Standardized Parenteral Nutrition in the Very Low Birth Weight Infant: A Systematic Literature Review

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Abstract

Nutrition of the premature infant has been gaining importance as evidence emerges that early support in the critical period plays an important role in the long-term health and neurodevelopment of very low birth weight neonates (VLBW). Traditionally, the components of total parenteral nutrition (TPN) were prescribed individually, but more recently, standardized formulations have been introduced which may result in cost savings without affecting overall nutrition and growth. This systematic literature review comprehensively synthesized the existing evidence to date to determine if standardized TPN is an evidenced-based, cost-effective means to deliver early nutrition to VLBW infants.
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Neonates delivered at less than 30 weeks gestation are born at a time of rapid brain and body growth. Abrupt cessation of the only source of nutrients for the fetus, the placenta, makes the premature infant vulnerable to nutritional deficiencies unless enteral or parenteral nutrition is established quickly after delivery (Simmer, Rakshasbhuvankar, & Deshpande, 2013). Compared to intrauterine growth profile, infants of very low birth weight (VLBW; less than 1500 grams at birth) experience postnatal growth failure that extends even past hospital discharge from the neonatal intensive care unit (NICU). The National Institute of Child and Human Development Neonatal Research Network indicates that 16% of extremely low birth weight infants are small for gestational age at birth, but by 36 weeks corrected age, 89% have growth failure as described by weight less than the 10th percentile on the growth chart. Follow up at 18 to 22 months corrected age shows that 40% still have weights, length and head circumference less than the 10th percentile (Dusick, Poindexter, Ehrenkranz, & Lemons, 2006). Early nutritional support in the early critical period plays an important role in the long-term health and neurodevelopment of VLBW infants (Ziegler, 2009). Suboptimal growth is common in very low birth weight infants, and postnatal growth failure is now recognized as a potentially reversible risk (Dusick et al., 2006). In very early preterm infants, the risks of early enteral feedings are extremely high and feedings are often delayed for several days or weeks and then established slowly (Dusick et al., 2006). This occurs in order to help prevent necrotizing enterocolitis (NEC), an infection with a
high mortality rate in preterm infants. One of the Healthy People 2020 objectives is to reduce the rate of neonatal and post-natal deaths with a target of a 10 percent improvement under the MICH (Maternal, Infant, and Child Health) 1.4 and 1.5 objectives (Healthy People, 2015). Early, adequate parenteral nutrition that can support an infant while enteral feedings are slowly established may be a part of reducing the rate of neonatal deaths due to NEC or other diseases.

Background

Parenteral nutrition remains the sole means of providing hydration, calories and nutrients to VLBW infants in the first few days and weeks after delivery. Many studies have supported the use of early TPN in neonates, starting immediately after birth. Ehrenkranz et al. (2006) found that greater growth velocity exerts a significant positive effect on neurodevelopmental and growth outcomes at 18-22 months corrected age. However, controversy still exists as to the optimal composition of TPN. Inadequate or inconsistent nutritional strategies may be one barrier to delivering effective parenteral nutrition in the VLBW infants (Morgan et al, 2011). Time, cost, and effectiveness of parenteral nutrition all must be considered when establishing guidelines and protocols for VLBW infants.

Clinical Question/Statement

The objective for this project was to complete a systematic review of the literature to determine if standardized TPN solutions provide adequate growth while maintaining metabolic stability in the first few weeks after birth to VLBW infants. Is standardized parenteral nutrition a safe and effective means to deliver total parenteral nutrition to very low birth weight infants during their first days to weeks after birth? Morgan, Herwitker, Badhawi, Hart, Tan, Mayes, Newland & Turner (2011) reported that the prescription and formulation of neonatal parenteral nutrition is critical to achieving optimal protein and calorie intake but has received little
scientific evaluation. The hypothesis is that postnatal growth of premature infants can be improved or maintained with a standardized parenteral nutrition.

Justification of Scholarly Project

This project was sparked by the idea that each day, a practitioner may spend a considerable amount of time individualizing each patient’s TPN, and many of the decisions about the additives seemed to be subjective to the ordering practitioner. Was there a better, evidence-based approach to provide early and continued standardized TPN to very low birth weight infants in a safe and effective manner? Beecroft, Martin, and Puntis (1999) discovered that 82% of individualized prescriptions deviated with respect to one or more nutrients from the regimen recommended by the computer program. However, only 44% of abnormal biochemical results prompted a change in prescription (Beecroft, Martin, & Puntis, 1999). Therefore, most deviations were not based on any data from the patient but at the discretion of the provider. Standardized TPN formulations are easy and safe to implement to avoid errors and may be cost effective (Bolisetty, Osborn, Sinn & Lui, 2014). Standardized TPN formulations became popular and are beginning to be implemented in NICUs all over the world since 2010 (Bolisetty, Osborn, Sinn & Lui, 2014). The earliest study dates back to 1989 when a pharmacist assigned to a NICU at Ohio State University Hospitals simplified the process of ordering and compounding neonatal TPN solutions (Bolisetty, Osborn, Sinn & Lui, 2014). Hartwig and Gardner (1989) discovered 26 years ago that standardizing TPN solution yielded time and cost savings while decreasing the risk of error and enabling neonates to receive adequate calories from a standard solution. Few studies have looked at the growth difference between using standardized TPN and even fewer have looked at the potential for cost savings. Hospital pharmacies have the potential to save thousands of dollars using a standardized formulation (Hartwig and Gardner, 1989). Advanced
nurse practitioners, physicians and dieticians who order TPN may save time by using a standardized formulation rather than calculating and ordering each individual component.

