

**PARENTERAL NUTRITION PRACTICES AND OUTCOMES OF NEONATAL
AND PRETERM INFANTS IN FOUR PUBLIC HOSPITALS IN
QUITO, ECUADOR FROM 2012- 2017**

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Fulfilment of the Requirements for the Degree of Master of Science
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ABSTRACT

Background: Parenteral nutrition (PN) is a treatment provided to very low birth weight neonates during their hospital stay. PN is comprised of the essential nutrients, minerals, fluids, and electrolytes required for sustenance. If healthcare personnel follow the current published infant PN guidelines of an internationally recognized nutritional organization (e.g., American Society for Parenteral and Enteral Nutrition), they can improve the efficacy of their PN treatment. While a host of PN practices in developed countries have been described in scientific literature, there is a lack of knowledge about the PN practices in developing countries (Katoue, Al-Taweel, Matar, & Kombian, 2016). This lack of evidence also applies to the PN practices employed in Ecuador. Ecuadorian PN practices have not been well studied and, therefore, relevant literature is unavailable.

Objectives: Describe the current PN practices and resources in public hospital neonatal wards (n=4) in Quito, Ecuador. Furthermore, identify whether current PN practices are standardised and examine the prevalence of the most common side effects associated with PN.

Design: Survey of health professionals delivering PN treatment at four neonatal intensive care unit (NICU)s. Furthermore, a retrospective chart review of neonates who received PN treatment from June 2016 to June 2017.

Setting: Four public neonatal wards in Quito, Ecuador

Results: Our study showed that thirteen out of sixteen interviewees follow PN protocols or consensus developed by their units or by the Ecuadorian Ministry of Health or published guidelines. Furthermore, all of the NICUs developed an Excel conversion spreadsheet to help professionals automate the ordering PN solutions to avoid potential errors during the prescription of this treatment. Other findings noted that the lack of a formal and functional nutritional support team was common in the observed NICUs and that there is little participation from dietitians in PN treatment. Finally, our study found that during week one to week four of PN treatment, the

mean levels of amino acids, lipids, energy intake, the glucose infusion rates, and conjugated bilirubin differed significantly between Hospital Gineco-Obstetrico Isidro Ayora's and Hospital Gineco-Obstetrico Nueva Aurora's NICUs.

Conclusions: The participants at the public NICUs in Quito endeavoured to meet the recommendations of published guidelines, despite the observed challenges and limitations. Our study found that there are opportunities for safety and quality improvement. Awareness of these opportunities will allow NICUs to fill gaps in their procedures to ensure better practices and, therefore, safer PN treatment.

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DEDICATION

To

My God and Lord for always holding my hand.

My parents, Julio and Maria de Lourdes, who taught me to be persistent and never give up.

My lovely husband, Ramon, who supported and encouraged my studies.

The engine that drives me to be always a better human being, Isaac Elian.

My brothers, David and Julio Andres, for being my friends

and an essential part of my journey.

“For God has not given us a spirit of fear, but of power, of love, and of a sound mind”

(2 Timothy 1:7, King James Version)

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LIST OF ABBREVIATIONS

AAP - American Academy of Pediatrics
ACD- Automated Compounding Device
APN- Aggressive PN
ASPEN- American Society for Parenteral and Enteral Nutrition
BPD- Bronchopulmonary dysplasia
BUD- Beyond-Use Date
ACD- Automated Compounding Device
CaHPO₄- Dibasic calcium phosphate
CDC- The Centers for Disease Control and Prevention
CFU- Colony-Forming Unit
CBC- Complete Blood Count
CLABSI- Central Line-associated Bloodstream Infection
CPOE- Computer-Prescriber Order Entry
CRBSI- Catheter-related bloodstream infections
CSP- Compounded Sterile Preparations
CB- Conjugated Bilirubin
dL- Deciliter
EN- Enteral Nutrition
ELBW- Extreme Low Birth Weight
ESPEN- European Society for Clinical Nutrition and Metabolism
ESPGHAN- European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GA- Gestational Age
GF- Growth Failure
GI- Gastrointestinal
GIR- Glucose Infusion Rate
HGONA- Hospital Gineco-Obstetrico Nueva Aurora
HGOIA- Hospital Gineco-Obstetrico Isidro Ayora
HGDC- Hospital General Docente de Calderon
HGEG- Hospital General Enrique Garces
IVFE- Intravenous Fat Emulsion
LE- Light-Exposed
LGA-Long for gestational age
LP- Light-Protected
LBW- Low Birth Weight
MDI- Mental Development Index
Mg- Milligram
mM- mmol/L
NEC- Necrotizing Enterocolitis
NICU- Neonatal Intensive Care Unit

NI- Nosocomial Infection
NST- Nutritional Support Team
PCVL- Percutaneous Central Venous Line
PICC- Peripherally Inserted Central Catheters
PIV- Peripheral Intravenous Catheter
PNAC- Parenteral Nutrition-Associated Cholestasis
PBPs- Potential Better Practices
Q6h- every 6 hours
Q8h- every 8 hours
SGA- Small for Gestational Age
SPN- Standard Parenteral Nutrition
SMOF- Soybean oil, Olive oil, Medium-chain triglycerides, and Fish oil
TB- Total Bilirubin
TG- Triglyceride
VAS- Visual Analog Scale
VLBW- Very Low Birth Weight

1. INTRODUCTION

1.1 Rationale

Parenteral nutrition (PN) is one of the treatments provided to very low birth weight (VLBW) and extremely low birth weight (ELBW) neonates, defined as an infant born under 28 days of age weighing less than 1500g and 1000g respectively (World Health Organization, 2003). During their hospital stay, many infants will require PN for approximately three weeks. (Porcelli, 2004). PN is comprised of nutrients including d-glucose, vitamins, dietary minerals, lipids, and amino acids (Mirtallo et al., 2004). When no significant nutrition can be provided to the neonate by enteral routes, such as breastfeeding, PN is administered. PN is called total parenteral nutrition (TPN) and partial parenteral nutrition (PPN) when it is a total or partial component of a neonates diet respectively (Mirtallo et al., 2004). In this study, the word PN is used to describe the collective practices and resources used in public hospitals in Quito, Ecuador.

The dose of specific nutrients in the PN formulation is administered within accepted age-based standards but can vary according to clinical situations. If healthcare personnel follow the published clinical guidelines of an internationally recognized nutritional organization (e.g., American Society for Parenteral and Enteral Nutrition) for the safe prescription and administration of PN, the risk of complications is reduced, and the health outcomes of these vulnerable infants are improved (Duggan et al., 2002). Although PN practices in developed countries are well described in the existing literature, this is not the case for the procedures and policies used in developing countries (Katoue, Al-Taweel, Matar, & Kombian, 2016). This limitation affects neonatal PN use in public neonatal intensive care units (NICUs) in Quito where practices have not previously been described in scientific literature.

This study will describe the current PN practices, resource availability, and complications associated with PN practices in four public hospital NICUs in Quito, Ecuador. The methodology consists of a face-to-face closed-ended and open-ended questionnaire of 58 questions. Three to five healthcare personnel from each neonatal unit who are responsible for delivering PN treatment

to infants were queried. Through the survey, we will be able to obtain a clear snapshot of current PN practices, resources, challenges faced and lessons learned, and gain a clearer understanding of how PN practices and outcomes compare to those in other developed and developing countries. As well, a retrospective medical record review of neonates who received PN will be conducted which will capture practices and outcomes from June 2016 to June 2017. We will have access to approximately one hundred neonate medical records from each hospital. These records will also be used to determine any complications associated with PN. Additionally, the medical records will provide direct bilirubin, blood glucose levels, and blood and catheter microbial culture information.

1.2 Objectives of this study:

1. describe the current PN practices and resources
2. identify if current PN practices are standardized
3. examine the prevalence of the most common complications associated with PN in patients who received PN

2. LITERATURE REVIEW

2.1 Parenteral nutrition as a nutritional treatment for neonate patients

Humans have struggled with providing medical care for neonates and premature babies, including determining their feeding requirements and the best types of nutritional treatments, since the origin of nutritional support care. In the 17th century, for example, physicians suggested using opium, wine, and oil (Grant, 1980). Modern PN was first introduced to provide nutritional support to postoperative neonates in 1969 (Burjonrappa & Miller, 2012). Prior to this, PN was administered to adult patients with gastrointestinal tract issues that hindered their uptake of adequate nutrition (Grant, 1980). This nutritional treatment was then extended to very low birth rate (VLBW) and premature infants, along with those suffering from protracted diarrhea and those who had undergone major gastrointestinal surgery (British Association of Perinatal Medicine, 2016; Chaudhari & Kadam, 2006). At the onset of its use, PN was provided to VLBW and ELBW neonates.

Presently, PN is used to promote the physical, psychomotor and neurodevelopmental growth of neonates (British Association of Perinatal Medicine, 2016). In his cohort study, Stephens (2009) aimed to determine the association between early protein and energy intake and growth and neurodevelopment in 124 ELBW infants who received parenteral and enteral nutrition during their first four weeks of life. This study found that there was an association between higher protein intake with lower probability of length <10th percentile at the 18-month follow-up visit. Furthermore, it showed that for every 10 kcal/kg/day of energy intake and a protein intake of 1g/kg/day were independently associated with 4.6 and 8 points increase in the Bayley Mental Development Index second edition (MDI-II) (MDI mean 79± 16, MDI <70 29%) respectively at the 18-month follow-up visit (Stephens et al., 2009). The MDI-II is an integrative developmental assessment which measures language development and early cognitive function in young children (Lowe, Erickson, Schrader & Duncan, 2012).

In addition to the Stephens' study findings, a similar randomized clinical trial was designed to determine if the early provision of amino acids was associated with better growth and

neurodevelopmental outcomes in patients. At the 18-month follow-up visit, the early intervention group of male neonates who received $\geq 3\text{g/kg/day}$ of parenteral amino acids and high energy intake during the first five days of life had a reduced probability of having a head circumference under the fifth percentile compared to the late intervention group of neonates who did not receive the minimum of 3g/kg on any single day during the first five days of life. Despite this finding, the study did not find any significant differences between early and late groups in terms of weight, length, and MDI-II scores (MDI mean 78.1 ± 16 , MDI <70 33% and MDI mean 79 ± 18.2 , MDI <70 32% respectively) (Poindexter, Langer, Dusick, & Ehrenkranz, 2006).

As it has been shown in the aforementioned studies, the early provision of parenteral amino acid and energy intake to neonate patients promotes positive outcomes in the infant's length and head circumference. Even though Poindexter's study found no statistical difference between the early and late groups relating to their neurodevelopmental outcomes, the MDI mean and MDI <70 scores obtained by both groups in this study were quite similar to the scores obtained by the neonates in Stephen's study. This similarity suggests that the neonates in both studies experienced a positive impact on their neurodevelopment due to the early provision of the amino acids through the PN treatment.

2.2 PN Clinical guidelines

Currently, PN treatment is considered by the Institute for Safe Medication Practices to be a high-risk medication (Institute for Safe Medication Practices, 2017). Due to the potential risks, especially the risk of PN formulation contamination, it is important to develop and implement policies, procedures, and practices that are science and evidence-based (Boullata, 2012). Specific protocols and guidelines can and should be developed as these guidelines may reduce the potential complications associated with PN treatment (Mirtallo et al., 2004). Guidelines suggest that a standardized ordering step should be developed following protocols and that a regular audit should be periodically performed (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014).

Hudson and Boullata (2014) argued that both standardizing each step of PN treatment, including prescribing, reviewing, formulating, administering, monitoring and weaning the neonate, and improving communication are important strategies to minimize the risk of possible

complications associated with PN administration. Thus, over the ten years period of their quality improvement study, they identified fifteen opportunities for improvement in all the PN processes. At the baseline of the study, thirteen gaps were identified and corrected to meet the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines' recommendations (Hudson & Boullata, 2014). One clear example of this intervention was noted in the reviewing step when a previous recommendation described that a pharmacist should "review or verify each PN order," while the optimum criteria proposed that guidelines "identify the individual who reviews/verifies each PN" order (Hudson & Boullata, 2014, p. 383).

In addition to the standardization of the PN process, the British Association of Perinatal Medicine (2016) and Mirtallo (2004) suggest that only trained healthcare professionals should be allowed to prescribe PN, perform compounding, and administer PN to avoid dangerous mistakes. In fact, a multidisciplinary team comprised of physicians, dietitians, pharmacists, and nurses must be responsible for delivering PN treatment according to these guidelines (British Association of Perinatal Medicine, 2016; Mirtallo et al., 2004).

Among clinical guidelines, there are discrepancies related to the recommended indications for initiating and stopping PN in neonate patients. Some of these guidelines indicate that PN should be initiated primarily in neonates below 30 or 32 weeks of gestational age, infants below 1250g or 1500g of body weight, and infants suffering from a failure of successful enteral nutrition (British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). Other guidelines recommend that all neonates below 35 weeks of gestation should receive PN treatment (Fusch et al., 2009). The main goal of these recommendations is to reach the full enteral nutrition (150-180ml/kg/day) in the shortest time (two to one weeks depending on the birth weight of the patient, <1000g or 1000-1500g respectively), assuring adequate growth and avoiding potential complications (Dutta et al., 2015).

2.2.1 PN composition and daily requirements

Newborns requiring PN should receive a glucose and amino acid formulation immediately after birth and lipids 24 hours after birth; postponed therapy given three days after birth greatly compromised the health of the neonates (British Association of Perinatal Medicine, 2016; Embleton, Pang, & Cooke, 2001). Neonates who receive protein support in the first day of life are known to have positive health outcomes in terms of a shorter hospital stay, positive nitrogen

balance, and earlier introduction of enteral nutrition. Additionally, receiving protein support on the first day of life can avert a negative nutrient balance (Trivedi, & Sinn, 2013; Schanler, Shulman, & Prestridge, 1994). Heimler, Bamberger, and Sasidharan (2010) in their randomized controlled trial in VLBW infants, which aimed to evaluate the effects of early parenteral amino acid on neonates' weight, metabolic parameters, and fluid compartments, found that plasma urea levels were significantly higher in the early group, neonates who received 1.5 g/kg of amino acids within 24 hours of life compared to the late group, neonates who received 1g/kg of amino acid at 78 hour of life. In addition, the early group presented a positive nitrogen balance and the late group a negative nitrogen balance. There were no statistical differences between the two groups in terms of weight and plasma ammonia levels (Heimler, Bamberger, & Sasidharan, 2010).

Similar to Heimler et al.'s study, a previous randomized open trial in VLBW neonates received 2.4g/kg per day of parenteral amino acids within two hours of life also who had a positive nitrogen balance at postnatal day two while patients who did not receive this macronutrient within the two first days of life had a negative nitrogen balance (Van Den et al., 2006). Another randomized control trial which supported the positive outcomes of early PN administration showed that the early administration of amino acids to randomized VLBW and low birth weight (LBW) neonate patients allowed them to regain birth weight earlier when compared to the control group (mean 11.7 (SD 4.6) days versus 14.1 (SD 4.1) respectively). Furthermore, the treated group had a shorter hospital stay and time to full feeds compared to the control group (mean 33.1 (SD 13.9) days versus 40.3 (SD 15.7) and mean 13.9 (SD 4.3) versus 16.1 (SD 4.7) days respectively) (Trivedi, & Sinn, 2013).

To avoid essential fatty acid deficiency, the British Association of Perinatal Medicine (2016) recommends that a neonate must receive a 20 % lipid emulsion within the first 24 hours of life. Parenteral iron is not recommended in the first three weeks of life (British Association of Perinatal Medicine, 2016). PN should include both fat-soluble and water-soluble vitamins. Supplementation with magnesium, phosphate, and trace elements should be included if the PN therapy is expected to exceed seven days (Fusch et al., 2009). Despite decades of PN use, there is still no consensus as to the concentration of nutrients and the daily dose provided to infants (British Association of Perinatal Medicine, 2016). Table 2.1 shows the range of specific ingredients and the daily PN dose recommendations from a variety of sources.

Table 2.1 Varying range of ingredients and the daily PN dose recommendations.

Nutrient	Safe Practices for PN (ASPEN) (Mirtallo et al., 2004)	ESPGHAN & ESPEN Guidelines (Koletzko, Goulet, Hunt, Krohn, & Shamir, 2005)	British Association of Perinatal Medicine (British Association of Perinatal Medicine, 2016)	Practice of PN in VLBW and ELBW Infants. (Embleton & Simmer, 2014)	Neonatology/ Paediatrics Guidelines on PN (Fusch et al., 2009)
Amino acids (g/kg/day)	3-4 (preterm)	1.5- 4 (preterm) 1.5- 3 (term)	2-2.5 after birth 2.7-4 (day 5) (preterm) 3 (day 5) (term)	>2 (day 0) >3.5 (day 1-2) 3.5-4 (day 3)	
Glucose (mg/kg/min)		4-8 (preterm) Max. 13 (term)	4 – 12 (preterm & term)	7-12	Max 12 (term)
Lipid emulsion 20% (g/kg/day)	3 (preterm) Use 20% of lipid emulsion	0.25 to 3- 4 (preterm) 0.1 to 3-4(term)	2 (day 1) increase to maximum 3.5-4	>2 (day 0) 3-4 (day 1-2-3)	0.25 to 3-4 (preterm) 0.1 to 3-4 (term)
Fluid (mL/kg/day)	130-150 (<1.5kg) 110-130 (1.5- 2kg) 100 (2-10kg)	80-90 (day 1) 160-180 (day 6) (<1500g) 60-80 (day 1) 140-160 (day 6) (>1500g) 60-120 (day 1) 140-180 (day 6) (term)	60-100 (day 1)	150 (day 3) Not exceed 150175 first few days	
Energy needs (kcal/kg/day)	90- 120 (preterm)	110-120 (preterm)	100-120 by 72 hours of age	60-80 (day 0) 80-100 (day 1- 2) >100 (day 3)	110-120 (preterm) 90-100 (term)
Na (mEq/kg/day)	2-5 (2-5 mmol/kg/day) (preterm & term)	0-3 (0-3 mmol/kg/day) (preterm & term)	1-3 (1-3mmol/kg/day) from 48-72h of life and cautious during the two first days of life		
K (mEq/kg/day)	2- 4 (2-4mmol/kg/day) (preterm & term)	0-2 (0-2 mmol/kg/day) first week of life (preterm& term)	1-2 (1-2mmol/kg/day) from-72h of life		
Ca (mEq/kg/day)	2-4 (1-2mmol/kg/day) (preterm) 0.5-4 (0.25-2mmol/kg/day) (term)	2-8(1-4mmol/kg/day) (preterm) 2.6-6 (1.3-3 mmol/kg/day) (term)	3 (1.5mmol/kg/day)		
P (mmol/kg/day)	1-2 (preterm) 0.5- 2 (term)	0.75-3mmol/kg/day (preterm) 1-2.3 mmol/kg/day (term)	0.18-0.2 mmol/kg/day		

PN= parenteral nutrition

2.2.2 Ordering Process

Among neonatologists and pediatricians, there are a variety of practices for prescribing PN to infant patients; indeed, an effective method for avoiding errors during the ordering process is providing education to healthcare personnel (Boullata et al.,2014; Dutta et al.,2015). The British Association of Perinatal Medicine denotes that senior physicians should make the decision to initiate PN in neonate patients; however, their order forms should be reviewed by other healthcare personnel, including pharmacists, dietitians, and other clinicians (British Association of Perinatal Medicine, 2016). Boullata (2012) instead suggests that when a nutritional support team (NST) is not available in the facility, other professionals such as knowledgeable nurses or physician's assistants could prescribe PN (Boullata, 2012). In addition, order forms should be standardized, include the complete information of the patient, and be clearly written (Mirtallo et al., 2004).

