the study expiration date. It is recommended you submit this xform 4-6 weeks prior to the expiration date to allow time for processing. Your study approval expires on **May 2, 2019 at 11:59pm** and cannot continue until re-approved by the Spectrum Health IRB. If your study has been completed, terminated, or if you do not wish to continue, please submit the Study Completion Notification before the expiration date.

If you have any questions please contact the Spectrum Health IRB office at 616-486-2031, email [irbassist@spectrumhealth.org](mailto:irbassist@spectrumhealth.org), or visit us on the web at [www.spectrumhealth.org](http://www.spectrumhealth.org).

Sincerely,



Jeffrey Jones MD  
Chair, Spectrum Health IRB

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