Conceptual Framework

The Barker theory provides an interesting framework for this study. Barker (2012) reports that the growth of every human fetus is constrained by the limited capacity of the mother and placenta to deliver nutrients to it. In the case of a preterm infant, the capacity for growth is limited by nutrition provided intravenously and enterally as the placenta is no longer functioning at all. Adverse influences can permanently change body structure and function: a phenomenon known as “programming” during development. During development, there are critical periods during which a system or organ has to mature. These periods are brief and occur at different times for different systems, most occurring before 40 weeks post conception age. Much of human development is completed during the first 1000 days after conception (Barker, 2012). When an infant is challenged and does not have sufficient resources to perfect every aspect of the body, a hierarchy of priorities is developed. Brain growth is at the top of this hierarchy. Brain growth is defined as the change in head circumference for the purpose of this study. If the growth of a fetus falters because of malnutrition, such as being born prematurely and losing the placenta as the source of nutrients, it has the ability to return to its growth trajectory by accelerated growth. Growth is defined as the change in weight and length of each infant for the purpose of this study. During this time, the fetus or newborn must be supplied with energy to allocate for catch-up growth.

Assumptions

Very preterm infants have a gut that is too immature to digest milk right after they are born to meet their nutritional requirements (Morgan et al., 2011). One assumption is that nearly
all preterm infants less than 29 weeks gestation and/or less than 1500 grams require parenteral nutrition for a period of time that depends on gestational birthweight and other morbidities (Morgan et al., 2011). Preterm infants born at less than 29 weeks gestation also have the highest incidence of early and late growth failure and long term neurocognitive disability (Morgan et al., 2011). Effective parenteral nutrition delivery is essential to help avoid major early nutritional deficits in these infants (Morgan et al., 2011).

Hypothesis

The first hypothesis is that the standardized parenteral nutrition given to neonates in the first several day to weeks after birth will provide sufficient nutrients for adequate growth and minimize growth failure in the first two weeks. Another working hypothesis is that providing a standardized formulation will not negatively alter fluid and electrolyte balances. A third hypothesis is there will be a cost savings to hospitals through the use of a standardized solution.

Definition of Terms

Several key concepts must be defined for the purpose of this study. Very low birth weight infants (VLBW) are born with a weight of less than 1500 grams. Growth is defined as the change in grams in weight between two periods in time and the change in centimeters in length and head circumference. Standardized TPN is defined as intravenous nutrition that is either commercially made or batched by the local pharmacy. The composition of the standardized formulation is always the same within the institution. This standard solution is pre-mixed in the pharmacy or bought commercially and often resides in a locked pharmacy cart directly in the NICU until it is needed. Individualized or custom TPN is defined as solution designed daily on a computer program or hand written by the practitioner for each individual patient.
Postnatal growth has been studied extensively in the literature. Fenton & Kim (2013) report the ideal growth pattern of preterm infants remains undefined. The current charts provided in the literature are growth references, and not growth standards. The closest information about growth standards are based on intra-uterine fetal growth, which from 25-30 weeks is 15-20 grams per kilogram per day, therefore adequate post-natal growth for VLBW infants would be 10-15 grams per kilogram per day on average (Fenton & Kim, 2013). Metabolic stability can be defined as a serum sodium level of between 130mmol/l and 150mmol/l, as well as a potassium level less than 6.5mmol/l according to Iacobelli, Bonsante, Vintejoux, & Gouyon (2010).

Chapter II

Review of the related literature

Very-low-birth-weight (VLBW) infants are born at a time of otherwise rapid intrauterine brain and body growth. Rapid establishment of postnatal nutrition is essential to provide continued support of growth. Lucas, Morley, & Cole (1998) reported that animal and human studies have shown that periods of under nutrition may result in irreversible deficits in brain growth. Lucas, Morley, & Cole (1998) also reported the early weeks of life are a critical period for neurodevelopment in VLBW infants. A literature review revealed many studies support the use of early, aggressive TPN in VLBW infants (Riskin, Shiff, & Shamir, 2006). Ibrahim et al. (2004) showed that aggressive intake of amino acids and intralipids can be tolerated immediately after birth by VLBW infants. Several studies indicate that sick, premature infants tolerate the early administration of amino acids (Riskin, Shiff, & Shamir, 2006). Also, early TPN usage significantly increased positive nitrogen balance and caloric intake, without increasing the risk of metabolic acidosis in sick premature infants (Adamkin & Radmacher, 2014). Heimler, Bamberger, & Sasidharan (2010) reported early administration of amino acid
improved preterm infant weight with less numbers of infants below the tenth percentile in the growth curve, although there was a slightly higher incidence of bronchopulmonary dysplasia.

Summary

Although the data supports the use of early TPN in VLBW infants, there may be some controversy as to the type of TPN formulation to use during the first few weeks after birth when enteral feedings are not yet fully established. Several retrospective, observational studies have been conducted around the world to look differences in TPN usage during this time (Embleton & Simmer, 204). A few retrospective studies have shown there is no clinical advantage of improved biochemical control with individualized TPN regimes (Yeung, Smyth, Maheshwari & Shah, 2003). Lenclen et al. (2006) found that standardized TPN solutions were superior in terms of higher intakes of glucose and amino acids. The main weakness and gap in the literature is the small sample sizes of most of the studies and the lack of randomized, controlled trials (RTC) that have been conducted.