The 2003 Task Force for the Revision of Safe Practices for Parenteral Nutrition survey found widespread non-standardization of PN ordering practices within healthcare institutions. Additionally, the study noted critical errors in the units used in the prescription, omission errors, and miscommunication in the prescription (Mirtallo et al., 2004). Standardized request forms specifying components and suppliers can help ensure that a validated set of procedures is used and that every step of these procedures is documented (British Association of Perinatal Medicine, 2016). This standardization is especially vital in the event of an error as the documentation will allow PN professionals to determine the step of the process during which the mistake occurred. Uniformity in the ordering process can also avoid misinterpretation and confusion. For this reason, it is suggested that a standardized ordering process must be implemented and permanent quality auditing must be performed to ensure the patient's safety (Mirtallo et al., 2004).

In addition, to standardization and education, surveillance and supportive technology can help improve the safety of the PN ordering process. Curtis (2018) argued that there are significant potential safety benefits to implementing computer-prescriber order entry (CPOE). CPOE can reduce the risk of potential transcription errors during PN prescribing and compounding. CPOE alerts the compounding professional of medication interactions and adjustments according to the patient's medical condition (Curtis, 2018).

2.2.3 Compounding Process

Compounding processes must take place in an aseptic pharmacy unit under a laminar flow hood, and changes to PN formulations at the patient's bedside should be avoided (British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). The pharmacist who is compounding the PN formulation is responsible for appropriately preparing, labelling, storing, dispensing, and distributing PN formulations (Mirtallo et al., 2004). Preparing PN formulation can be completed manually or automatically. Manual compounding consists of the admixture of the PN ingredients separately using syringes, needles or sterile transfer equipment performed by a health professional while automated compounding is performed by an automated compounding device (ACD), which uses "computer-assisted commands" and is "connected to special hardware housed with [a] sterile, disposable compounding set" (Mirtallo et al., 2004, p.558). Automated compounding devices can admix the formulations in a sterile environment using disposable compounding sets, thereby further avoiding potential errors (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016).

Automated compounding device can prevent compounding mistakes; however, Ayers et al.'s study (2014) aimed to describe pharmacists' practices within hospitals noted errors when the ACD was used to compound PN. The compounding error rates were lower in the ACD compared to manual compounding (22% versus 37% respectively). Furthermore, this study showed common errors during the compounding process, including contamination, miscalculations, and bypassing the built-in safety check systems on ACDs (Ayers et al., 2014). For this reason, verifying and reviewing PN prescriptions is mandatory during this step whether the compounding is manual or automatic.

During the first step, the compounding pharmacist should verify that the PN order is error-free and perform a clinical and pharmaceutical review to ensure the appropriateness and compatibility of the PN elements (Boullata, 2012). The ASPEN guidelines highlight that the formulation and unintentional delivery of macro precipitates solids, resulting from the addition of incompatible salt combinations to the PN formulation, or liquids, which develop when there is a phase separation with the liberation of free oil in the TPN formulation, exceeding five microns constitute a hazardous threat to infants' lives and may result in embolic deaths. These guidelines recommend that in order to prevent the potential formation of dibasic calcium phosphate

(CaHPO₄), one of the most threatening solid precipitations, the phosphate should be added first, and at the end of compounding, the use of calcium gluconate is preferred (Mirtallo et al., 2004).

During and after the compounding process, the PN formulation must be gravimetrically, chemically and refractometrically analyzed and in-process tested following the guidelines for sterile product admixture (Mirtallo et al., 2004). PN bags should be labelled with clear and accurate information describing exactly what the neonate patient is receiving (Boullata, 2012; Mirtallo et al., 2004). These labels must include the route of administration, administration date, beyond-use date, dosing weight, and rate of infusion (Mirtallo et al., 2004). Finally, when not in use, PN formulations should be kept in a refrigerator, and if the patient is going to receive a refrigerated PN, it should be removed from the refrigerator 30 to 60 minutes prior to administration to allow the solution to reach room temperature (British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014; Boullata, 2012).

2.2.4 Additions to PN formulations

Concerns and questions have arisen with respect to the appropriateness of adding other medications to the PN formulation. Current guidelines recommend avoiding adding other medication to PN formulations due to the complexity of the PN itself (British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014; Cohen, 2012; Mirtallo et al., 2004). However, if the administration of other medication is mandatory, the pharmacist is responsible for assuring that the admixture is safe, stable, and compatible (Mirtallo et al., 2004). Supporting this recommendation, the ASPEN clinical guidelines suggest that heparin should not be added to PN formulations even if the purpose of this procedure is to prevent the potential risk of thrombosis (Boullata et al., 2014).

Two contradictory randomized, double-blind, controlled studies in neonate patients receiving PN examined the effects of heparin when used to prevent catheter blockage. Kamala, Boo, Cheah, and Birinder's study (2002) aimed to determine if the addition of heparin at 1 IU/ml dose to the TPN emulsion would prevent the blockage of peripherally inserted central catheters (PICC) in neonate patients. They found that there were no statistical differences between the group of infants that received heparin and the group which did not receive heparin with respect to the incidence of blocked catheters, catheter-related sepsis, hypertriglyceridemia,

hyperbilirubinemia, coagulopathy or intraventricular hemorrhage (Kamala, Boo, Cheah, & Birinder, 2002).

Conversely, Uslu, Ozdemir, Comert, Bolat, and Nuhoglu's study (2010) that aimed to evaluate the effect of heparin on peripherally inserted percutaneous central venous catheter patency and catheter occlusion and came to notably different conclusions. This study found that the duration of catheter patency on neonates who received heparin at 0.5 IU/kg/hour was longer when compared to the non-heparin group. These results were noted to meet the criteria for statistical significance. In addition, this study found that there were a higher number of neonates on heparin group that could complete the TPN treatment compared to the neonates in the non-heparin group. Finally, the incidence of catheter occlusion in the heparin group was lower compared to the non-heparin group (Uslu, Ozdemir, Comert, Bolat, & Nuhoglu, 2010).

To address the controversial use of heparin to prevent thromboembolic complications in patients receiving PN treatment, the ASPEN guidelines recommend that alternatives to heparin be used to prevent thromboembolic complications. These alternatives must consider catheter type, venous access line care, and line placement. This guideline highlights that polyurethane catheters are less prone to catheter blockage than polyethylene catheters (Boullata et al., 2014). Thus, the guideline recommends that polyurethane catheters are used as an alternative method of adding heparin to the formulation for preventing blockage in neonate patients on PN treatment.

2.2.5 Administrating PN

Procedurally, it is suggested that PN should be administered in neonate patients using a central line preferably positioned at the inferior vena cava or the superior vena cava using an umbilical venous catheter or PICC if the PN is expected to be delivered for more than a few days and if the PN formulation osmolality is > 1000 mOsm/L (British Association of Perinatal Medicine, 2016; Mirtallo et al., 2004). Despite this, some guidelines recommend that peripheral lines be used whenever possible (Fusch et al., 2009). According to the Nutritional Care of Preterm Infants Guidelines, if the PN is composed of 12.5 to 15% dextrose, it should be administered using a central line and that PN within the range of 800 to 1200 mOsm/L should be administered peripherally (Embleton & Simmer, 2014). Conversely, ASPEN clinical guidelines recommend that PN with osmolality up to 900 mOsm/L can be administered with a peripheral line without causing any significant risk to the infant patient (Boullata et al., 2014). This lack of consistency

between guidelines' recommendations with respect to the safe upper limit of osmolality for PN administered through a peripheral cannulae could be, as Boullata et al. argues, due to a shortage of evidence to support the ideal safe osmolality, since most relevant studies were designed as observational and more randomized control trials are needed (Boullata et al., 2014).

Although the placement procedure of a peripheral cannulae can be easier compared to central venous catheter placement, which requires an experienced professional and specialized technique, the use of peripheral cannulae to deliver PN is associated with some potential complications, such as subcutaneous infiltration which can cause skin damage such as ulceration, infection, and scarring, and thrombophlebitis associated with a high osmolality of the PN formulation (Ainsworth & Mcguire, 2015; Boullata et al., 2014 ; Mirtallo et al., 2004). Two recent randomized control trials compared the effectiveness of the percutaneous central venous lines versus peripheral intravenous lines. Thus, Barria, Lorca, and Munoz's study (2007) of seventyfour neonate patients who required intravenous therapy (IV) for more than five days found a statistically higher incidence of phlebitis in the group who used a peripheral intravenous catheter (PIV) compared with the PICC group (40.5% versus 10.8% respectively). Furthermore, the PIV group presented three cases of tissue necrosis by fluid extravasation. There were no differences with respect to the length of stay and the incidence of sepsis (Barría, Lorca, & Muñoz, 2007). Similarly, Wilson, Verklan, and Kennedy's study (2007) of ninety-six VLBW infants who required IV therapy for at least five days, found that there were no significant differences regarding systemic infection, death, and length of stay between the PIV group compared to the percutaneous central venous line (PCVL); however, the number of skin punctures was significantly greater in the PIV group compared to the PCVL group (14.5 versus 9 respectively) (Wilson, Verklan, & Kennedy, 2007).

To support the previous findings, a long-standing randomized trial of forty-nine neonate patients who received PN for at least five days compared sepsis rates between patients receiving this treatment through PCVL and peripheral cannulae. This study found that there were no statistical differences between both groups (46% versus 40% respectively) regarding sepsis rates. Nonetheless, there was a statistically higher percentage of median PN shortfall in the PCVL group compared to the peripheral cannulae group (10.3% compared to 3.2% respectively). The main reasons for the PN shortfall were technical problems after changing bags in the PCVL group and a lack of venous access in the peripheral cannulae group (Ainsworth, Furness, & Fenton, 2001).

The findings of these three trials comparing the use of central and peripheral lines suggest that the use of peripheral lines can be significantly associated with critical complications; however, the bloodstream infection rate as a complication of peripheral lines was not significantly different between venous access sites.

Ainsworth and Mcguire' systematic review (2015) of six randomized control trials evaluated the effects of the use of central versus peripheral lines to deliver PN on the neonate's development, nutrition, infection, and skin damage. One reviewed study found that the use of a central line increased the nutrient input in the patient receiving PN, and three studies found that the use of a central line decreased the number of catheters/cannulae needed to deliver the PN. Finally, the author concluded that more trials are needed to determine which venous access line is better in terms of the nutrition, growth, and development of the patient (Ainsworth & Mcguire, 2015). Ainsworth and Mcguire noted that recent trials are needed to determine which venous access site provides advantages in term of growth and development and presents fewer complications for the patient. Central venous catheters' complications will be described later in the review in the section that discusses the complications associated with PN.

In addition to the central or peripheral access point, in-line filters must be discussed during PN administration. In-line filters can help reduce micro precipitates, microorganisms, pyrogens, and air during PN administration (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). ASPEN guidelines recommend the 0.22 micron in-line filter for 2-in-1 solutions (amino acids and dextrose admixture); while a 1.2-micron filter is suitable for 3-in-1 emulsion or total nutrient admixtures (amino acid, dextrose, and lipids emulsion). The authors outline that in-line filters are extremely useful for preventing potential complications; however, they have limitations, including causing "decrease[d] flow rates, clogs, or airlocks." An additional recommendation described in these guidelines suggests using an electronic infusion pump that features safety alarms for air, pressure, rate cycling, and free flow protection features to ensure that the accurate volume of PN is provided and safely administered (Mirtallo et al., 2004).

Further addressing the administration process, the 2003 Task Force Survey of PN Practices found critical issues with PN administration, including PN rate and volume errors, administration to the incorrect recipient patient, and improper venous access line use (Mirtallo et al., 2004). To prevent these errors, the British Association of Perinatal Medicine (2016) recommends that prior

to delivering PN treatment to the patient, the professional administering the formulation should ensure that there are no errors in the identification of the patient with two other identifiers and verify that the venous access site of administration, labels, aspects of the PN formulation, and beyond-use date (BUD) are correct (British Association of Perinatal Medicine, 2016). BUD is defined by the United States Pharmacopeia chapter <795> (USP) as the date which a compounded sterile preparation possesses the same properties and characteristics that it did at the time of compounding (McElhiney, 2009). In addition to these recommendations, ASPEN guidelines provide details to be verified during the PN bag visual inspection. This inspection should determine the presence of leaks, changes in colour, cracking of emulsion, and turbidity of the PN emulsion. If any of these signs are present in the PN formulation, it should not be administered, or administration should be suspended immediately (Mirtallo et al., 2004).

During the infusion step, in order to avoid potentially hazardous peroxide generation in PN formulations, the Nutritional Care of Preterm Infants Guidelines recommend that PN bags should be protected from the light and use amber tubing (Embleton & Simmer, 2014). Peroxides are a product of oxidation which have the potential to cause an oxidative issue with general or local repercussions in neonates who have immature antioxidant defences (Lavoie, Belanger, Spalinger, & Chessex, 1997). A randomized trial in fifty-nine preterm neonates aimed to evaluate the effects of shielding TPN formulation from the light on blood glucose and triglyceride (TG) concentrations. The photoprotection was applied in the compounding and delivery process using a covering for the PN bags (protecting amino-acid, dextrose, and lipid emulsion) and syringes, and amber tubing. This study found over the first nine days of life that the light-exposed (LE) TPN formulation group presented a significantly higher mean blood glucose levels compared to the light-protected (LP) TPN group (6.6 (SD 0.2) mM versus 6.0 (SD 0.1) mM respectively). Furthermore, at eight days of life, the LE group presented significantly higher mean plasma TG levels compared to the LP group (1.5 (SD 0.3) versus 0.9 (SD 0.1) mM respectively) (Khashu, Harrison, Lalari, Lavoie, & Chessex, 2009).

In contrast to Khashu et al.'s findings, a randomized controlled trial in VLBW neonates that aimed to determine if the photoprotection of PN can reduce the rates of bronchopulmonary dysplasia (BPD) and death, did not find any statistical differences between the LE group compared to the LP group with respect to BPD and death rates at 28 days of life. Furthermore, a multivariate analysis showed no significant effect from shielding PN from the light on BPD and death (Laborie

et al., 2015). Despite these contradictory findings, the British Association of Perinatal Medicine (2016) recommends photoprotection of PN bags and giving sets (British Association of Perinatal Medicine, 2016).

If there is suspected contamination or if the formulation has been compromised after PN administration, the ASPEN guidelines recommend that PN bags should be changed using aseptic procedures. This guide suggests the 3-in-1 formulation must be changed every 24 hours, and 2-in-1 solutions must be changed every 72 hours. Furthermore, this guideline recommends that for intravenous fat emulsion (IVFE) that is an admixture to compound TPN formulation, the safe BUD for its delivery should be 24 hours (Mirtallo et al., 2004). Additionally, Boullata et al. (2014) suggest the BUD for IVFE delivered separately in the original container should be 12 to 24 hours and the BUD for repackaged IVFE should be 12 hours (Boullata et al., 2014).

2.2.6 Monitoring patients on PN

Due to the high fluid volume, high body water content, immature regulatory mechanisms and low blood volume of preterm neonates, cautious monitoring is required in patients on PN treatment (Fusch et al., 2009). Anthropometrically and biochemically monitoring the patient receiving PN treatment allows medical professionals to evaluate the efficacy of the PN treatment, prevent potential complications, and determine the clinical condition and clinical outcomes of the patient (Mirtallo et al., 2004). According to the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, biochemical monitoring allows for the administering professional to assess the patient's clinical and nutritional status, and the anthropometric assessment enables the clinician to evaluate the nutritional status of the patient (Koletzko, Goulet, Hunt, Krohn, & Shamir, 2005).

The Nutritional Care of Preterm Infants Guidelines recommends measuring the infant's weight daily and measuring their length weekly in order to evaluate the nutritional support and growth in the patient. The ideal nutritional support for premature infants will provide optimal growth and allow them to obtain nutrient accretion similar to a fetus at the same gestational age. This guideline recommends that in order to promote adequate growth in VLBW neonates, the PN should provide 120kcal/kg/day of energy and 3.8g/kg/day of protein by the first seven days of

life. Finally, this guideline recommends the use of birth weight-bases intrauterine curves to monitor growth in preterm infants at the NICUs (Poindexter, 2014).

Among PN guidelines, there is consensus that infants who are receiving PN should undergo a complete evaluation of electrolytes, blood glucose test, fluid balance test, sepsis monitoring, and anthropometric measurements, such as body weight, length, head circumference (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016; Embleton & Simmer , 2014 ; Fusch et al., 2009). However, according to the Nutritional Care of Preterm Infants: Scientific Basis and Practical-Guidelines, the frequency and method of monitoring to determine the efficacy of the PN treatment depends on the clinical condition of the patient and duration of the PN treatment, and this frequency varies from NICU to NICU (Embleton & Simmer , 2014; Pedrón, 2017). Monitoring the patient on PN not only varies between NICUs but varies within published guidelines as well. Table 2.2 shows the recommended frequency of anthropometric and biochemical assessments of patients receiving PN treatment from the British Association of Perinatal Medicine guidelines and two comparable sources.

Table 2.2 Frequency of anthropometric and biochemical assessment of neonate patients who are receiving TPN

Assessments	British Association of Perinatal Medicine (British Association of Perinatal Medicine, 2016)		Practice of Parenteral Nutrition in VLBW and ELBW Infants (Embleton & Simmer, 2014)	Neonatology/Paediatrics Guidelines on Parenteral Nutrition (Fusch et al., 2009)	
	1 st week of PN	Stable PN		Initial phase of PN	Medium & Long-term PN
Anthropometric assessment wt/length/head circumference	Daily (wt) Weekly (length & head circumference)	Twice weekly (wt) Weekly (length & head circumference)	Daily or alternate days (wt) Weekly (length & head circumference)		Weekly
Fluid balance	Daily	Twice weekly		Daily	Weekly
Full blood count	weekly	weekly			
Blood glucose	q6h to q8h	Daily	Daily (first 3-4 days)	Daily	Weekly
Electrolytes	Daily	Twice weekly	Daily (first 3-4 days)	Daily	
Hepatic enzymes (LFTs, Alkaline phosphatase)	Daily or twice weekly	Weekly	Weekly		Y-GT weekly Alkaline phosphatase every 2 weeks
Urea, Creatinine	Daily	Twice weekly			Weekly
Triglycerides Cholesterol	Twice weekly	Twice weekly	Twice weekly (or if lipemic serum)		
Proteins/ Albumin	Daily	Twice weekly			
Bilirubin	Daily	Weekly			
Mineral & Vitamins		Monthly (long term PN)			

q6h= every 6 hours

q8h= every 8 hours

2.2.7 Weaning PN

A wide range of practices exists between clinical guideline recommendations regarding the indications to cease PN and begin enteral nutrition in infants on PN treatment. A retrospective chart review on neonates below 32 weeks of gestational age which aimed to identify during which phase of an infant's stay they are most likely to present with poor growth and potential growth

failure (GF) (discharge weight below the 10th percentile). The patient's stay was divided into three phases: first or full PN, second or transitional PN and enteral nutrition (EN), and third phase or full EN. During the transitional phase, PN infusion was decreased when trophic feeds exceeded 20ml/kg/day to reach a total of fluids at 140ml/kg/day. PN was discontinued when EN reached 100mL/kg/day. This study found that 49 percent of neonates were discharged with GF, that the poor growth incidence was highest during the transition phase (46%), and that protein intake decreased as PN was weaned (Miller et al., 2014).