Chapter III

Methodology Design

The project design of this study was to complete a thorough systematic literature review of all relevant data related to standardized parenteral nutrition in very low birth weight infants. Using the Matrix Method (Garrard, 2014) as a guide, a plan to manage a search of the literature was established. First, key words were determined in order to provide consistency when searching many different databases. The controlled vocabulary terms used in MEDLINE/PubMed (also called MeSH) were standardized parenteral nutrition and neonate. Second, inclusion criteria for the sample of this literature review were identified and included the population of very low birth weight infants (birthweight < 1500 grams) and those who had
received a standardized parenteral nutrition for any length of time. The types of studies included were randomized controlled trials, retrospective and observation comparative studies. Systematic literature reviews, consensus statements, retrospective chart reviews, prospective reviews and protocols were all included in the search in order to be completely exhaustive. Other key words that were included were: *very low birth weight infant, preterm infant, and standardised.*

Inclusion for outcome measures included growth, biometric measures and/or cost analysis. Exclusion criteria included adult and pediatric subjects, and studies involving a standardized feeding protocol (including both parenteral and enteral feeding changes). Languages other than English that were unable to obtain translation were also excluded.

Project setting

The setting of this project included accessing multiple databases, including PubMed, ProQuest Allied Health Source, Cochrane, and MEDLINE. In addition to individual databases, areas of synthesized research studies were explored. Review articles, meta-analysis, practice guidelines and the Cochrane Library were examined as tertiary sources of information for this study. The time frame of publications included in this project ranged from 1985 to present.

Internal Review Board

The protection of human subjects is documented in each article and reviewed by the individual institution’s internal review board (IRB). This systematic literature review study did not require a separate IRB approval as each study completed this separately.

Time frame

Data collection was completed using the named databases searching for scholarly publications on June 20, 2015 and reviewed again on July 10, 2015. Data analysis commenced by using the key words *standardized parenteral nutrition* and *neonate* or *very low birth weight*
*infant* in a PubMed search, Cochrane review and ProQuest database. This search revealed 705 results. The abstracts were reviewed to determine the relevance and inclusion for this literature review. Articles were excluded for pediatric population, including enteral feedings or other variables in the protocol, duplicates or using infants with a birthweight >1500 grams. Of the 40 that passed abstract screen results, nine met the inclusion criteria. Two other articles were cross-referenced from the reference list in other articles, meeting the inclusion criteria, for a total of 11 articles reviewed. Data analysis for each article was completed and the evidence graded using the Strength of Recommendation Taxonomy (SORT) method. Levels of evidence from one to three for individual studies are defined. The SORT scale addresses quality, quantity and consistency of evidence of the individual studies or bodies of evidence (Ebell, Siwek, Weiss, Woolf, Susman, Ewigman, & Bowman, 2004). An A-level recommendation is based on consistent and good-quality patient-oriented outcomes that measure changes in morbidity or mortality; a B-level recommendation is based on inconsistent or limited-quality patient-orientated evidence; and a C-level recommendation is based on consensus, usual practice, opinion, disease-oriented evidence or case studies (Ebell et al., 2004).

**Limitations of design**

A limitation of this study includes the possibility of not including some articles that are in different languages other than English or new articles may be published since this paper was written. Another potential limitation is the population studied excluded some neonates that require parenteral nutrition as well (>1500 grams), although these infants tend to have a better growth trajectory during their NICU stay and better neurodevelopmental outcomes compared with VLBW infants (Ehrendranz et al., 2006). These limitations or barriers were addressed by
Chapter IV

Results

Randomized Controlled Study

Morgan, McGowan, Herwitker, Hart & Turner (2014) conducted the only randomized controlled study in this systematic literature review. Two groups of very preterm infants (birthweight of <1200 grams) were randomized to a group receiving a standardized, concentrated with added macronutrients parenteral nutrition (SCAMP) \((n=74)\) or a control group receiving the standardized, neonatal parenteral nutrition formulation in current practice \((n=76)\). All infants in both groups received the same clinical standard of care and followed the same protocols for fluid management and biochemical monitoring. The primary outcome analysis compared the change in head circumference at 28 days between the two groups. Infants were recruited over a 30 month time frame and randomized right after consent obtained. The article reports a statistically significant difference in head circumference between the two groups after 28 days postnatal age, reporting a greater change in head growth in the SCAMP group (Morgan et al., 2014). The study reports no statistical differences in mortality or major preterm complications were identified. There was a trend towards more major cranial ultrasound scan abnormalities in the SCAMP group (grade 3/4 intraventricular hemorrhage and periventricular hemorrhage) \((n=11\) in SCAMP group and \(n= 5\) in the control group). The study did report higher protein and calorie intakes over the 28 day period in the SCAMP group compared with the control. The SCAMP group was able to obtain closer to the recommended 3.5 grams per kilogram per day of protein (2.8-3.6 per day) compared to the control group (2.4-3.0 per day). Based on the SORT algorithm for determining
the level of evidence for an individual study, the Morgan et al. (2014) is a Level of Evidence One (See Table 1 for details).

Review articles

Four review articles discussed the current trends and practices of parenteral nutrition in very low birth weight infants in this systematic literature review. Embleton and Simmer (2014) reported in their review, standardized parenteral nutrition has advantages over individualized parenteral nutrition including better provision of nutrients, less prescription and administration errors, decreased risk of infection and cost savings. The trend of several studies reviewed tends to be the idea of providing the amino acid requirements in a relatively small volume, assuring that nutrition is not compromised when fluids are restricted in VLBW infants. Adamkin and Radmacher (2014) report that standardized TPN formulations are gradually being accepted in many neonatal intensive care units in the United States and abroad. Advantages of standardized solutions include promotion of safer administration and consistent adherence to guideline-based protocols. Standardized TPN increases the timeliness of administration because the pre-mixed solutions can be stored in the NICU and started as soon as orders are received (Adamkin & Radmacher, 2014).

A review by Riskin, Shiff & Shamir (2006) looked at the advantages and disadvantages of both individualized and standardized TPN in infants < 1500 grams. The main advantage of individualized TPN was it provided the most precise biochemical control because the prescription can be changed on a daily basis, reflecting the patient’s most recent laboratory test results (Riskin, Shiff & Shamir, 2006). The main advantage for standardized TPN provided ready availability as ward stock, enabling early initiation of parenteral nutrition. Standardized TPN could reduce pharmacy and practitioner workload and costs, as well as increase safety
(Riskin, Shiff & Shamir, 2006). Riskin, Shiff & Shamir (2006) offered the possibility of using a combination of standardized TPN and individualized solutions based on the severity of illness of the neonate. Riskin, Shiff & Shamir (2006) also suggested gathering data from local experts to determine the best possible formulations for standardized TPN. This study was set in Israel, where the use of standardized TPN may be very different than in the United States.

The final article by Kochevar, Guenter, Holcombe, Malone, & Mirtallo (2007) reviewed the current literature associated with standardized TPN solutions and provided some recommendations. This article was not included in the overall body of evidence for this project but worth mentioning in the paper, as the Task Force reviewing the literature did not set a patient age criteria. The statement is based on all ages of patients from infants to adults. The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an interdisciplinary organization whose members are involved in the provision of clinical nutrition therapies, including parenteral and enteral nutrition. A.S.P.E.N. supports clinical practice, research and education. One of the interesting recommendations from this paper states than when an organization implements standardized TPN formulations, a mechanism should be established to provide or make available customized TPN for individuals who have complex requirements (Kochevar et al., 2007). Another statement discusses the evidence suggesting advantages in efficiency and economy with the use of standardized TPN formulations compared with individualized formulations in select populations.

**Retrospective, observational studies**

Five retrospective articles were identified in the cohort discussing standardized TPN. Doublet, Vialet, Nicaise, Loundou, Martin & Michel (2013) strictly looked to determine if the TPN goals for the neonate were achieved better with a standardized formulation or
individualized prescription. The authors compared two one-year periods, before and after a move from individualized to standardized formulations. Daily goals for glucose, lipids and amino acids are defined in a written policy in the unit where the study was conducted. During the standardized TPN period, seven formulations were available, and the practitioner chose the standardized formulation best suited for that neonate that day. More than 3500 prescriptions were included (n=1474 individualized and n=1740 for the standardized group). The data were analyzed using a generalized estimating equation and the group effect was tested via the Wald Chi test, with values of $p<0.05$ considered statistically significant. There was no statistical difference in the demographic data of the two groups. The goals were better achieved in the standardized group (44%) than in the individualized group (9%), a statistically significant difference. The differences between the two groups were significant for each nutrient when looked at separately as well on days 7 and 14 for glucose, amino acids and lipids. The standardized group achieved goals significantly more often than the individualized group ($p<0.001$, Doublet et al., 2013). This study did not identify any growth or cost variables.

Another retrospective study by Smolkin, Diab, Shohat, Jubran, Blazer, Rozen & Makhoul (2010) compared two groups of VLBW infants receiving either individualized or standardized TPN. The three outcome variables were growth parameters, complications and cost. This study was different from the others in the fact the standardized group were infants born between January 1, 2000 and December 31, 2001, compared with the matched, individualized group born between January 1, 2006 and December 31, 2007. In all the other studies, the standardized group was born after the individualized group. During the standardized TPN period, five parenteral pre-set formulations were available containing various glucose and amino acid concentrations. Smolkin et al. (2010) found the infants in the individualized TPN group achieved
full enteral feedings faster than the standardized TPN group, and achieved significantly greater weight gain during the first week of life ($p=0.036$) and over the first month of life ($p=0.0004$). The study reports the infants in the individualized group had significantly higher mean levels of glucose (still in the normal range) but lower levels of potassium, phosphorous, albumin and direct bilirubin compared with the standardized group. The cost analysis completed by Smolkin et al. (2010) reported that individualized TPN costs slightly more than the standardized solution (1.5 dollars/infant/day).

Lenclen, Crauste-Manciet, Narcy, Boukhouna, Greffray, Guerrault, Bordet, & Brossard (2006) implemented a change to three standardized parenteral formulations and completed a retrospective, observational study to evaluate the relevance of the implemented standardized TPN regime. Twenty preterm infants who had received standardized TPN in 2003 were matched for twenty infants who had received individualized TPN in 2001. The outcome variables compared nutrient intake and biochemical parameters between the two groups. The results of this study showed a statistically significant difference in cumulative intakes during the first week of life in amino acids, nitrogen, calcium, and phosphate. The standardized group had higher levels of all four nutrients listed previously. Lenclen et al. (20060) identified some differences in biochemical parameters between the two groups as well. Blood creatinine was less in the standardized group on day three. The phosphorous level was less in the individualized group on day three but by day eight, the only difference was in the total carbon dioxide level (16.1 mmol/l versus 19.4 mmol/l, $p=0.016$, which was less in the individualized group. The results show a standardized solution provides better nutrient supplies, especially with respect to amino acids. Although this study did not report any data on growth, the higher amino acid intake is in
compliance with current practice to optimize early protein supplies in the VLBW infants (Ziegler, Thureen, & Carlson, 2002).