Based on this study, the British Association of Perinatal Medicine recommended that PN should be weaned when 75 percent of enteral nutrition is tolerated. In preterm infants, a milk intake of at least 120ml/kg/day is suggested (British Association of Perinatal Medicine, 2016). Conversely, the Nutritional Care of Preterm Infants Guideline recommends that neonates reach higher enteral nutrition before stopping PN. This guide recommends that when 125-150ml/kg/day of enteral nutrition is tolerated, PN should be weaned (in the first few days, the neonate should not exceed 150 to 175 ml/kg/day of total fluid intake) (Embleton & Simmer, 2014).

In their review, Dutta et al. (2015) recommend providing trophic feeds or small volumes of milk, approximately 10 to 15ml/kg/day starting within 24 hours of life. This trophic feed should be provided to progressively introduce enteral feeds, and extreme caution should be exercised when administering the feed to ELBW or extremely preterm neonates. However, in cases of intestinal obstruction or ileus trophic feeds, this recommendation is contraindicated (Dutta et al., 2015). Dutta et al. based their recommendation of the early introduction of the trophic feed on two systematic reviews of the level of evidence 1a, a systematic review of a homogeneity of randomized controlled trials (Oxford Centre for Evidence-Based Medicine-Levels of Evidence, 2009).

The first systematic review of nine randomized or quasi-randomized controlled trials in VLBW and ELWB neonates that aimed to evaluate the effect of early trophic versus enteral fasting on feed tolerance, growth and development, and incidence of necrotizing enterocolitis (NEC) and mortality, found that in six studies the early introduction of the trophic feeds (15 to 25ml/kg/day on day one of life) did not affect the feed tolerance (time to establish full enteral feeding) in the trophic feeds group compared to the fasting group. In five of the nine trials there were not significant effects on the days it took the neonates to regain their birth weight and on the incidence of NEC respectively (Morgan, Bombell, & McGuire, 1997). The second systematic

review of nine randomized controlled trials in VLBW infants aimed to determine the effect of early versus late enteral nutrition (after four days of life) on the incidence of NEC, mortality, and morbidity found that in eight trials the early introduction of enteral feeds did not increase the risk of NEC. In six trials there were not significant effect on feed intolerance (Morgan, Young, & Mcguire, 2011).

This inconsistency in PN practice requires further research to develop PN recommendations that are safe for VLBW and ELBW infants (Adamkin & Radmacher, 2014). Similarly, Embleton and Simmer (2014) highlight that guidelines' recommendations are based primarily on expert opinion and rely on limited evidence as only a few large randomized controlled trials have been conducted (Embleton & Simmer, 2014) suggesting that, although guidelines are an invaluable resource for the personnel delivering PN at the NICUs, there are opportunities for improvement.

2.3 PN Complications and expenses associated with PN administration

While the benefits of providing PN to neonates is obvious, there can be undesirable complications if administered improperly or if the concentrations of ingredients are too high (Dudrick, Macfadyen Jr, Van Buren, Ruberg, & Maynard, 1972). These oversights may cause harmful complications, described in the pertinent literature, which result from PN delivery responsibility being placed on health care workers unfamiliar with the delivery guidelines and processes (Mirtallo et al., 2004). This risk of complication is why administering PN is a complex procedure requiring significant training for health care personnel who administer and formulate the medication. Among the complications associated with PN treatment, the literature describes negative pharmaceutical interactions, including potential precipitation of salt caused by the interaction between calcium and phosphate, described previously in this review, venous access line associated sepsis, hyperglycemia, hypoglycemia, parenteral nutrition-associated cholestasis (PNAC) and other complications (British Association of Perinatal Medicine, 2016; Mirtallo et al., 2004; Uthaya & Modi, 2014).

Since PN consists of protein, dextrose, lipids, trace elements, vitamins, and minerals, it can encourage microbial growth when contaminated by microbes, thereby leading to sepsis in neonates (Tresoldi et al., 2000). Furthermore, microbial contamination of the delivery venous access lines or catheters can result in the introduction of pathogens into neonates (Sitges-Serra,

Linares, Perez, Jaurrieta, & Lorente, 1985). These lines can be either peripheral or central venous access sites. Peripheral line complications were described previously in this review. The most important complication associated with the central venous catheter described in the literature is the nosocomial infection (Ainsworth, & Mcguire, 2015).

Catheter-related bloodstream infections (CRBSI) are defined by the American Academy of Pediatrics (AAP) as a positive blood culture in the presence of a central venous catheter after another source of infection in a symptomatic patient has been excluded (i.e., fever, chills, and /or hypotension) (Oliveira, Nasr, Brindle, & Wales, 2012). The AAP's guidelines for the prevention of intravascular catheter-related infection outlines that CRBSI is confirmed when "a positive semiquantitative (>15 CFU/catheter segment) or quantitative (>10³ CFU/catheter segment catheter) culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and the peripheral blood" (O'Grady et al., 2002, p. 2).

The Garland et al.'s study (2008), which aimed to define the pathogenesis of CRBSI in eighty-two neonates with PICC placed in situ for a mean of twenty days (SD 12), reported twenty-three of the neonates were diagnosed with nosocomial bloodstream infection (BSI), and fifteen of these cases (18%) were reported to include either definite or probable CRBSI. The microorganism found in fourteen cases was coagulase-negative staphylococci. This study reported that 67%, 20% and 13% of the CRBSI cases were caused by intraluminal, extraluminal, and indeterminate contamination respectively (Garland et al., 2008). Another prospective study which aimed to identify the incidence of nosocomial infection (NI) (infection occurring 48 hours after admission) in Danish NICUs found that the incidence of NI was 13.2 per 100 patients and 8.8 per 1000 patient days. On the other hand, the incidence of BSI was 7.6 per 100 patients and 5.1 per 1000 hospital days (Olsen et al., 2009).

Other complications associated with PN administration are metabolic complications including hypoglycemia and hyperglycemia. The AAP defines hypoglycemia as a medical condition that requires an immediate parenteral treatment when the serum concentration of glucose is less than 45mg/dL (2.5mmol/L) before each feeding in symptomatic neonates (non-specific clinical signs include abnormal respiratory patterns, cardiovascular signs, and neurologic findings) and less than 25mg/dL(1.3 mmol/L) at birth to 4 hours of age or 35mg/dL (1.9 mmol/L) from 4 to 24 hours of age in asymptomatic neonates (Adamkin, 2011). However, there is still disagreement regarding the definition of hypoglycemia. Currently, Saugstad (2017) describes that

hypoglycemia is most accurately defined as when a patient's blood glucose level is less than 47mg/dL (2.6 mmol/L) (Saugstad, 2017). Adamkin describes the method used to test blood glucose levels in patients and notes that at low glucose concentration test-strips have a great variation compared to the actual plasma glucose concentrations. For this reason, results must be confirmed by a rapid laboratory blood or plasma concentration test (Adamkin, 2011).

Pildes, Forbes, Apos, Connor, and Cornblath's research (1967) found that 14 of 244 LBW infants participating in its study had two or more blood glucose values below 20mg/dL (1.11 mmol/L) during the first five days of life, an incidence of 5.7 %. Furthermore, the study describes symptoms including eye rolling, weak or high-pitched crying, sweating and poor feeding in hypoglycemic patients (Pildes, Forbes, Apos, Connor, & Cornblath, 1967). Another study, which defined hypoglycemia as a blood glucose level below 30mg/dL (1.66mmol/L), examined neonates who were tested for blood glucose levels at birth, after three to four hours after birth (fasting) and at the third or fourth day after birth (fasting). This study found that 184 out of 1617 patients experienced hypoglycemia (11% of expected incidence) during the first three to six hours after birth. In addition, this study found that neonates who were small for their gestational age group had the highest incidence of hypoglycemia, 27 out of 70 cases (32%), compared to neonates who were considered the appropriate size for their gestational age, 23 out of 226 cases (10%), and infants who were large for their gestational age, 9 out of 78 cases (11%) (Lubchenco & Bard, 1971).

Conversely, the AAP defines hyperglycemia in preterm infants as occurring when their plasma glucose level is over 150mg/dL (8.3mmol/L) or over 125mg/dL (6.9 mmol/L) in blood glucose concentrations (Rozance & Hay, 2010). The Bryan, Wei, Hamilton, Chance, and Swyer's study (1973), which aimed to evaluate the effects of a dextrose fibrin hydrolysate solution in neonates less than 1300 grams, found that seven out of eleven patients who received dextrose 10% with 3.5% fibrin hydrolysate and only dextrose solution (23%) had blood glucose levels over 150mg/dL (Bryan H, Wei, Hamilton, Chance, & Swyer, 1973). Furthermore, Dweck, Brans, Summer, and Cassady (1976) found that 43 of 50 (86%) of neonates weighing less than 1100 grams presented plasma glucose levels over 125mg/dL, and 36 of those 43 (84%) of infants had one or more serum glucose level over 300mg/dL (Dweck, Brans, Summers, & Cassady, 1976).

Lastly, another complication associated with parenteral nutrition administration is PNAC. Klein, Ravenis, Kusenda and Scavo (2010) outlined that the term PNAC "is commonly used in

publications to indicate PN associated hyperbilirubinemia with cholestasis but actual determinations of cholestasis are not often reported” (Klein, Ravenis, Kusenda, & Scavo, 2010, p. 1685). The AAP defines abnormal conjugated bilirubin as a conjugated bilirubin concentration over 1mg/dL (17.1umol/L) when the total bilirubin (TB) is at or below 5mg/dL (85umol/L) or over 20% of the TB when the TB is higher than 5mg/dL (Maisels et al., 2004). In the reviewed scientific literature, clinical trials of infant patients receiving PN defined PNAC conjugated bilirubin levels as 1.8mg/dL (30.8umol/L), over 2mg/dL (34.2umol/L), and 2.9mg/dL (49.6umol/L) (Puligandla et al., 2004; Wright, Ernst, Gaylord, Dawson, & Burnette, 2003; Köglmeier, Day, & Puntis, 2008).

Klein et al. (2010) noted that PNAC is diagnosed by exclusion by generating a differential diagnosis from obstructive causes, primary liver disease, metabolic liver disease, and sepsis. Furthermore, the author describes that diagnostic tests (hepatobiliary ultrasound, hepatobiliary scintigraphy, hepatobiliary magnetic resonance imaging, and liver biopsy), biochemical markers (conjugated bilirubin ≥ 2 mg/dL) and clinical signs (jaundice, pale stools, itchiness, hepatomegaly, splenomegaly, ascites) are considered during the evaluation of PNAC (Klein, Ravenis, Kusenda, & Scavo, 2010).

Puligandla et al.’s study (2004) aimed to compare the outcomes of intrauterine growth-restricted infants with gastroschisis to those without growth restriction receiving TPN. This study found that 26 out of 76 (34%) of patients with less than 37 weeks of gestational age (GA) had PNAC compared to 5 out of 37 (13.5%) of patients with more than 37 weeks of GA (Puligandla et al., 2004). Conversely, Wright, Erns, Gaylord, Dawson, and Burnette’s study (2003), which aimed to compare the incidence of PNAC in infant patients who received PN amino-acids Aminosyn Pediatric formula and Trophamine, found that 24 out of 661 patients developed PNAC (3.6%). The same study found a PNAC incidence of 17% in infants who received PN for more than 21 days as 24 out of 141 infants developed this complication (Wright, Ernst, Gaylord, Dawson, & Burnette, 2003).

Aside from the harmful complications, PN represents a significant allocation of funds within the health care system of each country. Based on research conducted in NICUs in the United States, the average stay is 42.2 days which costs an average of \$65,600 per neonate (Russell et al., 2007). The costs and length of stay can be higher for ELBW neonates. Nevertheless, in their quality improvement study, Boitano, Bojak, Mccloskey, Mccaal, and

Mcdonough (2010) found that implementing ASPEN practice guidelines, including revising the PN order form, providing additional education to staff, and initiating PN rounds in the institution, provided both quality improvements and cost savings. In total, these changes provided savings of \$5.3 million in PN charges and \$107,000 in pharmacy expenses (Boitano, Bojak, Mccloskey, Mccaull, & Mcdonough, 2010).

Due to the mortality, morbidity, and the high costs associated with PN administration, steps to standardize PN formulations and guidelines for its delivery according to the weight of the neonate have been recommended. Standardization of PN bags means that they can be mass produced which would thereby result in decreased costs (Bolisetty, Osborn, Sinn, & Lui, 2014; Uthaya & Modi, 2014). According to the Yeung, Smyth, Maheshwari, and Shah's study (2003), the cost of standardizing TPN bags in an Australian NICU was 30% lower compared to the cost of using individualized bags (\$88 per bag versus \$130 respectively) (Yeung, Smyth, Maheshwari, Shah, 2003).

2.4 Standardized PN versus Tailored PN

Standardized PN bags can decrease issues such as contamination and errors in the formulation or concentration of the ingredients, are readily available to initiate PN within the first hour of life of the neonate patient, and can optimize clinical outcomes and reduce the risk of complications (Berlana et al., 2014; Turpin et al., 2012; British Association of Perinatal Medicine, 2016). Thus, Yeung et al.'s study (2003) aimed to determine the difference in nutrient intake and biochemical response between neonates less than 33 weeks of gestational age who received standardized TPN compared to neonates who received individualized TPN from day two to seven of life. This study found that neonates who received standardized TPN formulations received significantly more protein daily and cumulatively during the first week of life compared to neonates receiving individualized TPN (13.6g/kg versus 9.6g/kg). Infants receiving standardized TPN received 25% more calcium and phosphate from day three, and less sodium and no potassium on day two (Yeung et al., 2003). Furthermore, Rigo et al. (2012) found that the use of commercial three-chamber PN bags, which contain amino acids, dextrose, and lipids, ensures ease of bag manipulation. This was measured by visual analog scale (VAS) (the method used to measure the quality of practical handling and ease of use). The VAS scores were higher for bag manipulation

and prescription-to-infusion time than TPN ward compounding. In addition, there were no adverse events related to the PN treatment (Rigo et al., 2012).

This is not to say that individualized PN formulations will not have a place in the arsenal of attending physicians. In fact, a study found that those receiving individualized PN formulations experienced significantly higher protein intake during the first week of life compared to the standardized group (23.2/kg/week versus 19.6g/kg/week respectively). Furthermore, this study found significantly higher lipid, glucose, and energy intake during the first and second week of life in the early individualized group compared to the standardized group. Another finding of this study was that the time to regain birth weight was significantly shorter in the individualized group compared to the standardized group (10.4 days versus 12.8 days) (Eleni-Dit-Trolli et al., 2009).

2.5 PN practices in developed countries

In developed countries, there had been numerous improvements in PN practices. This includes annual reviewing and auditing with recommendations to improve PN processes. A study, which aimed to describe experiences with nutrition- NEC in a focus group as part of a quality improvement project in NICUs in the United States of America (USA), reported that after eight potential better practices (PBPs) were applied, patients in all three participating institutions demonstrated significant improvements. This project employed a self-assessment survey for health personnel, retrospective chart reviews of VLBW neonates, a literature review, and benchmarking with centers of excellence (centers with a low rate of NEC) in order to develop the PBPs. One example of these PBPs was that the “initiation of TPN should be done as soon as the infant is medically stabilized, preferably within the first 24 hours of life” (Kuzma-O'Reilly et al., 2003, p. e464).

Additionally, this study found that patients in the group that implemented the PBPs experienced improvements in growth patterns compared with the baseline group (83% versus 98% of infants discharged with <10th percentile respectively). Also, infants in the group that implemented the PBPs reached full enteral nutrition in a shorter time compared to the baseline group (23.7 versus 34 days respectively). Finally, the intervention group had a decreased incidence of NEC in two out of three institutions (from 16% to 6% and from 6% to 4%) (Kuzma-O'Reilly et al., 2003) demonstrating improvements in their nutrition support practice.

A telephone survey completed in the United Kingdom (UK) on PN administration and management in 57 NICUs showed diverse PN practices, knowledge, and management of complications between professionals in the UK, Wales and Scotland. The response rate obtained was 95% (54 out of 57 NICUs). Regarding the initiation of amino-acids, 24%, 43%, and 33% of NICUs begin amino-acids from 0 to 23 hours of life, between 24 to 48 hours of life, and after 48 hours of life respectively. Eighty-three percent of the NICUs used Intralipid 20%. Also, 6%, 48%, and 46% of the units initiated parenteral lipids from 0 to 23 hours, 24 to 48 hours, and after 48 hours of life respectively. It was also noted that there was a lack of knowledge of nutritional support among physicians. Two-thirds of middle-grade doctors (35 out of 54) were unaware of the concentration of amino-acid used in PN in their units while the other one third (19 out of 54) noted the maximum concentration of amino-acid used to begin PN treatment is 3g/kg/day (6 NICUs), 2.5g/kg/day (12 NICUs), and 2g/kg/day (1 NICU). Even though all units (54 out of 54) had a PN protocol, the authors highlighted the need for a standard evidence-based PN guideline across the UK to improve PN therapy practices. It was predicted that doctors would follow the recommended guidelines if they were precise and clearly stated (Ahmed, Irwin, & Tuthill, 2004).

Another survey on the delivery of PN in neonatal units in 67 hospitals in Australia reported that 40% of hospitals had PN teams and 74% noted that they had a PN protocol. Inaccessible or non-functional gastrointestinal (GI) tract was the most common reason to initiate PN treatment. Sixty percent of the participants reported that PN is ceased when at least half of the patient's requirements are met enterally or orally. Furthermore, 55% of the interviewees noted that patients on PN were biochemically monitored daily, 28% described monitoring patients three to four times per week, and 6% noted performing monitoring one to two times per week. Finally, the authors stated that the PN practices in the NICUs met the guideline recommendations; however, there is a significant variation in practices among physicians where there is no evidence to support the recommendations (Ali, Chapman-Kiddell, & Reeves, 2007).