A retrospective, observational study also evaluated the difference in nutrient intakes and biochemical responses in infants who received standardized versus individualized TPN regimes. Yeung, Smyth, Maheshwari & Shah (2003) studied 31 infants who had received individualized TPN compared with 27 infants who received standardized TPN formulations (two different solutions available to choose from) that were commercially batch produced. Data sets from the two groups of infants, between day two and day seven of age, were compared. There was no statistically significant difference between the standardized TPN group and the individualized TPN group in terms of daily glucose intakes. Infants in the standardized group received significantly more protein (p<0.02) each day and also received 25% more calcium and phosphate from day 3 that the individualized group (Yeung et al., 2003). This was a short term study of two methods of providing TPN during the first seven days of life, which makes this study more difficult to infer that standardized TPN should be used longer term for VLBW infants. The Yeung et al. (2003) study also has smaller sample sizes than other, comparative studies, making the results more difficult to interpret. (See Table 1 for breakdown of level of evidence for each individual study)

The final retrospective study by Morgan, Badhaw, Grime & Herwitker (2009) collected data prior and after the implementation of three different standardized configurations of TPN. The selection of choices one, two or three was based on clinical assessment and electrolyte measurements taken daily. The total number of infants in the study period was 118, with 59 in the individualized group and 38 in the standardized group. The data from this study show an increased effectiveness of the standardized TPN deliver, reflected in improved 14-day protein
intake when compared to individualized TPN group. Morgan et al. (2009) also showed an annual cost savings following the introduction of standardized TPN with a reduction of 38% compared with the previous individualized group.

**Prospective studies**

One prospective trial was identified in the literature. A prospective study by Iacobelli, Bonsante, Vintejoux & Gouyon (2010) compared fluid and electrolyte balance in preterm infants receiving either individualized or standardized TPN solutions in the first week of life. This study was conducted over two consecutive periods June 1 to October 31, 2006 (individualized group) and from November 1 to July 31, 2007 (standardized group). Eight different standardized solutions were used for day one to day seven of life. Icaobelli et al. (2010) found that standardized parenteral nutrition was associated with significantly reduced weight loss compared to the individualized nutrition. The study also concluded that there was no significant differences in water and sodium balance between the two groups. The risk of nonoliguric hyperkalemia was higher in the individualized TPN group compared with the standardized group. The design of this study may be a limitation as the groups were observed prospectively, not randomized, and the two groups were not completely homogeneous. Icaobelli et al. (2010) used a different standardized formulation every day, which differed by content of glucose, lipids and amino acids. Electrolyte additives also changed slightly each day for each bag (for example, potassium and phosphorous added on day 3). However, the assessment of early and increased amount of protein (as seen in the standardized TPN) intake in the first week of life limiting postnatal weight loss in VLBW infants confirms results already obtained by other investigators.
Pilot Study

A pilot study consisting of 30 admitted infants that could be followed for 30 days receiving a standardized formulation of nutrients was completed by Devlieger, Pourcq, Casneuf, Vanhole, de Zegher, Jaeken & Eggermont (1993). The NICU where the study occurred designed four amino acid-dextrose mixtures with a fixed nutrient load in four dilutions to administer to small sample of patients as a pilot. The solutions delivered a fixed amount of nutrients diluted with water corresponding to a fluid load of 90, 110, 130, or 170 milliliters per kilogram of total fluid per day. The goal of total parenteral nutrition in VLBW infants is to match as closely as possible the intrauterine growth rate and qualitative accretion rate. The Devlieger et al. (1993) study reported a weight gain corresponding to the intrauterine weight accretion after the initial 7-10 days of weight loss or stabilization. This study reported numerous advantages of a standardized solution including the time spent on individual prescription and preparation of the formula as well as errors in prescription and preparation are minimized. Devlieger et al. (1993) also looked at the safety of the preparation and storage of the standardized TPN solution. Samples of the TPN bags were sent for chemical analysis and bacterial counts. The study did not reveal how many bags, if any, were found to be contaminated. Devlieger et al. (1993) reported the solutions were prepared under aseptic conditions using a Millipore filter, under laminar air flow and sealed into 500 ml plastic bags. Overall, this study and the standardized system that was used turned out to have advantages in this specific NICU.

Analysis of Evidence

First, the study mean, range and characteristics are analyzed. All the subjects for the studies are very low birth weight infants. The mean for those studies that included a sample size (7 out of 11) in the systematic literature review was 89, with the range from 40 to 150. The
review articles were excluded in this data analysis as several of the studies cited were duplicates, and this would have artificially inflated the systematic review sample size. The small sample sizes may be due partly to the specific patient population reviewed in this literature.

Each individual article identified in this study was evaluated using the SORT taxonomy to grade the level of evidence provided in each paper. The first part of the algorithm for determining level of evidence is deciding if the key outcome of the study is based on patient-oriented evidence (improvement in morbidity, mortality, quality of life or cost). All eleven articles in this study passed this first criteria. The next step in the algorithm is to ascertain if the study is based on opinion, a guideline, usual practice, clinical experience or a case study (Ebell et al., 2004). None of the articles reviewed in this literature search were based on opinion, usual practice, experience or a case study, moving them up to a level one or two. The final step in establishing the level of evidence is to review the type of study (randomized controlled trial, prospective, retrospective study, etc.) and determine if each study meets the guidelines listed in Ebell et al. (2004) for level of evidence 1 or 2. See Table 1 for a detailed breakdown of each study and the level of evidence presented according to the SORT taxonomy.