In face-to-face or telephone interviews with nutrition and nursery staff at eight NICUs in North Carolina, it was found that the most common educational degree reported was Registered Dietitian. Pharmacists were the professionals responsible for compounding the PN formulation. Additional findings noted that six of the NICUs developed their own paper order forms to formulate PN containing a wide range of nutrition decision support; however, most of the self-reported medical errors were related to misinterpretation of the form, improper transcription or

procedural errors. The author highlighted that electronic PN management could reduce PN practice errors by 50 % (Porcelli, 2004). A study at Geneva University Hospital found that, while the PN prescription procedure met the clinical guidelines, the concentrations of glucose and protein were within the guidelines, but the vitamins and trace elements were, in 24% of patients, either nonexistent or inadequate for the patients' needs (Nardo et al., 2008). This same study found that 62% of the 200 studied patients were overfed while 14% were underfed. The authors of this study suggest that potential complications can be prevented by promoting the implementation of NSTs in hospitals.

In a study similar to the one described above, the neonatal team leaders in 296 French neonatal departments were queried using a closed-ended questionnaire as to their PN objectives for VLBW. This survey compared these objectives with the department's daily practices. The authors of the study reported a 58% response rate (172 out of 296 NICUs). Ninety-three out of 172 NICUs provided PN to VLBW, and 90 questionnaires were analyzed. Regarding the departments, PN objectives for VLBW, 49%, 40%, and 11% of the NICUs initiated amino-acids on day one, day two, and day three respectively. The amino-acid dosage used by 47%, 49%, and 4% were 0.5, 1, and 1.5 g/kg per day respectively. Seventy-eight percent of the NICUs initiated lipids after the third day of life. Similarly, 78% of the units used 0.5g/kg/day of lipids to initiate PN treatment. When asked about the congruency between nutritional protocol and daily practice, 56% of the participants noted that theoretical intakes were applied in all cases, while 22% of the interviewees responded that theoretical intakes were applied in 75% of cases. Respondents noted that the discrepancy between protocol and practice was mainly due to issues related to the patients' disease, venous access, and requests from the prescribers. The authors further noted that, given the numerous publications on nutritional guidelines for PN administration in neonates and preterm infants, further training was required (Lapillonne, Fellous, Mokthari, & Kermorvant-Duchemin, 2009).

Another recent report conducted an analysis of the error rate at a large pediatric facility after it had put in place an electronic system to order, transcribe, compound and administer the entire PN process (MacKay, Anderson, Boehme, Cash, & Zobell, 2016). The hospital's electronic system was built to comply with a national advisory group's recommendations and the ASPEN guidelines for ordering, transcribing, compounding, and administering PN. The authors reported that the error rate in their hospital was 0.27% as compared to the national average error rate of

1.6%. Such quality improvements in the entire PN process can reduce errors, improve health outcomes for neonates and preterm infants, and reduce PN associated costs as infants recover more quickly, and, therefore, the length of their hospital stay is reduced.

In Ireland, a study conducted on the appropriate use of PN in an acute adult hospital found that 82 percent of PN prescriptions were appropriate while five percent were inappropriate, and 13 percent were appropriate but avoidable (Smyth, Neary, Power, Feehan, & Duggan, 2013). A case report on quality improvement over a ten-year period at the Hospital of the University of Pennsylvania found 15 opportunities for improvement at the baseline in prescribing, reviewing, compounding, preparing, administering, monitoring, reassessing, and documenting. Thirteen gaps were corrected so that the practices met the ASPEN guidelines and recommendations. The authors identified that accomplishing a “safe PN process may require a cultural shift, resources, education, and ongoing work” (Hudson & Boullata, 2014, p. 384).

2.6 PN practices in developing countries

While the literature on PN practices in the developed world is thorough, this is not the case for developing countries. In a recent report on the adherence to PN guidelines in an adult hospital in India, it was found that 0.24% of the patients received PN treatment and 0.18% of them received PN treatment for at least three consecutive days. Fifty percent of the patients initiated PN due to major gastrointestinal surgery and 26% due to intolerance to enteral nutrition. Regarding the venous access site used to deliver PN, 64% of patients received PN through a peripheral vein, and 25% of patients received PN via a central venous line. Finally, the authors concluded that the appropriateness of PN indications and venous access sites to deliver PN needs to be reviewed. (Ramakrishnan, Shankar, Lakshmi Ranganathan, Bharadwaj, & Venkataraman, 2016)

Another study conducted in India in the 1980s researched PN use in Indian NICUs and found that it was very difficult for NICU units to follow guidelines due to the unavailability of optimum amino acids, as well as an overall lack of funds. In this study, the physicians themselves compounded and delivered the PN formulations, and were not able to conduct the preparation under sterile conditions due to the lack of laminar flow hoods. They also concluded that sepsis was the most important complication seen in patients, which had an incidence of 52% (Chaudhari & Vaidya, 1988). In a follow-up study to the above-described study, the neonatal leaders in the Indian neonatal department reviewed their PN practices. The authors of the study reported that

complications associated with PN were reduced by providing additional training to the healthcare personnel, compounding PN under a laminar flow hood, improving monitoring protocols, and supplying suitable intravenous equipment. Moreover, they updated their practices related to dose recommendations for amino acids and lipids in ELBW infants (Chaudhari & Kadam, 2006).

In 2013, a randomized controlled trial study was conducted in India evaluating the effects of aggressive parenteral nutrition (APN) on nitrogen retention in VLBW and ELBW infants. This study found greater nitrogen retention in the APN group compared to the standard parenteral nutrition (SPN) group on day four and seven of the treatment. The time to regain body weight in the APN group was less than in the SPN group, 9.5 and 11.5 days respectively. Moreover, the average APN patient hospital stay was less than the SPN patient hospital stay. The authors of the study suggested that more research about safe PN practices in developing countries is needed. Finally, they concluded that APN is safe and feasible in India (Tagare, Walawalkar, & Vaidya, 2013).

In the same year of the previous study, a retrospective cohort study on the appropriateness of PN indication in an adult patients' hospital was conducted in Singapore. This study was compared with the previous audit cohort study completed in the same hospital in 2001. The authors found that the appropriateness of PN administration was greater than indicated during the previous study; this improvement was due to the availability of an NST and increased awareness among staff (Chuah et al., 2013).

In 2000 in South Africa, a study was conducted evaluating the efficacy of the "Standard All-in-One Bag of PN" in a neonatology surgery centre. This study reported that this method would be an effective nutrition solution for developing countries if they do not have an NST, pharmacy unit, or knowledgeable staff to prepare PN. Because the formulation is prepared in a specialized centre and supplied within 48 hours to facilities that request it, this formulation is not subject to many of the risks associated with in-hospital PN preparation (Chowdhary, Chitnis, Choudhary, Gossen, & Lazarus, 2000). However, another study carried out in Egypt found that another method to improve PN practices in developing countries is education. In 2012, this study found that satisfactory knowledge about PN procedures improved from 10% to 90% after education was implemented. In addition, the practice of PN administration and monitoring for potential complications associated with PN was enhanced after a comprehensive guidelines program was provided to NICU nurses (Al-Rafay & Al-Sharkawy, 2012).

Finally, an interesting study on the evaluation of PN practices was conducted in Kuwait in 2016 where the researchers explored PN practices in seven hospitals (adult, pediatric, and neonate hospitals). Through interviews, this study found that there were no NST units at any hospital participating in the study: instead, physicians, pharmacists, dietitians, and nurses were involved in PN therapy. Order forms were handwritten, and all PN formulations were made according to the patient's needs. Quality audits were performed in all the hospitals, and PN guidelines or protocols were developed in six of the seven NICUs (Katoue, Al-Taweel, Matar, & Kombian, 2016).

2.6.1 Conclusions

Around the world, there are still significant inconsistencies in the ordering, transcribing, compounding, and administering of PN to neonates and preterm infants. As this literature review has demonstrated, there are a host of errors that can compromise the process. Even with a strong system and clinical guidelines in place, there are irregularities in the rate of delivery, inadequate ingredients, and over and underfeeding. This research outlines the rationale, objectives, and methodology which will be undertaken to study PN practices in NICUs in Quito, Ecuador. These practices have not been previously described. This research will also provide an opportunity to develop a baseline manuscript of hospitals' practices to help them improve the outcomes for these fragile patients because "it is difficult to invite change if current practice is unknown" (Kuzma-O'Reilly, 2003, p. e462).

3. PARENTERAL NUTRITION PRACTICES IN FOUR PUBLIC HOSPITALS IN QUITO: SURVEY RESULTS

3.1 Objectives:

Describe the current PN practices and resources

Identify if current PN practices are standardized

3.2 Methods:

3.2.1 Methodology

A qualitative grounded-theory methodology was used in this study. According to Creswell (2006), the grounded-theory approach helps to explain a practice or provide a framework for future research based on the views of participants, primarily through interviews (Creswell, 2006). An in-depth survey was administered to participating health care personnel between November 2017 and February 2018 to describe the current PN practices and resources in the four public hospitals in Quito and to identify if the practices were aligned with published guidelines: ASPEN, ESPGHAN & ESPEN, British Association of Perinatal Medicine, and Practice of Parenteral Nutrition in VLBW and ELBW Infants. Through their representatives in the “Eugenio Espejo hospital of Specialities Ethics Committee,” the Ecuadorian Ministry of Health Ethics Committee approved this project for all participating hospitals: Hospital Gineco-Obstetrico Nueva Aurora (HGONA), Hospital Gineco-Obstetrico Isidro Ayora (HGOIA), Hospital General Docente de Calderon (HGDC), and Hospital General Enrique Garces (HGEG). In addition, the University of Saskatchewan Ethics Committee approved this research project.

3.2.2 Participants:

To obtain the most accurate information, four health care professionals from the NICUs at HGOIA and HGDC, three from HGEG, and five from HGONA participated in this study. A recruitment meeting was held with each leader of the four NICUs with the aim of obtaining a list

of names of professionals nominated to participate in this survey. These professionals were selected because they were considered the most knowledgeable personnel in relation to the hospital's PN procedures. As such, the interview participants included physicians, nurses, pharmacists, and a dietitian. A total of sixteen professionals were asked to and consented to participate in the interviews.

3.2.3 Survey

The open-ended and closed-ended questionnaire was developed based on a literature review. The questionnaire was content validated by a pediatrician and a neonatologist at HGONA who did not participate in the study, and a pediatric surgeon, two dietitians and members of the research team. This questionnaire consisted of seven sections. The first section consisted of 12 short-answer questions which inquired about the number of hospital and neonatal beds, the number of patients admitted yearly and what percentage of these admissions are neonates below 2.5 kg, and the profession of the interviewee, their role, their years of experience, and their shift work. The second section inquired about the number of neonatal beds in each unit, including basic, intermediate, and intensive care units. This section also asked about the presence of laminar flow hoods used to compound PN.

The third section described the patient population of the neonatology area. The questionnaire inquired about the incidence of neonates and VLBW neonates on PN and the common reasons for initiating PN. Section four asked about the presence of an NST, its members, and their roles. Section five gathered information about parenteral nutrition design. The questionnaire included 27 questions which inquired about the methods used to prescribe, calculate, prepare, package, label, store, and administer PN; the clinical guidelines used to manage PN; the regimen of PN that is used most frequently; the doses of amino acids, dextrose, and lipids used to initiate PN; and the most frequent venous access line used to administer PN. Section six asked about the frequency of biochemical and anthropometric assessments of patients before beginning PN and after PN has been initiated. Section seven gathered data about the guidelines used to manage complications. The last section inquired about the health care professional responsible for discontinuing PN, the reasons for stopping this treatment, and the guidelines or protocols used to guide this aspect of the PN treatment (See Appendix A).

This survey contained eleven open-ended questions which allowed participants to fully explain potential changes, issues, or limitations during PN administration. Furthermore, these questions let them explain in detail what precautions are taken to avoid potential complications and errors. The open-ended questions included:

1. What are the barriers to having a functional NST?
2. Have there been any changes in the past five years in regards to the PN design? What?
3. Have you faced any difficulties, problems, or challenges during the period that you have been involved in PN administration? What?

3.2.4 Data Collection

All interviews were carried out individually and face-to-face except for one interview which was performed by phone. All interviews were conducted privately at an agreed upon location. Prior to the start of the interview, a brief explanation of the project was delivered, and a consent form signature was obtained for participation in the study and the creation of an audio-record of the conversation. All participants agreed to be interviewed and audio recorded. Questions were clarified if the participant required additional explanation. Then, all interviews were transcribed and translated from Spanish to English.

3.2.5 Addressing credibility in qualitative research

Some of the strategies suggested to assess trustworthiness in qualitative research are triangulation which is the use of multiple and different sources to corroborate evidence, peer review, in member checking which uses the participant's point of view of the confirmability of the findings, and rich description of the participants and environment (Creswell, 2006). In this study, the strategies used to assess the credibility of the findings included a detailed description of the participants and resources from the NICUs and triangulation. The sources used to corroborate the evidence include a medical record review and published PN clinical guidelines.

3.2.6 Data Analysis

In-depth interviews were audio recorded, transcribed, and translated verbatim. Closed-ended questions were presented as frequencies with their respective percentage and means with standard deviation. Open-ended questions were analyzed for content; thus, answers were coded and then a list of potential themes was created. Those themes represented participants' opinions regarding

parenteral nutrition practices during delivery of PN in their NICUs. All statistical analyses were performed using IBM SPSS Statistics 25 for Windows Server 2012 R2.

3.3 My experience during the study of parenteral nutrition practices in four hospitals in Quito-Ecuador

How are parenteral nutrition practices being developed in public hospitals in Quito, my home city? This question came to mind after working as a junior practitioner in one of the pediatric hospitals in Quito. Upon receiving a participation interest letter from one of the participant hospitals and the approval of my research proposal, the journey to find the answers to my inquiries had begun. My next step was to develop the main purpose of the study, which is to gain in-depth knowledge about PN practices and to help improve these practices, if necessary, for the hospitals participating in this project. At the end of several meetings and conversations with the representatives of the Academic Department and NICU in each hospital, three more hospitals expressed their interest in participating in this study and thus their willingness to open their doors to the opportunity to change and improve their parenteral nutrition practices. It is important to note that the study was originally proposed as a six-hospital participant project; however, two of these hospitals declined to participate due to the ongoing restructuring of their NICU's procedures. They expressed that the potential data collected will not accurately reflect their current practices.

With four participation interest letters issued by the four participating hospitals and a detailed research protocol proposal, the Ecuadorian Ministry of Health Ethics Committee through their representatives at the "Eugenio Espejo Hospital of Specialities Ethics Committee" issued a letter of approval on November 7, 2017. This letter approved the execution of this project in the four participating hospitals within the time frame of one calendar year. This approval letter guaranteed the researcher both logistic cooperation and the provision of the information required for this study by each hospital and its health care personnel.

Data collection was initiated immediately after obtaining the ethics approval letter from the Ecuadorian Ministry of Health Ethics Committee. The first hospital visited was the HGONA, our research partner in Ecuador. Ninety-eight neonate medical records were reviewed, and four health care personnel involved in TPN treatment were interviewed at this institution. Next, face-to-face interviews were conducted with all health care personnel at HGDC, HGEG, and HGOIA, except one interview with the dietitian which was performed via phone. Lastly, for approximately two months, 104 medical records were reviewed at HGOIA. Representatives and personnel at

these four hospitals provided all the support and transparency required to execute this project at their institutions.

The data collection was completed without major difficulty; however, there were three notable issues faced during this process. First, obtaining the participation letter from each hospital was a long and bureaucratic process. This is because, during the authorization process, directors and personnel at the NICUs held numerous meetings and discussions before finally granting their approval. Second, the long distance between hospitals, around one to two hours, posed a logistical challenge. This means that a significant amount of this study's time was invested in transportation. Finally, because the medical records were not digital and the majority were handwritten, interpreting the records and locating missing pages was time-consuming.

At its completion, this project and its execution provided an enriching research experience and a path to pursue my professional and academic goals. This project provided enormous satisfaction in that it has allowed me to contribute, if slightly, to the welfare of Ecuadorian neonate patients at the NICUs in the public hospitals in Quito-Ecuador. "The likely solutions for nutrition problems lie less in unlocking biological pathways than in creating...environments that can deliver correct balances" (Lang, 2005, p. 731).

3.4 Results

3.4.1 Closed-ended questions results

Sixteen health personnel at four NICUs in public hospitals in Quito were proposed by their respective supervisors. A 100% (16 out of 16) rate of participation was obtained since all proposed professionals accepted the interview invitation. After analyzing the hospitals' official records, we determined that the mean number of neonatal beds was 32 (SD 18.2). HGONA has 40 neonatal beds, HGOIA has 55, HGDC has 15, and HGEH has 21. Furthermore, by analyzing the available information from HGONA and HGOIA's NICUs, we discovered that there were 257 and 216 neonates receiving PN annually respectively. Unfortunately, the official records of the patients receiving PN in the remaining two NICUs were not available. The description of the NICUs and the annual number of neonates on PN are showed in Table 3.1.

Table 3.1 Description of the neonatal units and demographic population in four public neonatal units in Quito

	Mean	SD	Total
Number of hospitals	4		4
Number of NICUs	4		4
Participants interviewed	16		16
Hospital beds*	216	80.5	864
Neonatal beds*	32	18.2	131
Places of basic care**	9	15.5	36
Places of intermediate care**	16	6.8	64
Places of intensive care**	10	2.3	40
Neonates receiving PN annually***	236	28.9	514

PN=parenteral nutrition NICUs= neonatal intensive care units

*Information obtained from official records

** Information obtained from survey answers

*** Information obtained from official records (HGONA and HGOIA)

3.4.1.1 Demographic characteristics of the participants

Five participants (31%) were pediatricians, and four were nurses (25%). One dietitian (6%) participated in this survey. The years of experience of the participants in their health care area ranged from five to eleven years. The demographic characteristics and roles of the interviewees (n=16) are shown in Table 3.2.

Table 3.2 NICUs' personnel professional background and role description

Academic degree	n (%)	Experience mean (years)	Experience SD	Shiftwork mean (hours)	Shiftwork SD	Role
Neonatologist	3 (19)	11.5	8.3	24	5.1	Responsible of the shift
Pediatrician	5 (31)	7.6	5.1	23.6	3.5	Responsible of the shift
Pharmaceutical biochemist	3 (19)	10.7	8.9	8.5	0.5	<ul style="list-style-type: none"> • Compound PN and medication control (n=2) • Pharmacy leader (n=1)
Nurse	4 (25)	10.6	14.2	11.7	1.2	Provide direct care of the patient
Nutritionist	1 (6)	5		6		PN supervisor and head of milk bank in the hospital

SD= standard deviation PN= parenteral nutrition Nutritionist (Ecuadorian degree) = dietitian degree

3.4.1.2 Parenteral nutrition practices

Closed-ended questions and their respective responses are shown in Table 3.3.