Table 3 presents data copulated from four different studies in this systematic review looking at safety and biochemical responses between groups receiving either standardized or individualized TPN. Several variables were lower in the standardized TPN solution group. These variables include a lower base deficit, insulin levels and incidence of hyperkalemia. Variables that were similar between the two groups include serum creatinine concentration and creatinine clearance. Only the mean serum glucose levels were higher in the control (individualized) group.

Growth and effectiveness were evaluated in Table 4. One study found better growth in the individualized group. Three other studies presented data supporting improved growth with a
standardized group. The other study that described the effectiveness or amount of time the parenteral nutrition goals were met favored the standardized TPN group at 44% versus the individualized group at 9.4%.

Chapter V
Discussion

The strength of recommendation for clinical practice change is based on the body of evidence and typically involves more than one study (Ebell, Siwek, Weiss, Woolf, Susman, Ewigman, & Bowman, 2004). To determine the strength of recommendation, one must take into account the level of evidence of individual studies, the number, consistency and coherence of the evidence as a whole (Ebell et al., 2004). A systematic review is a critical assessment of existing evidence that addresses a focused clinical question. The clinical question is standardized TPN safe and effective in providing nutritional support to VLBW infants is addressed in this project. The strength of recommendation that using standardized TPN solutions for VLBW infants is safe and effective can be classified as B level, a recommendation based on inconsistent or limited-quality patient-oriented evidence. The justification for the level B is that the individual studies were strong and well conducted, but the number and type of standardized TPN solutions differed for each study. There was little to no consistency in how many standardized solutions each study used. The exact composition of the TPN bags also differed in the studies, or weren’t identified in many of the studies.

First and foremost, the safety of a new clinical standard must be assured. Several of the studies in this systematic review reported no differences in biochemical responses (measuring electrolyte and kidney function) between the current standard or individualized usage TPN and new standardized TPN bags. In fact, Iacobelli et al. (2010) found nonoliguric hyperkalemia was
significantly more frequent in the individualized TPN compared to standardized bags of TPN. Iacobelli et al. (2010) also reported percentage of weight loss was significantly higher in individualized TPN than in the standardized TPN group, without differences in urine output and glomerular renal function. Yeung et al. (2003) reported a higher base deficit on day 6 for infants receiving individualized TPN, the only significant biochemical difference between the groups.

Second, the efficacy of the clinical standard should be assessed. Will VLBW infants grow as well or better given standardized TPN than the current practice? This was difficult to measure in this systematic literature review. Several articles used different numbers of standardized TPN solutions, with the range from two to seven (see Table 2). The nutrient intake was also different in several studies. The amino acid concentration ranged from 1.5-3 grams per 100 milliliters in order to achieve a goal of 3-4 grams per kilogram per day of protein (amino acids). The glucose concentrations also varied between standardized TPN bags (2.5-11%) (Smolkin et al., 2010). Several studies looked at the amino acid intake during the first few weeks, but did not report the actual growth measurements (Lenclen et al., 2006). Morgan et al. (2014) did measure head growth, finding the group receiving more protein and energy had a higher rate of head growth at day of life 28.

A third consideration of a new clinical standard is the cost. Four of the eleven articles reviewed in depth for this systematic literature review mentioned cost as a factor for standardized TPN. All four showed a benefit of up to 38% lower cost of the standardized TPN versus individualized TPN. In addition to a cost savings, several studies mentioned standardization reduces the chances of potential errors and is thus safer (Riskin et al., 2006). Standardization also has the potential to reduce the time a practitioner spends on calculating and ordering TPN (Riskin et al., 2006).
Limitations of studies

Several limitations can be identified in the included studies and in the systematic literature review. As stated previously, most of the studies used different numbers of standardized TPN solutions, ranging from two to seven. Also, most of the studies were retrospective reviews, with the change to a standardized solution occurring after the use of individualized solutions. Improvement in neonatal outcomes continues to improve over time, as many changes can occur over the time frame that would lead to better growth. One example of this is the push for more skin-to-skin care in NICUs over the last 5-10 years has been shown to help growth as well (Khanam, Khan, Sharma, Chawla, & Munki, 2014). Another limitation of this literature review is that it only included very low birth weight infants, so generalizability to all NICU infants is not appropriate.

As with many other studies and literature reviews, the more the data are reviewed, the more readers identify that future studies are needed to clarify results. More randomized, controlled trials between standardized TPN solutions could identify which concentrations benefit growth and nutrition the best.

Budget

The budget for this project was mainly based on the author’s time involved in researching, writing and then presenting the information. The assistance of the librarian liaison to the College of Nursing at the University was a wonderful help and paid in kind. Creating a poster about the project and speaking at conferences may account for a nominal cost.

Dissemination Plan

Publication is one of the most common forms of project dissemination. The first choice of publication for this paper is the American Journal of Clinical Nutrition. With an impact factor
of 6.9 for this journal, the article discussing standardized parenteral nutrition in the very low birth weight infant has the potential of reaching more people that may be in the clinical decision-making role, and thus utilize the information. The very low birth weight neonatal population is a small, specialized population of health care. Presenting the information gathered from the systematic literature review is another way to disseminate the information. Journal club meetings or state and national conferences may be a format to present this study. Speaking first-hand gives direct access to the researcher and offers an opportunity for questions and comments by other health care professionals.
References


Strength of recommendation taxonomy (SORT): A patient-centered approach to grading


Appendix A

Figure 1. Flow diagram of literature review search

705 Citations identified by literature search:
PubMed/Medline: 51
Cochrane: 6
ProQuest: 647
Clinicaltrials.gov: 1

Duplicates: 6

699 citations identified

Abstracts excluded: 659

31 articles excluded:
Included patients >1500 grams: 13
“Standardized” plan included enteral feedings: 9
Discussed early amino acid (“starter TPN”): 2
Discussed electronic/computer-assisted (not defined as standardized): 3
Written before 1985: 1
Not in English: 3

40 Passed abstract screening

11 articles included in systematic literature review:
1 RTC
3 review articles
5 retrospective, observational
1 prospective trial
1 pilot study

Cross-referenced: 2
Table 1. Matrix of systematic literature review

<table>
<thead>
<tr>
<th>Authors</th>
<th>Title</th>
<th>Journal</th>
<th>Year Published</th>
<th>Purpose</th>
<th>Design of Study</th>
<th>Number of subjects (if applicable)</th>
<th>Results</th>
<th>SORT level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamkin, D. Radmacher, P.</td>
<td>Current trends and future challenges in neonatal parenteral nutrition</td>
<td>Journal of Neonatal Perinatal Nutrition</td>
<td>2014</td>
<td>Review presenting recent research and improvements to guidelines</td>
<td>Review article looking at parenteral nutrition in VLBW and ELBW neonates</td>
<td>N/A</td>
<td>Early provision of amino acids and a standardized solution are supported by research, yet more is needed for VLBW.</td>
<td>Level 3</td>
</tr>
<tr>
<td>Embleton, N. Simmer, K.</td>
<td>Practice of Parenteral nutrition in VLBW and ELBW infants</td>
<td>World Review of Nutritional Dietetics</td>
<td>2014</td>
<td>Review of risks and benefits to parenteral nutrition in VLBW infants</td>
<td>Review article of current literature for parenteral nutrition</td>
<td>N/A</td>
<td>Benefits to standardized TPN provide safe and effective nutrition but frequent electrolyte supplementation may be necessary.</td>
<td>Level 3</td>
</tr>
<tr>
<td>Morgan, C. McGowan, P. Herwitker, S. Hart, A. Turner, M.</td>
<td>Postnatal head growth in preterm infants: A randomized controlled parental nutrition study</td>
<td>Pediatrics</td>
<td>2014</td>
<td>To compare a new standardized, concentrated parenteral nutrition to a control solution in infants with BW &lt;1200 grams</td>
<td>Randomized controlled trial</td>
<td>n = 74 (intervention group-SCAMP) n = 76 (control group)</td>
<td>The intervention group received 11% more protein, 7% more energy, and had greater growth in head circumference compared with control group.</td>
<td>Level 1</td>
</tr>
<tr>
<td>Doublet, J. Viallet, R. Nicaise, C. Loundou, A. Martin, C. Michel, F.</td>
<td>Achieving parenteral nutrition goals in the critically ill newborns: standardized better than individualized formulations?</td>
<td>Minerva Pediatrica</td>
<td>2013</td>
<td>Determine if TPN goals were better achieved in the first two weeks of life with individualized or standardized formulations</td>
<td>Retrospective study</td>
<td>n = 1471 prescriptions in individualized group n = 1740 prescriptions in standardized group</td>
<td>The TPN goals were better achieved in the standardized group compared to the individualized group, significant for each nutrient (glucose, lipids, amino acids).</td>
<td>Level 2</td>
</tr>
<tr>
<td>Iacobelli, S. Bonsante, F. Vintejoux, A. Gouyon, J.</td>
<td>Standardized parenteral nutrition in preterm infants: Early impact on fluid and electrolyte balance</td>
<td>Neonatology</td>
<td>2010</td>
<td>To compare fluid and electrolytes in preterm infants receiving individualized versus standardized TPN during the first week of life.</td>
<td>Prospective study n = 40 (individualized) n = 67 (standardized)</td>
<td></td>
<td>No differences in water or sodium balance between the two groups. The individualized group had higher risk of nonoliguric hyperkalemia. The standardized group had reduced early weight loss.</td>
<td>Level 1</td>
</tr>
<tr>
<td>Authors</td>
<td>Title</td>
<td>Journal</td>
<td>Year</td>
<td>Study Design</td>
<td>No. of Patients</td>
<td>Conclusion</td>
<td></td>
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<tr>
<td>Smolkin, T. Diab, G. Shohat, S. Jubran, H. Blazer, S. Rozen, G. Makhoul, I.</td>
<td>Standardized versus individualized parental nutrition in very low birth weight infants: A comparative study</td>
<td>Neonatology</td>
<td>2010</td>
<td>Retrospective study</td>
<td>n= 70 (individualized) n= 70 (standardized)</td>
<td>Individualized TPN group significantly better growth without added clinical or lab complications.</td>
<td></td>
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</tr>
<tr>
<td>Lenclen, R. Crauste-Mancet, S. Narcy, P. Boukhouna, S. Gefray, A. Guerrault, M. Bordet, F. Brossard, D.</td>
<td>Assessment of implementation of a standardized parenteral formulation for early nutritional support of very preterm infants</td>
<td>European Journal of Pediatrics</td>
<td>2006</td>
<td>Retrospective, observational study</td>
<td>n= 20 n=20</td>
<td>Standardized parenteral formulations provided higher early intakes of amino acid and glucose, a better calcium phosphate ratio while maintaining the same biochemical parameters.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riskin, A. Shiff, Y. Shamir, R.</td>
<td>Parenteral nutrition in neonatology: to standardize or individualize?</td>
<td>The Israel Medical Association Journal</td>
<td>2006</td>
<td>Review article</td>
<td>N/A</td>
<td>Concluded a combination of standardized TPN bags for most neonates with a small number tailored for individualized TPN could reduce workload and costs, along with increasing safety.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeung, M. Smyth, J. Maheshwari, R. Shah, S.</td>
<td>Evaluation of standardized versus individualized total parenteral nutrition regime for neonates less than 33 weeks gestation.</td>
<td>Journal of Paediatrics and Child Health</td>
<td>2003</td>
<td>Retrospective observational study</td>
<td>n= 27 n= 31</td>
<td>No significant clinical difference in biochemical responses and the standardized regime saved about 30% compared with individualized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devlieger, H. De Pourcq, L. Casneuf, A. Vanhole, C.</td>
<td>Standard two-compartment formulation for total parenteral nutrition in the neonatal intensive care</td>
<td>Clinical Nutrition</td>
<td>1993</td>
<td>Pilot study</td>
<td>n= 30</td>
<td>Weight gain was found to be similar to the normal fetal accretion in utero in all infants.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Zegher, F.</td>
<td>unit: A fluid tolerance based system</td>
<td></td>
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<tr>
<td>Jaeken, J.</td>
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<td>Eggermont, E.</td>
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</tr>
</tbody>
</table>
Appendix C