Table 3.3 Parenteral nutrition practices in the NICUs

Question	Answer	n (%)
Does this hospital have a laminar flow hood to prepare PN? *	Yes	5 (31)
	No	8 (50)
	Do not know	3 (19)
Is there a nutrition support team (multidisciplinary team of nutritional support) in this hospital? *	Yes	3 (19)
	No	12 (75)
	Do not know	1 (6)
Who is the health professional that prepares parenteral nutrition formulations? *	Pharmacist	11 (69)
	Nurse	3 (19)
	Do not know	2 (12)
Do you use paper orders or digital orders?	Paper orders	16 (100)
Do you write this order manually or digitally? *	Digital	12 (75)
	Manual	2 (12.5)
	Manual/Digital	2 (12.5)
Where is PN prepared? *	Pharmacy	3 (19)
	NICU	7 (44)
	Operating theatre	2 (12)
	PN unit	1 (6)
	Do not know	3 (19)
Do you use any PN calculation software (ABACUS, Baxter) to calculate PN? *	Excel conversion spreadsheet	14 (88)
	Manual	1 (6)
	Excel conversion spreadsheet/manual	1 (6)
Are manual or automated compounding devices used (ACDs) to prepare PN formulations? *	Manual	10 (62)
	Do not know	6 (38)
How many days does the PN unit work?	Operate daily	16 (100)
If you prepare PN bags for days when the PN unit is not operating, please explain how you store them? *	Not store PN	13 (81)
	Kept in refrigeration	3 (19)
What kind of PN regimen do you use frequently?	Always individual	16 (100)
	Always standard (first 24h of life)	4 (25)
Are you using a published clinic guideline to manage the PN? *	Yes	6 (38)
	No	9 (56)
	Do not know	1 (6)
Do you use an unpublished PN guideline to manage PN? *	Yes	7 (44)
	No	7 (44)
	Do not know	2 (12.5)
Who makes the decision to cease PN?	Physician	16 (100)

PN= parenteral nutrition

* Response inconsistent between all members in the same NICU

When asked whether there is a laminar flow hood to prepare PN in their hospital, eight participants (50%) noted that their institution did not have one while five interviewees (31%) stated that their institutions have laminar flow hoods. The response of the four interviewees at

one NICU was inconsistent. One respondent noted that the unit used a laminar flow hood, two of the respondents said that there was no laminar flow hood in the NICU, and the fourth respondent did not know whether or not the unit used a laminar flow hood. Twelve participants (75%) denied the existence of NSTs in their institutions. In one of the NICUs, half of its participants asserted that there is an NST while the other half of their participants denied the existence of this team. In the other NICU that presented the same issue, one of the interviewees noted that they have an official NST team while the rest of their colleagues denied that their hospital had an NST team. Three participants (19%) of the participants opined that their NICUs had non-official NSTs. These respondents described the members of the non-official team as including physicians, nurses, pediatrician-nutritionist, pharmacists, and dietitian. Another participant noted that a physician, nurse, and pharmacist were members of this team while the last participant described a physician and dietitian as the team's members.

Twelve participants (75%) agreed that PN orders were written digitally. In one of the NICUs, there was a discrepancy in the responses: half of the interviewees declared that they write the order forms manually while the other half said that orders are written both manually and digitally. Seven participants (44%) noted that PN is compounded in the NICU. In two of the NICUs, there was inconsistency in the participants' responses. In one of the NICUs, one participant noted that PN is compounded in the pharmacy unit while another interviewee said it was compounded in the PN unit. In another NICU, half of its members noted that PN is compounded in the pharmacy unit while the other half said that it was compounded in the operating theatre.

Regarding the use of calculation software, fourteen interviewees (88%) noted that they use an Excel conversion spreadsheet make PN calculations. The automate order entry helps the professionals with maximum defaults for electrolytes and maximum osmolarity of dextrose solution. In one of the NICUs, there was a discrepancy between participants' answers. While two interviewees said their unit uses an Excel conversion spreadsheet, other participant responded that the unit uses manual calculations, and another said the calculations are determined both manually and using an Excel conversion spreadsheet. Thirteen participants (81%) denied storing PN formulations, and three participants (19%) asserted that PN is kept in refrigeration (-4°C). In one of the NICUs, while half of the interviewees noted that their unit did not store PN, the other half said that they did. All interviewees (100%) noted that their units prepared PN formulations daily.

Six interviewees (38%) asserted that they use a published guideline to manage PN treatment and seven participants (44%) noted that they use an unpublished guideline, such as consensus, the protocol of their NICUs, or the Ecuadorian Ministry of Health protocol. Finally, eleven participants (69%) noted that the pharmacist is the professional who compounds PN formulations and three interviewees (19%) noted that a nurse prepares the formulations.

3.4.1.3 Reasons for beginning and ceasing PN

Among the frequently cited reasons for neonates receiving PN treatment are a weight below 1.5 kg (88%), necrotizing enterocolitis (75%), and digestive intolerance (63%). Furthermore, the most common reason to cease PN was the patient commencing an oral diet or enteral feeds (81%) followed by when patients' requirements are met (44%) (Table 3.4).

Table 3.4 Parenteral nutrition reasons for beginning and ceasing PN

Reasons	n (%)
<i>Reasons for beginning PN</i>	
Neonates <1kg & <1.5kg	14 (88)
Necrotizing enterocolitis	12 (75)
Digestive intolerance	10 (63)
Risk of necrotizing enterocolitis	9 (56)
Gestational age	10 (63)
GI malformations	8 (50)
Short intestine	7 (44)
Malabsorption syndrome	7 (44)
Chylous leak	4(31)
Esophageal rupture	4 (31)
<i>Reasons for ceasing PN</i>	
Patients' requirements are met	7(44)
Patient commence on oral diet or enteral feeds	13 (81)
Referring medical team makes the decision to cease PN	3 (19)
When complications appear	2 (12)

PN= parenteral nutrition GI= gastrointestinal

3.4.1.4 Parenteral nutrition order forms

All four NICUs have developed their own Excel conversion spreadsheets which help them make accurate calculations. This method includes dose limit and electronic computations. After designing the PN treatments using Excel, legibly printed orders are obtained. Paper orders at the four NICUs typically contain patient information; PN treatment information such as components,

dose, and amount to be delivered; glucose infusion rate (GIR); calories provided; osmolarity; nonprotein and protein ratio; flux of drip; and the venous access site. Finally, this order form is signed by the professional who prescribed the PN (Appendix B). The Excel conversion spreadsheet format (not identical spreadsheet) used by all NICUs is shown in Figure 3.1.

COMPOSICIÓN	CONCENTRA CIÓN INICIAL	UNIDADES	PRESCRIPCIÓN	VOLUMEN	Volumen + Purga (ml)	DENSIDAD DEL COMPONENTE	PESO TEÓRICO POR COMP. EN LA MEZCLA SIN	PESO TEÓRICO POR COMP. DE LA MEZCLA CON	Unidad Equivale ntes (equivalente a administrar al paciente en 24h)
Dextrosa líquido parente	50	mg por Kg por día	4.00	0	15.6	27.3	1.17	18.20	gr
Aminoacidos sin Electrolytos	10	g por Kg por día	2.00	27.0	0.0	47.5	1.03	27.81	gr
Acidos Grasos (LIPIDUMIN 20%)	20	g por Kg por día		0.0	0.0	0.0	0.99	0.00	gr
Sodio 3 mEq/ml (como Cloruro)	3.4	mEq por Kg por día		0.0	0.0	0.0	1	0.00	mEq
Potasio 2.68mEq/ml (como Cloruro)	2.68	mEq por Kg por día	2.00	10	1.0	1.8	1	1.01	mEq
(como Fosfato de Potasio)		mEq por Kg por día		0.00	0.0	0.0	1	0.00	mEq
Cloro Total		mEq por Kg por día	2.00		0.00				mEq
K 3.8mEq/ml E.P. 2.8mEq/ml	2.6	mmol por Kg por día		0.00	0.00	0.0	1	0.00	mEq
Equivalente a un aporte de K		mEq por Kg por día	0.00	0.00	0.00	0.0			mEq
Fosforo Total		mEq por Kg por día	0.00	0.00	0.00	0.0			mEq
Glucosato de Calcio 100:	10	mg por Kg por día	600	0.0	8.6	15.1	1	8.62	mg
Calcio Elemental		mEq por Kg por día	2.974	0.0	0.0	0.0	1	0.00	mEq
Sulfato de Magnesio 200:	20	mg por Kg por día		0.0	0.0	0.0	1	0.00	mEq
Magnesio Elemental		mEq por Kg por día	0.25	0.000	0.2	0.4	1	0.21	mEq

Figure 3.1 Excel conversion spreadsheet format

3.4.1.5 Monitoring patients receiving PN treatment

Thirteen interviewees (81%) asserted that they perform a biochemistry assessment before beginning PN administration in neonate patients in their units while two participants noted that they did not (Table 3.5).

Table 3.5 Biochemistry assessment before PN administration

Biochemistry assessment	n (%)
Yes	13 (81)
No	2 (13)
Do not know	1 (6)

Nine participants (56%) described that complete blood count (CBC) is always performed before beginning PN in the patient. Two participants noted that the CBC is evaluated occasionally. Eleven interviewees (69%) stated that blood glucose levels are always assessed before beginning PN treatment in the neonate patient, while two individuals (13%) said that they did not know if blood glucose levels were always measured before the initiation of PN. Electrolytes measurement was the test most frequently assessed. Twelve participants (75%) noted that they always test the

electrolytes before beginning PN. The frequency of assessment of other tests, such as hepatic enzymes, total protein and albumin, urea and creatinine, vitamins and minerals, and cholesterol and triglycerides are shown in Table 3.6.

Table 3.6 Frequency of biochemistry assessment before PN administration

Biochemistry assessment before PN administration	Always n (%)	Mostly n (%)	Sometimes n (%)	Never n (%)	Do not n (%)
Frequency of CBC assessment	9 (56)	1 (6)	2 (13)	0 (0)	1 (6)
Frequency of blood glucose level assessment	11 (69)	0 (0)	0 (0)	0 (0)	2 (13)
Frequency of electrolytes assessment	12 (75)	0 (0)	0 (0)	0 (0)	1 (6)
Frequency of hepatic enzymes assessment	9 (56)	1 (6)	1 (6)	0 (0)	2 (13)
Frequency of total protein/ albumin assessment	9 (56)	2 (13)	0 (0)	0 (0)	2 (13)
Frequency of urea/creatinine assessment	8 (50)	1 (6)	3 (19)	0 (0)	1 (6)
Frequency of vitamins and minerals assessment	2 (13)	0 (0)	2 (13)	7 (44)	2 (13)
Frequency of cholesterol/triglycerides assessment	7 (44)	3 (19)	0 (0)	2 (13)	1 (6)

CBC= complete blood count PN= parenteral nutrition

Five (31%) and six interviewees (38%) interviewees stated fluid balance and blood glucose level respectively are assessed every 12 hours in patients on PN treatment; however, there is a disperse range of frequency of assessment mentioned by the participants (Table 3.7).

Table 3.7 Assessment of fluid balance and blood glucose level in patients on PN

Assessment in patients on PN	n (%)
Fluid balance	
At least once a day	2 (13)
Every 12 or 6 hours	1 (6)
Every 12 hours	5 (31)
Every 8 hours	2 (13)
Every 12 hours or once a day	1 (6)
Every 8 or 12 hours	1 (6)
Every 3 or 6 or 12 hours	1 (6)
Do not know	3 (19)
Blood glucose level	
At least once a day	1 (6)
Every 3 or 6 or 12 hours	1 (6)
Every 12 hours	6 (38)
Every 8 hours	2 (13)
Every 8 or 12 hours	1 (6)
Every 6 hours	1 (6)
Every 6 or 12 hours or once a day	1 (6)
Do not know	3 (19)

3.4.1.6 Prescribed Macronutrients

Regarding amino-acid prescription, eleven participants noted that a range of amino-acids was provided from 1 to 4 g/kg per day in preterm neonates. Similarly, participants asserted that the appropriate range for this macronutrient in term neonates is 1 to 3.5g/kg per day. A range of glucose infusion rates, from 3.5 to 8 mg/kg per minute, is used to initiate PN in both preterm and term neonates according to the participants' responses. Finally, nine interviewees (56%) noted that they use a 20% lipid emulsion and that the dose range used is from 0.5 to 4 g/kg per day in preterm neonates and from 1 to 3g/kg per day in term neonates (Table 3.8).

Table 3.8 Prescribed macronutrients

Prescribed macronutrients	Preterm neonates n (%)	Term neonates n (%)
Amino-acids (g/kg per day)		
1.5 to 3.5	1 (6)	
1	1 (6)	
2 to 2.5	1 (6)	
2	1 (6)	
2 to 3	1 (6)	2 (12)
2.5	1 (6)	
3	1 (6)	
3 to 3.5	1 (6)	
3.5	1 (6)	2 (12)
3.5 to 4	1 (6)	1 (6)
4	1 (6)	2 (12)
1 to 3		
Do not know		
Do not use	5 (32)	1 (6)
		5 (32)
		3 (19)
Glucose Infusion rate (mg/kg per min)		
3.5 to 8	1 (6)	1 (6)
4 to 6	4 (25)	5 (32)
5 to 7	1 (6)	
4 to 8	1 (6)	
6	2 (13)	
5 to 6	1 (6)	1 (6)
Do not know		1 (6)
Did not mention	6 (38)	6 (38)
		2 (12)
Type of lipid emulsion		
10%	3 (19)	3 (19)
20%	9 (56)	9 (56)
10% & 20%	1 (6)	1 (6)
Do not know	3 (19)	3 (19)
Lipid (g/kg per day)		
0.5 to 3	1 (6)	
1	2 (13)	2 (13)
1 to 2	1 (6)	
1.5 to 2	1 (6)	
2 to 2.5	1 (6)	1 (6)
2 to 3	1 (6)	1 (6)
3	2 (13)	3 (19)
3 to 4	1 (6)	1 (6)
Do not know	1 (6)	
Do not use it	1 (6)	
Did not mention	5 (32)	5 (31)
		1 (6)
		2 (13)

As shown in Table 3.8, there is no consensus between health professionals with respect to the range of amino-acid dosages used to begin PN in preterm and term neonates. A similar

situation is observed when participants describe the range of glucose infusion rates and lipid dosages used to initiate PN in neonates. Raw data of this survey is shown in Appendix C.

3.4.2 Open-ended questions results

All open-ended question answers were listed by question and profession to provide a more nuanced appreciation and comparison. Nine essential, nonredundant themes arose from this data. Each theme is listed and described using direct quotes from the individual interviewed.

Theme 1: Physical and service changes in the NICUs

Thirteen of sixteen interviewees expressed that there have been changes regarding the number of beds /incubators or places of care in their units and the availability of laminar flow hoods to prepare PN. There were two specific areas of change. One area of change is alterations to the hospital's and unit's physical space. There have been increased numbers of beds or places of care, units, and changes in the infrastructure of their NICUs. Additionally, one institution acquired a laminar flow hood to prepare PN exclusively.

"We implemented the Canadian standards of care accreditation to improve our service. There was a remodelling process of the Intensive, Intermediate, and Basic Care Units".

Two physicians, one at the HGOIA and one at the HGEG, and one pharmacist at the HGDC, denied changes in their institutions.

The second area of change involves changes in the services provided. Interviewees noted that a cholestasis protocol had been introduced in one NICU, and the majority of the interviewees agreed that there had been an increase in the demand for services and, for that reason, an increase in the number of patients admitted in their NICUs.

"Many changes have occurred because this hospital has only been operating for three years. Every year there are great changes in infrastructure and the protocols implemented. This is a new hospital, so it changes constantly."

Theme 2: Availability is one change regards to the number of patients on PN and the reasons to begin PN.

Ten of sixteen interviewees expressed that there have been changes to the number of patients receiving PN in their units and the reasons used to initiate PN. There were changes in the availability of PN support in their NICUs for all neonates below 1500g or premature neonates. Interviewees also noted increased availability of early PN support, specifically the early delivery of lipids and amino-acids during the first 24 to 48 hours of life. As a result of the improved

availability of PN support, there has been an increase in the number of patients receiving PN in their respective NICUs. Finally, an Excel spreadsheet format to help health personnel make PN calculations accurately has been introduced.

"Yes, there have been changes. Previously TPN was delivered as it was believed necessary. Today we have established that bellow 1500g, we initiate TPN. Also, there has been a change regarding initiating TPN as early as possible on the first day of life. We have established a new protocol to treat cholestasis whereby we initiate TPN in cycles".

Two physicians at the HGEG, one pharmacist at the HGDC, one nurse at the HGEG, one nurse at the HGOIA, and a dietitian at the HGONA denied changes.

Theme 3: Shortages and PN training are the barriers to developing a functional Nutritional Support Team from humble beginnings

Twelve of sixteen interviewees expressed that there are two main barriers to developing a functional NST in their institutions. One of the limitations is the shortage of some elements needed to implement this team, including personnel, funding, and physical space. In addition, there are PN training barriers. Interviewees noted that there is a lack of familiarity with NSTs and their role in neonatal nutrition. Also, the respondents noted that an NST would require specifically trained personnel who exclusively participate in the nutritional support of neonate patients.

"I think the main limitation is the hospital's budget because an exclusive team should provide TPN. We, as pharmacists, know the necessity of this team and have tried to adapt the way we work. There should be an exclusive budget for a TPN pharmacist because we are contracted to work with a unit and TPN is an additional task that we must perform. We need more exclusive personnel to prepare therapies including physicians and nutritionists who work exclusively with nutritional therapy".

Three physicians, one at the HGONA, one at the HGOIA and one at the HGDC, and a nurse at the HGONA did not answer this question.

Theme 4. Compounding and Calculation changes in the PN treatment

Ten of the sixteen interviewees expressed that there are two main areas of change in their institutions. One area of change is in the PN compounding process. Most interviewees agreed that new personnel were involved in PN treatment. Initially, pharmacists did not participate in the PN process, but now they are an important part of the PN treatment. Also, respondents referred to changes in the roles of nurses and pharmacists. They noted that previously nurses compounded PN; however, currently, pharmacy personnel are responsible for compounding and preparing PN.

Additional reported changes included the acquisition of laminar flow hoods and the introduction of software to compound and calculate PN.

"Previously, the nurses prepared TPN. They were trained to do so. In this hospital, we did not provide a TPN but partial PN. Thus, we avoided administering lipids because there was a major risk of infection in the patients. TPN was restricted for that reason. Since there are a laminar flow hood and a better-organized pharmacy unit, we can use Total PN".

Five physicians, two at the HGONA, two at the HGEG, and one at the HGDC, and a nurse at the HGEG denied changes in their units.

Theme 5. Potential errors and measures to prevent them

All participants expressed that there have been errors related to the prescription, submission, and transcription of PN orders. Other errors were found on PN labels. Some interviewees noted that label information did not match the prescription. There have been errors in the PN schedule, and on some occasions, the PN did not last until the time stated on the prescription. In some units, measures have been taken to prevent potential complications related to PN treatment. Interviewees noted that their units now double check the patient information and dose, use sterile protocols, take PN cultures, and perform visual inspections of the PN bags. At the HGOIA, personnel specified performing other measures such as gravimetric analysis and microbiological tests.