Table 2. Number of solutions used and cost analysis

<table>
<thead>
<tr>
<th>Article</th>
<th>Number of standardized TPN solutions in the study</th>
<th>Cost savings presented in study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamkin et al. (2014)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Embleton et al. (2014)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Morgan et al. (2014)</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Doublet et al. (2013)</td>
<td>7</td>
<td>N/A</td>
</tr>
<tr>
<td>Smolkin et al. (2010)</td>
<td>5</td>
<td>Individualized TPN cost $1.50 more per infant per day</td>
</tr>
<tr>
<td>Iacobelli et al. (2010)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Morgan et al. (2009)</td>
<td>3</td>
<td>38% lower cost in standardized TPN group</td>
</tr>
<tr>
<td>Riskin et al. (2006)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lenclen et al. (2006)</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Yeung et al. (2003)</td>
<td>2</td>
<td>30% lower cost in standardized TPN group</td>
</tr>
<tr>
<td>Devlieger et al. (1993)</td>
<td>4</td>
<td>Stated standardized TPN group cost less but no specific data given</td>
</tr>
</tbody>
</table>
### Table 3. Safety

<table>
<thead>
<tr>
<th>Biochemical response</th>
<th>n= standardized group (STD)</th>
<th>n= control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base deficit- days 2, 7</td>
<td>27</td>
<td>31</td>
<td>p= 0.04 (0.01-2.27) lower in STD</td>
</tr>
<tr>
<td>Insulin infusion first week</td>
<td>20</td>
<td>20</td>
<td>p&lt;0.06 (lower in STD)</td>
</tr>
<tr>
<td>Mean urine output days 1-7</td>
<td>40</td>
<td>67</td>
<td>Day 4 p&gt;0.05 (lower in STD)</td>
</tr>
<tr>
<td>Hyperkalemia (K&gt;6.5)</td>
<td>40</td>
<td>67</td>
<td>p&lt;0.01 (lower in STD)</td>
</tr>
<tr>
<td>Serum bicarbonate concentration</td>
<td>40</td>
<td>67</td>
<td>P&lt;0.05 (higher in STD only day 6)</td>
</tr>
<tr>
<td>Serum creatinine concentration</td>
<td>40</td>
<td>67</td>
<td>Similar in 2 groups</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>40</td>
<td>67</td>
<td>Similar in 2 groups</td>
</tr>
<tr>
<td>Mean serum glucose levels</td>
<td>70</td>
<td>70</td>
<td>p&lt;0.0001 (higher in control)</td>
</tr>
</tbody>
</table>
Appendix E

Table 4.
Growth/Effectiveness

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = Standardized</th>
<th>n = Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of rx fulfilling PN goals</td>
<td>1740</td>
<td>1474</td>
<td>STD- 44%</td>
</tr>
<tr>
<td>Weight gain 1 week</td>
<td>70</td>
<td>70</td>
<td>p= 0.036 (control)</td>
</tr>
<tr>
<td>Weight gain 1 month</td>
<td>70</td>
<td>70</td>
<td>p=0.0004 (control)</td>
</tr>
<tr>
<td>DC weight</td>
<td>70</td>
<td>70</td>
<td>p=0.012 (control)</td>
</tr>
<tr>
<td>DC Head Circum</td>
<td>70</td>
<td>70</td>
<td>p=0.006 (control)</td>
</tr>
<tr>
<td>Intake AA (first week)</td>
<td>20</td>
<td>20</td>
<td>p=0.003 (STD)</td>
</tr>
<tr>
<td>Intake Ca (first week)</td>
<td>20</td>
<td>20</td>
<td>p=0.0001 (control)</td>
</tr>
<tr>
<td>Intake Phosphate</td>
<td>20</td>
<td>20</td>
<td>p=0.0001 (STD)</td>
</tr>
<tr>
<td>Protein intake 14 days</td>
<td>59</td>
<td>38</td>
<td>p&lt;0.001 (STD)</td>
</tr>
<tr>
<td>Protein intake 28 days</td>
<td>74</td>
<td>76</td>
<td>11% more (STD)</td>
</tr>
<tr>
<td>Difference in HC 28 day</td>
<td>74</td>
<td>76</td>
<td>p&gt;0.001 (95%CI) (STD)</td>
</tr>
</tbody>
</table>