"Sometimes the TPN prescription does not reach the pharmacy unit and is not prepared, which is inconvenient. When the TPN prescription does not reach the pharmacy unit, the TPN bag does not arrive (a missing TPN). Prescriptions should arrive in the morning to be prepared. When we receive TPN bags, we record their weight because we had an issue with TPN bags ending before their programmed time. We observe the appearance of the bags to verify that they are well sealed and do not have cracks. Also, we observe any extravasation in the patient. If the neonate does not require TPN or if we have concerns about the TPN quantity, we communicate with the physician"

Theme 6: Calculating, compounding, and administrating changes in the parenteral nutrition design

Thirteen of sixteen interviewees expressed that there are three main areas of change in their institutions. One area of change is in the PN calculation process. Mostly they agreed that new software was implemented to make PN calculations. Another area of change was to the PN compounding process; notably, changes to the pharmacists' and nurses' roles have occurred. Currently, the pharmacist compounds PN. Finally, there have been changes in the administration process. Participants noted that there has been earlier lipids administration. In addition, a higher

dose of macronutrients is currently used in PN administration. Finally, some respondents noted heparin disuse in their units.

"We try to initiate PN with higher values because we previously initiated with low values, around 0.5, and we performed slow increases. Thus, we did not reach the basal values to supply the needs of the patient, at least the protein. As I told you, we initiated with 0.5 mg of amino acids and lipids, for two or three days. On the fifth day, we would increase to 1mg. It was a slow TPN process".

One physician at the HGEG, and one pharmacist and a nutritionist at the HGONA denied changes in their units.

Theme 7: Complication management depends on patient needs.

In general, interviewees noted that if they observe complications related to PN, they discontinue its use. Nurses and pharmacists noted that they communicate these complications with the physician.

Hyperglycemia and Hypoglycemia Management

This was primarily addressed by physicians and nurses. They noted that if they observe hyperglycemia, they decrease or regulate the flux of PN or discontinue it until normal levels are restored. Interviewees noted that if they observe hypoglycemia in the patient, they increase or regulate the PN flux or discontinue its use.

Cholestasis Management

If cholestasis is observed in the patient receiving PN, physicians decrease the lipids and amino-acids, deliver the PN in cycles or discontinue the PN.

"It depends. For example, in hyperglycemia, I decrease the flux of glucose or discontinue the TPN. For hypoglycemia, I pass a dextrose bolus and increase the contribution of glucose or discontinue the TPN. For cholestasis, we just provide amino acids in the TPN and provide lipids twice per week. For patients with sepsis, we do not discontinue the TPN."

Sepsis Management

In the case of potential sepsis in patients receiving PN, physicians noted that they investigate all access to the patients. They perform a urine culture, stool culture, secretion culture, etc. The physicians' opinions regarding their responses to complications related to PN were very similar. Nurses and pharmacists agreed that they report these issues to physicians.

"If there is cholestasis, we stop the lipids. If there is sepsis, we investigate all access to the patient because TPN cannot cause this condition. For example, if the patient is in a mechanical ventilator and doing physiotherapy, that is probably how they were exposed to a microorganism. In the case of hyperglycemia or hypoglycemia and we suspect sepsis, we discontinue the TPN and provide the patient with adequate dextrose."

Theme 8: Cholestasis and hyperbilirubinemia management has changed in the NICUs

Only six participants expressed that there have been changes regarding the management of complications related to PN in their institutions. These participants expressed changes in the management of two specific complications. One of these complications is cholestasis. The respondents noted that a new cholestasis management protocol had been implemented in their units. Also, they noted that there had been an update to the criteria for the diagnosis of cholestasis. Finally, they mentioned that when a patient is diagnosed with cholestasis, they deliver a partial PN or deliver the PN in cycles to manage the complication. The other complication related to PN administration that was noted by interviewees was hyperbilirubinemia. Respondents asserted that new diagnostic charts were implemented in their NICUs. All of these changes were implemented in order to avoid complications in the neonate patient.

"Now, during cholestasis evaluation, we do not only evaluate direct bilirubin, we evaluate GOT GPT GGT to begin to reduce the TPN infusion, give an alternate TPN cycle or use a medication to help us manage the condition."

Theme 9: Personnel, training, protocol, physical space, and resources are the challenges faced by the participants

When asked about difficulties, problems, or challenges during the period that they have been involved in PN administration, all interviewees asserted that they had faced such challenges, except one physician at the HGEG who denied experiencing any problems during PN administration. Participants noted that they experienced difficulties related to the health care personnel involved in this treatment. They said that more specialized personnel are required to administer PN treatment in their units. Some of the interviewees said that in order to provide better quality PN treatment, an NST is needed in their unit.

"Now, what is needed is a nutritional support group to work towards excellence in TPN administration, calculations, and compounding, of course. Currently, we have a pharmaceutical biochemist, physician, and nurse on the shift, but not an exclusive person to administer the TPN treatment. A nutritional support team should exist. If this is the optimal method, we should use it. If I am working in a third level hospital, there should be a multidisciplinary team".

Also, they noted that more thorough and up-to-date training to address PN and PN complication management is needed to help unit personnel improve their skills.

"I believe that we need to study cholestasis cases more closely to determine whether to immediately stop the lipids or whether we need to decrease them progressively. I mean we need more training in cholestasis management. Also, training about caring for patients who received TPN for the short and long-term."

In order to standardize the procedures related to PN treatment, interviewees suggested that the development of PN management protocols is required in their NICUs.

"Despite that, we do not have a protocol, we have our methods well established for managing our patients. This is because we review the literature. We have no written protocol, but we have our management methods. It's likely that developing a protocol will be a necessity. We need to record our methods because there are guidelines that we have reviewed and used in the unit".

Participants also noted problems related to their NICUs' physical space and resources. Some respondents declared they lack an appropriate physical space for PN treatment compounding. An additional challenge noted by interviewees was the need for a laminar flow hood to compound PN in order to provide patients PN that meets sterile standards.

"We always have the ingredients to compound TPN formulations. We never have problems regarding the material provisions. In order to meet the aseptic norms, it is necessary to have a laminar flow hood to prepare the TPN".

3.5 Discussion

PN is used to improve health outcomes of VLBW and ELBW infants by promoting their growth and development thereby improving their health and likelihood of survival. Our findings indicate that the lack of a formal and functional NST is common in the observed NICUs and that there is little participation from dietitians in PN treatment. The absence of nutritional professionals was clear as there was only a single dietitian working at one of the four NICUs in this study. Our results replicate the findings of Katoue et al.'s survey (2016) study in which they found that none of the seven participating NICUs in Kuwait had an active NST, and similarly, dietitians had little participation in PN treatment (Katoue et al., 2016). Likewise, Hill's survey (2015) found that more than a half of South Africa's NICUs had no official NST and 50 % of dietitians worked jointly with physicians to support nutrition decision making (Hill, 2015).

In NICUs where there is no formal NST, physicians had extensive involvement in PN treatment. Katoue et al. (2016) pointed out that physicians in non-NST NICUs performed several duties, including making PN clinical decisions, and ordering and ceasing PN treatment (Katoue et al., 2016). Even compounding and monitoring patients on PN treatment was performed by the chief resident in an NICU in India (Chaudhari & Vaidya, 1988). However, ASPEN guidelines recommend that the NST, a multidisciplinary team comprised of physicians, dietitians, pharmacists, and nurses who coordinate the provision of PN, should ensure that PN treatment meets the quality and safety guidelines (Mirtallo et al., 2004). Knowledgeable dietitians included on NSTs at NICUs can assist in the improvement of the nutritional statuses and growth rates of

neonate patients (Sneve, Kattelman, Ren, & Stevens, 2008). This strategy is seen in many ICUs globally. Porcelli's study (2004) indicates that five of eight NICUs in North Carolina employ experienced neonatal dietitians who assist decision support (Porcelli, 2004). However, in our study, when participants described the professionals involved in PN treatment, we discovered that dietitians rarely carry out nutritional decision-making in NICUs. Only one of the NICUs in our study had a dietitian who was deeply engaged in PN treatment.

Similarly, an experienced pharmacist acting as a member of the NST is vital to ensure effective and safe PN treatment. Our study found that PN formulations were most often prepared by pharmacists; however, there was a small percentage of participants who indicated that the nurse staff compound the PN in their unit. These findings differ somewhat from Katoue et al.'s research (2016) which noted that in the studied NICUs in Kuwait, the pharmacist compounds PN formulations (Katoue et al., 2016). However, our findings indicate that approximately 70% of the PN treatment was compounded by pharmacists and 20% by nurses. These results replicate the finding of Neves's study (2014) which indicated that 76% of compounding was performed by pharmacy staff and 23% by nurse staff. (Neves, Pereira-Da-Silva, & Fernandez-Llimos, 2014). According to ASPEN guidelines, the pharmacist must be the professional who prepares, labels, stores, dispenses, and distributes PN formulations (Mirtallo et al., 2004). Based on their knowledge and expertise, pharmacists can carry out a pharmaceutical review of PN formulations ensuring the appropriateness and compatibility of the PN elements (Boullata, 2012).

In developed countries, it is more likely to observe NSTs providing PN treatment. Thus, studies performed by Sneve et al. (2008) and Traeger et al. (1986) noted significant positive outcomes in patients, such as higher growth rates and higher prescriptions of lipids, protein, calcium, phosphorous and sodium after implementing an NST. These teams are most often comprised of a physician, pharmacist, nurse, and dietitian in North American NICUs (Sneve et al., 2008; Traeger et al., 1986). However, there are still some NICUs in developed countries that report the absence of NSTs in their units. This is the case in many Australian NICUs where a nationwide survey found that more than half of these units did not have an NST (Ali et al., 2006). In our study, most of the participants pointed out that PN treatment is provided by a group of health professionals from different backgrounds, such as physicians, pharmacists, and nurses; however, these teams are not formally recognized in their institutions as NSTs, and their duties were not exclusively related to providing nutrition support. As the respondents opined, the lack

of a recognized NST was likely primarily due to the shortage of financial and human resources in their institutions.

Similarly, the lack of financial resources may account for the reason that only five of the sixteen participants noted that their units had a laminar flow hood designated for preparing PN treatment. Four of these five participants noted correctly that their NICU features a laminar flow hood. Of these five participants, the remaining participant asserted incorrectly that his NICU had a laminar flow hood while his colleagues, correctly, denied that their NICU had this device. Inconsistencies noted in this and other responses may result from health professionals lacking in-depth participation in their respective NICUs' PN practices.

Similarly, Chaudhari and Vaidya (1988) found that the PN formulation in their NICUs was not conducted under a laminar flow hood (Chaudhari & Vaidya, 1988). Nevertheless, twenty years later, the same researcher reported that the sepsis rate decreased after the implementation of a laminar flow hood and training on aseptic procedures (Chaudhari, & Kadam, 2006). Recognizing potential opportunities for advancement is the first step in improving practices and outcomes. The Institute for Safe Medication Practices' guidelines for safe preparation of compounded sterile preparations (CSP), including PN formulations, points out that a compounding area must have a laminar flow hood and that the preparing professional should not prepare multiple CSPs concurrently (Institute for Safe Medication Practices, 2016).

Our study indicated that seven out of sixteen interviewees follow protocols or consensus developed by their units or by the Ecuadorian Ministry of Health. Six out of sixteen participants referred to published guidelines, which differs from Katoue et al.'s findings. This study found that six out of seven pharmacists used protocols developed by their NICUs and, additionally, most also referred to ASPEN guidelines to manage PN treatment (Katoue et al., 2016). Similar to Katoue's findings, Alli (2006) noted that three-quarters of their study's participants said that their NICUs had a hospital protocol for PN management (Ali et al., 2006). ASPEN and the British Association of Perinatal Medicine suggest that the potential complications associated with PN treatment may be decreased by the use of PN guidelines and a regular audit process (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016). When the interviewees were asked about potential errors during PN practices and measures they take to prevent PN-related risks, the majority of participants of one NICU mentioned that as a part of preventive measures, their units

perform regular audits of PN formulations. However, audit practices during other stages of the PN process were not described (e.g., ordering, labelling, storing, administering).

In our study, the vast majority of professionals involved in PN treatment noted that they referred to either published guidelines, such as ESPGHAN, ASPEN, Asociacion Espanola de Pediatria, SIBEN, or unpublished guidelines, such as protocol or consensus for better PN practices. The use of these guidelines demonstrates our studies' participants' desire to provide a quality PN treatment; however, this may provide an opportunity for improvement for NCIUs to unify their practices and develop protocols based on published guidelines that meet the needs of their neonatal populations.

Our study also found that the range of amino acids (1 to 4g/kg/day) prescribed to preterm and term neonates at the beginning of their PN treatment is within the range recommended by ESPGHAN guidelines; however, the minimum dose prescribed to infants was slightly lower than the 1.5 to 3-4g/kg/day proposed by these guidelines (Koletzko et al., 2005). Other guidelines, including ASPEN, the British Association of Perinatal Medicine, and the Nutritional Care of Preterm Infants' guidelines, recommend higher minimum doses of amino acids at the beginning of PN treatment than the ESPGHAN guidelines. (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). Similarly, the range of lipids administered to preterm neonates by our study's participants was within the ESPGHAN range for preterm neonates which proposes minimum values of 0.25g/kg/day; however, doses administered to term neonates during our study were considerably higher than the doses proposed in these guidelines (Koletzko et al., 2005). Conversely, the ASPEN and the British Association of Perinatal Medicine, and the Nutritional Care of Preterm Infants' guidelines propose initiating PN with higher minimum values (2 to 3g/kg/day) of lipids for preterm and term infants (Mirtallo et al., 2004; British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014).

The glucose infusion rate ranges reported by interviewees are within the range recommended by the ESPGHAN guideline (4 to 8mg/kg/min) (Koletzko et al., 2005). However, the British Association of Perinatal Medicine and the Practice of Parenteral Nutrition in VLBW and ELBW Infants propose ranges with higher maximum doses from 4 to 12mg/kg per minute (British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). Our results reveal that study participants, for the most part, prescribe macronutrients, amino acids, glucose, and lipids according to published guidelines, most often the ESPGHAN guidelines.

Another finding of our study is that all of the NICUs developed an Excel conversion spreadsheet to help professionals automate entering and ordering PN solutions to avoid potential errors during the prescription of this treatment. Although the four NICUs are not using the same PN order form to prescribe PN and the information included in the Excel conversion spreadsheet varies, generally the ordering process at these NICUs could be considered standardized. Similarly, in their study Puangco, Nguyen, and Sheridan described the process of automating order entries and calculations in their institutions. Dietitians, pharmacists, and computer programmers developed PN software using tables and algorithms. This software assists the prescriber by providing maximum defaults for electrolytes and maximum osmolarity for dextrose solutions based on the venous access site used to deliver PN treatment. From a separate calculation entry, the appropriate dextrose, amino acid, and lipid levels are provided (Puangco, Nguyen, & Sheridan, 1997). In our study, participants, as noted previously, developed a conversion spreadsheet to calculate the appropriate maximum and minimum defaults for the PN ingredients to avoid catastrophic overdose complications.

Evidently, NICUs develop automated order entry systems according to their PN formulations to improve the quality of treatment. Lehmann, Conner, and Cox (2004) found that the development of an online PN order entry system at the NICU in Johns Hopkins Hospital allowed the NICU to decrease calculation errors and osmolarity beyond the range during the ordering process (Lehmann, Conner, & Cox, 2004). However, there are some NICUs at which the prescription process is still handwritten. Katoue et al. (2016) found that there were issues, including legibility and missing or inadequate ingredient amounts, on handwritten order forms at NICUs where automated ordering was not implemented (Katoue et al., 2016).

Finally, through this survey, our study found that the vast majority of interviewees reported performing a biochemistry assessment before initiating PN treatment in a patient. The most frequently performed test assessed the patient's electrolytes, blood glucose level, and CBC. In patients undergoing PN treatment, the fluid balance and blood glucose level were assessed approximately every 12 hours; but nevertheless, our respondents reported a disparity in the range and frequency of assessments within these parameters. The British Association of Perinatal Medicine recommends regular monitoring of patients receiving PN. These guidelines propose a weekly anthropometric assessment which measures the infant's length and head circumference, and daily measurement of the patient's weight during the first week of life. Similarly, during the

first week of a neonate's life, the fluid balance, electrolytes, proteins, and bilirubin tests must be performed daily, and blood glucose level monitoring must be performed every six or eight hours (British Association of Perinatal Medicine, 2016).

Statistically, VLBW, ELBW, and preterm neonates can die or suffer severe life-long consequences, including poor health and early mortality, if they do not receive adequate nutritional treatment. PN practice literature in the developing world, including Ecuador, is notably inferior to that of developed countries. For this reason, our findings provide insight into PN management in a country that has not been previously described in the literature. Understanding the experience of NICUs in countries that lack resources for providing PN has the potential to help improve these NICUs' PN practices. Our Ecuadorian study's results have the potential to help improve PN practices in other developing countries that face circumstances similar to those in Ecuador. Globally, NICUs in developing countries may find our research relevant to their situations which may allow them to deliver better PN care.

3.5.1 Limitations

Due to the study's limited timeframe and logistical challenges, the questionnaire was not validated for question validity. This limitation may result in the exclusion of some questions that were not adequately discussed and questions that were out of the range of some participants duties.

Our study's considerable quantity of data was challenging to manage. This is an established limitation of the grounded theory method and a limitation of our study.

3.5.2 Recommendations

Our study found previously unknown information which allowed us to understand and formulate a theory about practices in the four NICUs in Quito. It was gratifying to discover that most of the professionals deeply involved in the prescription of PN base their practice on published or unpublished guidelines; however, there are still opportunities for quality improvement. As described in the discussion section, regular auditing of PN practices should be a mandatory part of the PN program to identify and correct deficiencies. In addition, the creation of an NST which exclusively provides nutritional support and the development of protocols or consensus that translates into unified criteria has the potential to help professionals from different backgrounds better serve their neonate populations.

Furthermore, the implementation of a laminar flow hood will help the PN compounding process meet the published safety recommendations. Also, as was mentioned in the discussion section, the ordering process could be considered standardized at the studied four NICUs. However, regular inter-hospital meetings between NICU professionals with the aim of sharing experiences and resources will further help these NICUs standardize the entire PN process. This unified practice between the NICUs could allow hospitals to make considerable quality and safety improvements. Further in-depth research on the PN compounding process is needed to allow researchers to better understand how pharmacists and nurses manage this important step of the PN treatment.

3.6 Conclusion

The PN practices in the four NICUs in Quito were not previously documented in the literature. Through this study, we discovered that the PN practices in these units are similar to many of the practices described in studies on PN practices in NICUs in developing countries. Our study shows that NICUs in Quito similarly refer to guidelines or protocols; therefore, the ranges of amino acids, lipids, and glucose infusion rates are within the ranges proposed by recognized guidelines. Nevertheless, our study found that there are opportunities for safety and quality improvement. Awareness of these opportunities will allow NICUs to fill gaps in their procedures to ensure better practices and, therefore, safer PN treatment. The absence of an official NST in some of the NICUs is one such opportunity for improvement. Furthermore, only half of the NICUs have developed a PN protocol or consensus to assist them in providing PN treatment. Finally, this survey found that a small percentage of NICUs have a laminar airflow hood in the compounding area for PN formulation.

4. PRESENCE OF COMPLICATIONS RELATED TO PARENTERAL NUTRITION TREATMENT IN NEONATE PATIENTS RECEIVING THIS TREATMENT: A RETROSPECTIVE CHART REVIEW

4.1 Objective:

Examine the prevalence of the most common complications associated with PN in patients who received PN

4.2 Methods:

4.2.1 Methodology

The inpatient medical records of infants undergoing PN treatment, from June 1, 2016, to June 30, 2017, were reviewed. Neonate patients were selected as they are one of the main patient populations who receive parenteral nutrition treatment. This retrospective medical record review was conducted to determine the prevalence of hypoglycemia, hyperglycemia, PN-associated cholestasis (PNAC), and central line-associated bloodstream infections (CLABSI) in neonatal patients undergoing PN treatment. In assessing the credibility of the interview findings, this retrospective medical record review and PN guidelines allowed us to corroborate them.

Patient medical records from HGDC and HGEG were not reviewed because they were not provided by their respective NICUs. Meanwhile, the medical records department and NICUs at HGOIA and HGONA provided the official records of patients who received PN treatment, paper health records, and an appropriate place to review these records. Through their representatives at the “Eugenio Espejo Hospital of Specialities Ethics Committee,” the Ecuadorian Ministry of Health Ethics Committee approved this project for all participating hospitals: HGONA, HGOIA, HGDC, and HGEG. All hospitals involved in this project agreed to contribute to the improvement of PN practices in their institutions and agreed to participate in this study. In addition, the University of Saskatchewan Ethics Committee approved this research project.

4.2.2 Sample

In order to obtain the research population, inclusion and exclusion criteria were applied to the medical records of neonates who received PN treatment. For the power calculation of the sample size, a ninety-five percent level of confidence and a five percent margin of error were proposed. Finally, 98 and 104 medical records of neonate inpatients admitted to the HGONA and HGOIA's NICUs from June 1, 2016, to June 30, 2017, inclusive, who were less than 28-days-old and had received one round PN treatment for more than three consecutive days were randomly selected from a list in excel.

4.2.3 Inclusion criteria

All the medical records of neonate patients who had received one round of PN treatment from June 2016 to June 2017, who were less than 28-days-old, and who had received more than three consecutive days of PN treatment were included in the population.

4.2.4 Exclusion criteria

Infant patients with congenital hepatic or biliary disorders, major cardiac anomalies, or other congenital or acquired disorders associated with hepatic disease, who were more than 28days-old, who had received less than three days of PN treatment, or more than one round of PN treatment were excluded from the population.

4.2.5 Analytic Methods

The prevalence of hyperglycemia, hypoglycemia, and PNAC in neonate patients at HGONA and HGOIA was determined by examining the laboratory reports and biochemical tests. Based on the AAP cut-offs, hypoglycemia was defined as serum concentrations of glucose less than 45mg/dL (2.5mmol/L) and hyperglycemia as serum concentrations of glucose over 150mg/dL (8.3mmol/L) or over 125mg/dL (6.9 mmol/L) in blood glucose concentrations in one or more occasions (Adamkin, D. ,2011; Hwang, Newman, Philla, & Flanigan, 2018). In this study, the prevalence of PNAC in neonate patients was defined as a conjugated bilirubin \geq 1mg/dL (17.1 umol/L) as the AAP considers abnormal conjugated bilirubin as a conjugated bilirubin concentration over 1mg/dL (17.1umol/L) when the total bilirubin (TB) is at or below 5mg/dL (85umol/L) or over 20% of the TB when the TB is higher than 5mg/dL (Maisels et al., 2004).

Although the term direct bilirubin and conjugated bilirubin are not synonymous, the term conjugated bilirubin is used in this study.

The Centers for Disease Control and Prevention (CDC) defines CLABSI as “a primary bloodstream infection (BSI) in a patient that had a central line within the 48-hour period before the development of the BSI and is not due to an infection at another site...The CLABSI surveillance definition overestimates the true incidence of CRBSI” (O'Grady et al., 2011, p 20). The National Center for Biotechnology Information outlines that the evaluation of CLABSI requires a blood culture for organisms that are not commonly present on the skin, and two or more blood cultures for organisms that are commonly present on the skin (Haddadin & Regunat, 2018). The etiology of CLABSI involves organisms such as gram-positive bacteria (coagulase-negative Staphylococci, enterococci, and Staphylococcus aureus) gram-negative bacteria (Klebsiella, Enterobacter, Pseudomonas, E. Coli, Acinetobacter) Candida, and others (Atilla, Doğanay, Kefeli Çelik, Demirağ, & Kiliç, 2017; Haddadin & Regunat, 2018). In this study, CLABSI was determined by the presence of a positive blood culture reporting growth of any of the previously described pathogens in patients receiving PN treatment.

4.2.6 Statistical Analysis

Biochemical results and microbiologic data were presented as a frequency with its respective percentages and averages, standard deviation, minimum and maximum values. Chi-square and independent t-tests were performed to test for significant differences between the two hospitals. All statistical analyses were performed using IBM SPSS Statistics 25 for Windows Server 2012 R2.

4.3 Results

4.3.1 Medical records review results

4.3.1.1 Demographic characteristic of the patients on PN

From June 2016 to June 2017, 279 neonate patients received PN at HGONA and 235 at HGOIA. To determine which patients met the inclusion and exclusion criteria, all medical records of neonate patients who received PN treatment were reviewed at both hospitals. At HGONA, 128 patients met the criteria, and 142 patients met the criteria at HGOIA. At HGONA, the sample size consisted of 98 records, and the sample size at HGOIA consisted of 104 records. The gender

distribution in the HGONA records was 57 male patients (58%) and 41 female patients (42%). In the HGOIA records, there were 47 male patients (45%) and 57 female patients (55%). A Chi-square test of goodness-of-fit was performed to determine whether there is a statistical difference between gender populations in both hospitals. The gender population was equally distributed between both hospitals, $p=0.065$ (Table 4.1).

Table 4.1 Gender distribution in HGONA and HGOIA

Gender	HGONA n (%)	HGOIA n (%)
Male	57 (58)	47 (45)
Female	41 (42)	57 (55)

The mean weight when initiating PN treatment at HGONA was 1832 (SD 628.5) grams, while at HGOIA the mean weight was 1637 (SD 628.3) grams. The weight of patients at the beginning of PN treatment at HGONA was statistically higher compared to the weight of patients at HGOIA, $p=0.029$. Similarly, birth length was statistically higher at HGONA, 42cm (SD 4.0) compared to the patients' length at HGOIA, 40cm (SD 4.3), $p=0.010$. Although the weight of neonates upon completion of their PN treatment was not statistically different between both NICUs, $p=0.202$, weight gain was higher for HGOIA's patients: 149 grams compared to 68 grams of weight gain in HGONA's neonates. Gestational age was measured by the Capurro method. Birth weight did not differ significantly between the hospitals, $p=0.112$ (Table 4.2).

Table 4.2 Neonate population's gestational age, weight, and length

Variable	HGONA		HGOIA	
	Mean (min-max)	SD	Mean (min-max)	SD
Gestational age (weeks)	34.1 (28-42)	2.7	34.0 (28.3-40)	2.5
Birth weight (g)	1906 (815-4190)	640.6	1759 (640-3570)	665.1
Weight begin PN (g)*	1832 (815-4460)	628.5	1637 (580-3310)	628.3
Weight finish PN (g)	1900 (755-4305)	622.2	1786 (540-3445)	635.6
Birth length (cm) *	42 (34-53)	4.0	40 (30-49)	4.3

SD= standard deviation, min= minimum value, max= maximum value

PN= parenteral nutrition

* $p < 0.05$

The mean age of neonates at the beginning of PN treatment at HGONA was 2.5 (SD 3.9) days, while at the HGOIA the mean age at the beginning of treatment was 3.7 (SD 3.2) days. The age of patients at the beginning of PN treatment at HGONA was statistically lower compared to the age of patients at HGOIA, $p=0.024$. Similarly, the age of patients upon completion of their PN treatment was statistically lower at HGONA, 12.6 (SD 6.9) days compared to the patients' age at HGOIA, 15.7 (SD 8.3), $p=0.005$. Additionally, the mean birth weight recovery in HGONA patients was statistically lower, 11 (SD 5.7) days compared to the birth weight recovery in HGOIA patients, 15 (SD 7.5) days, $p=0.0006$. The duration of PN treatment and hospitalization length did not differ significantly in the populations at the hospitals, $p=0.351$ (Table 4.3).

Table 4.3 Neonate population's age, duration, birth weight recovery regard to PN treatment

Variable	HGONA		HGOIA	
	Mean (min-max)	SD	Mean (min-max)	SD
Age begin PN* (days)	2.5 (0-27)	3.9	3.7 (0-23)	3.2
Age finish PN* (days)	12.6 (3-37)	6.9	15.7 (4-50)	8.3
Duration of PN (days)	10 (3-29)	6.4	11.9 (3-46)	8.4
Birth weight recovery* (days)	11 (0-27)	5.7	15 (1-43)	7.5
Hospitalization length (days)	27 (8-75)	14.2	29 (6-99)	17.2

SD= standard deviation, min= minimum value, max= maximum value, PN= parenteral nutrition * $p < 0.05$

The regimen of PN treatment at HGONA was 86% individual formulation and 14% standard and individual formulations. Conversely, at HGOIA 100% of the PN treatment was individual formulations. A Chi-square test of goodness-of-fit was performed to determine whether there is a statistical difference between the regimens of PN formulation at the hospitals. The regimen of PN formulation provided to the patients was not equally distributed $p= 0.0001$ (Table 4.4). Similarly, there were statistical differences between the two NICUs regarding the reasons for ceasing PN treatment. Thus, at HGONA 84% of patients' PN treatment ceased due to an increase of enteral feeds and 16% due to other reasons. On the other hand, 67% of HGOIA's patients ceased PN treatment due to increased enteral feeds and 33% because of other reasons $p=0.013$ (Table 4.5). Reasons to begin PN and venous access site were equally distributed in both hospitals, $p=0.473$ (Table 4.6 and Table 4.7).

Table 4.4 Regimen of PN formulation

Variable	HGONA		HGOIA	
	individual	standard/ individual	individual	standard
Regimen*	86%	14%	100%	0%

*p < 0.05

Table 4.5 Reasons to cease PN treatment

Variable	HGONA		HGOIA	
	Increase of enteral feeds	Others	Increase of enteral feeds	Others
Reasons to cease PN*	84%	16%	67%	33%

PN= parenteral nutrition

*p < 0.05

Table 4.6 Reasons to begin PN treatment

Variable	HGONA		HGOIA	
	<1.5kg	Others	<1.5kg	Others
Reasons to begin PN	24%	76%	28%	72%

PN= parenteral nutrition

Table 4.7 Venous access site

Variable	HGONA		HGOIA	
	PICC	Others	PICC	Others
Venous access site	95%	5%	93%	7%

PICC= peripherally inserted central catheter

The majority of patients used a PICC line as the venous access site to receive PN treatment in both NICUs. A very low percentage of patients received PN treatment through other venous access sites, including a central line and umbilical line followed by a central line, an umbilical line followed by a PICC line and an umbilical line exclusively.

Among other reasons to begin PN, 49% and 33% of patients presenting diagnoses of respiratory distress syndrome who were connected to mechanical ventilation received PN treatment at HGONA and HGOIA respectively. Furthermore, other reasons, such as necrotizing enterocolitis and digestive intolerance, are shown in Table 4.8.

Table 4.8 Reason to begin PN

Reasons to begin PN	HGONA n (%)	HGOIA n (%)
<1500g	23 (24)	29 (28)
Caloric protein malnutrition	1 (1)	3 (3)
Digestive intolerance	4 (4)	2 (2)
GI malformations	3 (3)	14 (13)
Necrotizing enteritis	5 (5)	4 (4)
Pneumothorax	1 (1)	3 (3)
Respiratory distress syndrome	48 (49)	34 (33)
Risk of necrotizing enteritis	3 (3)	4 (4)
Post-surgical myelomeningocele	0 (0)	1 (1)
NPO	10 (10)	10 (9)

NPO= nil per os (nothing by mouth)
GI= gastrointestinal

Among the other reasons to stop PN treatment, patient records listed catheter infiltration, hyperbilirubinemia, hyperglycemia, septic shock, erythematous zone related the PICC access site, etc. The distribution of the reasons to cease PN is shown in Table 4.9.

Table 4.9 Reasons to cease PN

Reasons to cease PN	HGONA n (%)	HGOIA n (%)
Catheter infection suspicion	1 (1)	0 (0)
Catheter infiltration	1 (1)	3 (3)
Cholestasis	1 (1)	5 (5)
Hyperbilirubinemia	2 (2)	1 (1)
Increase of enteral feeds	82 (84)	70 (67)
Septic Shock	2 (2)	3 (3)
Hyperglycemia	4 (4)	2 (2)
Arm edema related to the PICC area	1 (1)	2 (2)
Death	0 (0)	7 (6%)
Hemodynamic decompensation	0 (0)	1 (1)
Coagulopathy	0 (0)	1 (1)
Erythematous zone related to the PICC area	2 (2)	1 (1)
Low volume to deliver	0 (0)	1 (1)
Surgery	0 (0)	1 (1)
Catheter afuncional	0 (0)	1 (1)
N/R	2 (2)	5 (5)

PICC= peripheral inserted central catheter N/R= not reported

As previously described, the reasons to cease PN treatment were significantly different at the hospitals' NICUs. At HGONA and HGOIA respectively, 84% and 67% of patients stopped

treatment due to an increase of enteral feed. Therefore, HGOIA showed a significantly higher percentage of patients who ceased PN for other reasons (33% versus 16%). In order to obtain a reason that might account for this difference, the birth weight and medical conditions of patients who stopped PN for other reasons were reviewed.

Even though the birth weight cut-offs, below 1.5kg and over 1.5kg, were equally distributed in both NICUs ($p=0.328$ and $p=0.986$ respectively), a higher percentage of neonates (17.1%) who stopped PN at HGOIA were ELBW compared to 7.1% of neonates at HGONA. Due to the small values, a Chi-square test of goodness-of-fit was not appropriate to determine whether there is a statistical difference between ELBW infants at both NICUs (Table 4.10).

Table 4.10 Birth weight of patients who were ceased PN for other reasons

	HGONA n (%)	HGOIA n (%)
<1000g	1 (7.1)	5 (17.1)
<1500g	5 (35.6)	13 (44.6)
>1500g	9 (64.2)	16 (55.1)

Similarly, the medical conditions of patients who ceased PN for other reasons were reviewed. There were four cases of gastrointestinal malformations (GI) (13.8%) in HGOIA patients compared to zero cases in HGONA's patients. Two cases of pneumothorax (6.9%) were described in HGOIA's patients, and zero cases were noted at HGONA. The distribution of medical conditions is shown in Table 4.11.

Table 4.11 Medical conditions of patients who were ceased PN for other reasons

Medical conditions	HGONA n (%)	HGOIA n (%)
VLBW	4 (28.5)	8 (27.5)
Risk of necrotizing enteritis	1 (7.1)	2 (6.9)
Necrotizing enteritis	0	1 (3.4)
GI malformation	0	4 (13.8)
Pneumothorax	0	2 (6.9)
Respiratory distress syndrome	7 (50)	7 (24.1)

VLBW= very low birth weight GI= gastrointestinal

As is shown in Table 4.10 and 4.11, ELBW cases and other medical conditions may account for the differences in the two NICU's other reasons to stop PN.

4.3.1.2 Prescribed Macronutrients

The mean amino-acid dose prescribed when initiating PN treatment at HGONA was 2.6 (SD 0.4) g/kg per day while at the HGOIA the mean dose was 2.9 (SD 0.4) g/kg per day. The amino-acid dose at the beginning of PN treatment at HGONA was statistically lower compared to the amino-acid dose used at HGOIA, $p=0.0001$. Similarly, the D-glucose infusion rate used at the beginning of PN treatment was statistically lower at HGONA, 5.2 (SD 0.8) mg/kg per minute compared to the rate used at HGOIA, 7.5 (SD 1.6), $p=0.0001$. Additionally, the lipid dose used at HGONA was statistically higher, 2.1(SD 0.6) g/kg per day compared to the dose used in HGOIA's patients, which was 1.5 (SD 0.5) g/kg per day, $p=0.0001$. Finally, energy intake was significantly higher at HGONA, 102.1 (SD 24.3) kcal/kg per day compared to the intake of HGOIA's patients, which was 91.7 (SD 34.6) kcal/kg/day, $p=0.019$. The D-glucose dose used to begin PN treatment was not significantly different at the two studied hospitals, $p=0.684$ (Table 4.12).

Table 4.12 Prescribed Macronutrients

Prescribed Macronutrient	HGONA		HGOIA	
	Mean (min-max)	SD	Mean (min-max)	SD
Amino-acid (g/kg/day) *	2.6 (1.2-3.6)	0.4	2.9 (1.7-3.8)	0.4
D-glucose (g/kg/day)	10.6 (3.3-29)	4.3	10.8 (5.6-17)	2.4
D-glucose infusion rate (mg/kg/min) *	5.2 (2.8-7.2)	0.8	7.5 (3.8-12)	1.6
Lipid (g/kg/day) *	2.1 (0.4-3.3)	0.6	1.5 (0.2-2.8)	0.5
Energy intake (kcal/kg/day) *	102.1 (52-150)	24.3	91.7 (18-182)	34.6

* $p < 0.05$

4.3.1.3 Complications associated with PN treatment

Conjugated bilirubin (CB) levels over or equal to 1 mg/dL (17.1 μ mol/L) at patients' baselines were equally distributed in HGONA's and HGOIA's NICUs, $p=0.638$; however, during week one to week four of PN treatment, these hospitals reported statistical differences ($p=0.002$, $p=0.020$, $p=0.0001$, and $p=0.005$ respectively). HGONA presented more cases of PNAC during the first four weeks of treatment than HGOIA. Conversely, plasma glucose levels below 45mg/dL were not significantly different at the hospitals as these levels were responsible for 1% of the cases

reported at HGONA compared to 6% at HGOIA, $p=0.069$. Furthermore, blood glucose levels over 150mg/dL were not statistically remarkable, $p=0.171$ (12% at HGONA versus 7% at HGOIA). Finally, the presence of positive blood cultures was noted in 1% of cases at HGONA's NICU and 8% of cases at HGOIA's NICU or 1.0 cases per 1000-line days and 6.4 cases per 1000- line days respectively. Due to the small number of cases observed, a Chi-square test of goodness-of-fit was not appropriate to determine whether there is a statistical difference between the NICUs (Table 4.13).

Table 4.13 Complications associated with PN treatment

Test and Culture	HGONA			HGOIA			Combined data	
	YES	NO	Not reported	YES	NO	Not reported	Total cases %	Mean %
CB baseline \geq 1mg/dL (17.1 μ mol/L)	16%	81%	3%	14%	86%	0%	30	15
CB week 1 \geq 1mg/dL (17.1 μ mol/L) *	35%	54%	11%	18%	80%	2%	53	26.5
CB week 2 \geq 1mg/dL (17.1 μ mol/L) *	29%	39%	32%	19%	60%	21%	48	24
CB week 3 \geq 1mg/dL (17.1 μ mol/L) *	14%	12%	74%	9%	45%	46%	23	11.5
CB week 4 \geq 1mg/dL (17.1 μ mol/L) *	6%	4%	90%	5%	26%	69%	11	5.5
CB week 1 to 4 (combined data)							33.7	16.8
Blood glucose <45mg/dL (2.5mmol/L)	1%	96%	3%	6%	93%	1%	7	3.5
Blood glucose >150mg/dL (8.3mmol/L)	12%	86%	2%	7%	92%	1%	19	9.5
Positive Blood culture	1%	0%	99%	8%	0%	92%	9	4.5

CB= direct bilirubin TB= total bilirubin * $p < 0.05$

4.4 Discussion

As previously described in the Methods section of this study, patients' medical records at HGDC and HGEH were not assessed because an official record of patients undergoing PN treatment was not provided by their NICUs. For this reason, only HGOIA's and HGONA's patients' medical records were reviewed to examine the presence of complications associated with PN treatment. Based on the interviews, the researchers noted that HGOIA's NICU has a laminar flow hood to prepare PN while HGONA's NICU does not. HGONA's NICU reported having a dietitian as a part of the NICU team that provides PN treatment. Furthermore, from official records, it was reported that HGONA has 40 and HGOIA has 55 neonatal beds. The number of neonates receiving PN annually was 257 and 216 respectively. Although there is no great difference in the number of neonatal beds and patients receiving PN treatment at these two

hospitals, there may be value in comparing these NICUs to evaluate potential benefits or drawbacks of involving a nutritionist and laminar flow hood in PN treatment.

Our study found that the reasons to stop PN were statistically different at HGONA and HGOIA's NICUs; at HGONA, the vast majority of neonates ceased PN because they reached full enteral feeds while in HGOIA's NICU, approximately one-third of patients stopped PN due to other reasons, including complications or even death. These other reasons were present in both NICUs; however, in HGONA's patients, these other reasons constituted the reason to cease PN in a significantly lower percentage of cases. The literature describes that early initiation of enteral feeding could reduce the time required to reach full enteral feeds and decrease the number of days on PN treatment thereby reducing the side effects associated with prolonged use of PN (Kuzma-O'Reilly et al., 2003). In our study, both NICUs reported using milk banks and following the protocol of beginning early trophic enteral feeding in patients on PN. Enteral feeding of patients receiving PN nutrition was not recorded in our study, which is an apparent limitation of this study. This enteral feeding information may help us explain why there is a statistical difference in the reasons to cease PN at the two studied institutions. Other health conditions, however, may account for the discrepancy in reasons to stop PN.

The age of neonates at the beginning of PN was significantly younger at HGONA compared to HGOIA. In their study, Kuzma-O'Reilly et al. found that after the implementation of improved practices, the mean day to start PN in VLBW patients was 1.81 ± 0.88 days; additionally, this study found an earlier initiation of PN resulted in reaching enteral nutrition earlier (Kuzma-O'Reilly et al., 2003). The early age of infants at the beginning of PN treatment may account for the reason that HGONA has a higher percentage of patients who stop PN due to reaching full enteral feed. Even though ESPGHAN guidelines note that the initiation of PN should depend on the individual circumstances of the patient, age, and weight, the British Association of Perinatal Medicine and ESPGHAN guidelines recommend that PN treatment in newborn infants should be commenced shortly after birth. The British Association of Perinatal Medicine notes that glucose and amino acids must be initiated soon after birth and lipids within 24 hours of birth (British Association of Perinatal Medicine, 2016; Koletzko et al., 2005).

However, there could be other reasons that explain the difference in the number of cases of patients that stopped PN for other reasons at HGOIA. Even though birth weights showed no significant difference between both NICUs, the weight at the beginning of PN treatment and the

birth length were significantly lower in HGOIA' patients. Additional exploration of the birth weight and the medical conditions of patients who stopped PN for other reasons at the two NICUs was performed. There were no significant differences in birth weights at the lower cut off, 1500 grams and over 1500 grams; however, a Chi-square test of goodness-of-fit to determine whether there was a statistical difference between ELBW infants at HGONA's and HGOIA's NICUs was not possible due to the very low number of cases (one and five respectively). Similarly, the cited medical conditions were not comparable due to the presence of so few cases; however, HGOIA' patients presented cases of necrotizing enteritis, GI malformations, and pneumothorax, but HGONA's patients did not. Medical conditions and the extremely low birth weight of the patients at HGOIA may account for the other reasons to cease PN treatment.

Our study found that the mean amino acids, glucose infusion rate, and energy intake prescribed were significantly higher at HOGIA's NICU compared to HGONA's NICU; nevertheless, the mean lipid prescription was higher at HGONA's NICU compared to HGOIA's NICU. According to ASPEN, ESPGHAN, British Association of Perinatal Medicine, Practice of Parenteral Nutrition in VLBW and ELBW Infants, and the Neonatology/Paediatrics-Guidelines on Parenteral Nutrition, the range of amino acids doses and the GIR prescribed by HGOIA's NICUs are within the recommended range. However, the minimum dose of amino acids and GIR prescribed by HGONA are slightly lower than the dose recommended in these guidelines. The maximum prescribed dose was within the recommended range. The energy intake provided by both NICUs was beyond the minimum recommended intake. This might be explained by the fact that patients who were receiving partial PN; their enteral nutrition were not recorded in this study. The lipids prescribed by both NICUs were within the appropriate range recommendations, but our study found that HGONA's patients were prescribed significantly more lipids than patients at HGOIA. Lipids are the source of essential fatty acids, linoleic acid, and alpha-linolenic acids. During the data collection, we observed that HGOIA's NICU prescribed 20% intravenous lipids and soybean oil, olive oil, medium-chain triglycerides, and fish oil (SMOF) lipids. When personnel prescribe SMOF lipids, there is an additional order form which specifies the use of this type of fat, but its use is limited to very few patients.

On the other hand, HGONA's PN order form did not specify the use of SMOF lipids; however, a professional deeply involved in PN treatment noted that this unit prescribes SMOF lipids to a small number of patients as well. The British Association of Perinatal Medicine notes

that, based on the available evidence, the benefits and potential hazards of these new lipids are still unclear (British Association of Perinatal Medicine, 2016). Further studies on the outcomes of patients on PN solutions that contain SMOF lipids are needed.

Finally, our study found that there was no significant difference between the two NICUs regarding the prevalence of blood glucose levels over 150mg/dL (8.3mmol/L) or below 45mg/dL (2.5mmol/L) which can diagnose hyperglycemia and hypoglycemia. The average hyperglycemia prevalence (9.5%) found in the combined data from HGONA's and HOGIA's NICUs is lower than the prevalence of hyperglycemia (57%) found in a retrospective chart review study of 93 ELBW infants admitted to Texas Children's Hospital, Houston, USA from January 1, 2001 to December 31, 2001. This study aimed to determine the prevalence of hyperglycemia, defined as at least one value above 150mg/dL during the first week of life, in ELBW neonates undergoing PN treatment (Hays, Smith, & Sunehag, 2006).

Another retrospective chart review study of 169 ELBW neonates admitted to University Hospital, San Antonio, Texas, from January 1998 to December 2001, found an 88% incidence of hyperglycemia (defined as a plasma glucose level ≥ 150 mg/dL) in ELBW infants receiving PN treatment during the first two weeks of life in a predominantly Hispanic population (Blanco, Baillargeon, Morrison, & Gong, 2006). Conversely, Kao's retrospective observational study (2006) of 201 ELBW infants undergoing PN treatment at two centers in Houston, Texas, from March 2000 to November 2003, aimed to determine the association between hyperglycemia, mortality, and infections. This study found a lower incidence (28%) of mild hyperglycemia (as serum glucose level 120-179mg/dL), and a 7% incidence of severe hyperglycemia (≥ 180 mg/dL) (Kao, 2006).

Our results appear lower when compared to previous studies. This may be primarily because the neonate patients included in this study were patients of different birth weights not only ELBW infants which the previous studies used as their target groups. Thus, in our study, the mean weight at which PN was initiated was 1832g (815- 4460) and 1637g (580-3310) at HGONA and HGOIA respectively. From reviewing the pertinent literature, it is evident that in preterm infants limited insulin secretion capacity, activation of the hepatic glucose production, intermittent hypoxia, and other forms of stress lead to hyperglycemia (Rozance, & Hay 2010). Other potential reasons for this low prevalence may include the low GIR values used by HGONA and HGOIA (mean of 5.2mg/kg/min [2.8- 7.2] and 7.5mg/kg/min [3.8-12] respectively) compared

to the guidelines' recommended ranges (4-8, 4-12, or 7-12mg/kg/min) (Koletzko, Goulet Hunt, Krohn, & Shamir, 2005; British Association of Perinatal Medicine, 2016; Embleton & Simmer, 2014). Finally, other potential reason might be a misreporting of hyperglycemia in patients undergoing PN treatment.

Our study found a prevalence of hypoglycemia (3.5%) lower than the incidence found in a Scottish randomized control trial in 29 neonates below 2000g undergoing three PN formulations during the first 48 hours of life: glucose, 2 in 1, and 3 in 1 formulations (55%, 90%, and 25% respectively). In this study, hypoglycemia was defined as a plasma glucose level < 46mg/dL (2.55mmol/L) (Murdock, Crighton, Nelson, & Forsyth, 1995). Similarly, an observational study in ten patients less than two weeks of age requiring cycled long-term PN admitted to Boston Children's Hospital and Brigham and Women's Hospital, Boston, USA, reported an incidence of hypoglycemia (glucose concentration <40mg/dL using reagent strip and capillary samples) of 1.15% of all collected glucose concentrations and a 20% of incidence of hypoglycemia in neonate patients (Collier, Crouch, Hendricks, & Caballero, 1994).

As was previously noted in the discussion of the prevalence of hyperglycemia, including neonate patients in the same data set as infants of all gestational ages and birth weights may explain the low prevalence of hypoglycemia in our study. Lubchenco and Bard (1971) reported a higher (67%) incidence of hypoglycemia (glucose level <30mg/dL) in the preterm small gestational age (SGA) group compared to the term SGA (25%) and the post-term SGA (18%) groups in a randomized study of 374 infants over a 2-year period at Colorado Medical Center. Furthermore, this study showed a lower incidence of hypoglycemia in the large for gestational age (LGA) group when compared to the preterm LGA (37%), term LGA (4%), and post-term LGA (7%) groups (Lubchenco, & Bard, 1971). The incidences reported in Lubchenco's study may account for the low prevalence of hypoglycemia found in our study. Finally, other potential reason might be a misreporting of hyperglycemia in patients undergoing PN treatment.

Due to the small number of cases where a positive blood culture was observed, a Chi square test of goodness-of-fit was not an appropriate method of determining whether there is a statistical difference between the NICUs in our study. The average prevalence of CLABSI observed in the combined data of HGONA's and HGOIA's NICUs was 4.5% or 4.06 cases per 1000-line days. This prevalence is slightly higher compared to the prevalence found in Patrick et al.'s study (2013) of newborns admitted from January 1, 2008, to December 31, 2010 (1.7% or

18 CLABSI cases per 1000 patients). In this study, Patrick aimed to confirm the reliability of hospital records compared with CLABSI confirmed by sepsis control system (Patrick et al., 2013). Another study in North Carolina's NICUs, which aimed to reduce CLABSI rates, reported a reduction of 71% from 3.9 infections per 1000-line days to 1.6 infections per 1000-line days (Fisher et al., 2013).

With a similar objective of reducing the incidence of CLABSI cases, a prospective study from January 2012 to September 2013 in Greece's NICUs found a pre-intervention incidence rate of 12 cases per 1000-line days; however, after a quality intervention was implemented, the incidence decreased to 3.4 cases per 1000-line days (Rallis, Karagianni, Papakotoula, Nikolaidis, & Tsakalidis, 2016).

Conversely, when compared to previous results, our study demonstrated a statistical difference between our hospitals' rates of PNAC in patients receiving PN treatment from week one to week four. HGONA's NICU presented more cases of PNAC than HGOIA's NICU in the four weeks of the treatment. Our study found the mean prevalence of PNAC (16.8%) in both NICUs from week one to week four of PN treatment was lower than the incidence (24%) of PNAC (as two consecutive tests of conjugated bilirubin $> 2\text{mg/dL}$) found in Javid et al.'s study (2011). Javid et al.'s study was a retrospective review of 176 surgical infants undergoing PN treatment admitted from 2001 to 2006 at Seattle's NICU. This study also found that prematurity was significantly associated with the development of cholestasis (Javid et al., 2011).

Furthermore, Christensen, Henry, Wiedmeier, Burnett, & Lambert (2007), in their historic cohort study of 9861 neonates admitted from 2002 to 2006 to Utah's NICUs, found that the incidence of PNAC (as direct bilirubin $> 2\text{mg/dL}$) is significantly correlated with the duration of PN treatment. This study found an incidence of 14%, 43%, 72% and 85% of PNAC in neonates receiving PN treatment for 14 to 28 days, 29 to 56 days, 52 to 100 days, and over 100 days respectively (Christensen, Henry, Wiedmeier, Burnett, & Lambert, 2007). Finally, Repa's double-blind randomized study (2018) of 230 ELBW neonates receiving PN treatment admitted from 2012 to 2015 at Austria's NICUs, aimed to evaluate if a mixed lipid emulsion decreases the incidence of PNAC (as conjugated bilirubin $> 1.5\text{mg/dL}$ or 25umol/L) in ELBW infants. This study reported an incidence of 10.1% in the intervention group and 15.9% in the control group (Repa, 2018). The prevalence of PNAC found in our study is slightly higher compared to the

incidence found in Christensen's study; however, our findings are consistent with the incidence observed in the control group in Repa's study.

It is crucial to note that the potential complications presented in this study are only correlated with PN treatment. We are not attributing the causation of these complications to PN treatment. To identify the cause and effect relationship between PN treatment and these potential complications, further research in these NICUs is required.

Other possible causes of hyperglycemia, hypoglycemia, and PNAC will be discussed. According to the AAP, hypoglycemia is commonly observed in infants who are small for their gestational age, late-preterm infants, and those who are born to diabetic mothers (Adamkin, 2011). Similarly, the APP notes that hyperglycemia is frequently observed in ELBW neonates and is most commonly caused by postnatal corticosteroid therapy, stress caused by surgery, respiratory distress syndrome, and sepsis (Hwang et al., 2018). Finally, PNAC in infants can be caused, not only by PN treatment, but by obstructive and hepatocellular factors. The most common medical conditions included in these categories are extrahepatic biliary atresia and idiopathic neonatal hepatitis (Harb, & Thomas, 2007).

4.4.1 Limitations

Since the medical records we examined were physical and mostly handwritten, revision, interpretation, and potentially missed or omitted information were indeed limitations of this study.

An additional limitation of this study was our inability to review the other two NICU's documents due to the absence of records of patients who received PN treatment. This review would have allowed us to better understand their practices. Reviewing the medical records of all hospitals in our study would have provided a more comprehensive research base.

The time to first full enteral feeding and the amount of nutrition provided were not recorded in our study. This information may have allowed us to explain some of our results, such as birth weight recovery and reasons to cease PN treatment. This unrecorded information is another limitation of our study.

4.4.2 Recommendations

As noted in the discussion section, this project only studied the association of potential complications (hyperglycemia, hypoglycemia, PNAC, and CLABSI) with PN treatment. For

quality and safety improvement in the participating NICUs, further research on the direct relationship between PN and these complications is strongly recommended.

A regular audit of PN treatment in the NICUs is also recommended by our study. Regular auditing in NICUs that aim to provide safe PN treatment and better outcomes for their patients is a strongly endorsed practice.

Even though the CLABSI rates in this study are slightly higher compared to the rates reported in NICUs in developed countries and the PNAC prevalence is consistent with the prevalence found in developed countries, it is strongly recommended that hospitals develop a protocol of regular surveillance and clinical diagnosis of these and other complications associated with PN therapy.

The discussion section also indicated that a limitation of this study was that the time to first enteral feeding and the amount of this feeding were not recorded; further studies should research, not only PN treatment, but also enteral nutrition as this may better account for some growth outcomes in patients receiving both treatments.

Further observational study of these NICUs' PN practices is recommended. Observations, in combination with our interviews and medical record reviews, will allow for a broader understanding of the PN practices in these units. The digitalization of the medical records may bring better and more flexible management of patient information. This digitalization might also be an excellent tool to increase the speed and efficiency of the PN auditing process.

4.5 Conclusion

Reviewing the patients' medical records and PN guidelines allowed us to assess the credibility of our theory and obtain a better understanding of the PN practices in the public NICUs in Quito; however, as described in the recommendations, observations of the PN practices in the NICUs would expand this theory. Our study found that there were statistical differences between NICUs in several of the measured variables. Among these findings, were that PN was initiated significantly earlier and that there was a higher percentage of patients who ceased PN treatment because they reached full enteral feeds in HGONA's patients. Regarding the range of amino acids, lipids, and glucose prescribed, there is consistency with the guidelines' recommendations and the interviewees' responses; however, there are a few prescribed minimum doses that exceeded the recommended range. Finally, there were no significant differences observed regarding the

potential complications associated with PN treatment, except for the prevalence of PNAC which was significantly higher in HGONA's NICU compared to HGOIA's NICU.

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Appendix A

SURVEY

I. GENERAL INFORMATION

Number of questionnaire _____ Date _____ Name of Interviewer _____
 Hospital name _____ Total beds number _____ Neonatal beds number _____
 How many neonate's patients are admitted yearly in this hospital? _____
 How many are VLBW neonate's patients are admitted yearly in this hospital? _____
 Academic Degree _____ Role _____ Years of experience _____ Average Number of hours that you work at the hospital _____

II. DESCRIPTION OF THE NEONATOLOGY AREA

1. How many beds/ incubators/ places of care does the neonatology area at this institution have?
 Places of basic care (Definition: basic care) _____
 Places of intermediate care (Definition: intermediate care) _____
 Places of intensive care (Definition: intensive care) _____
2. Does this hospital have a laminar flow hood to prepare TPN? If your answer is YES, please mention the number of laminar flow hoods at the hospital.

Yes	No	How many?
-----	----	-----------
3. Have been any change in the past 5 years? What? _____

III. DESCRIPTION OF THE PATIENT OF THE NEONATOLOGY AREA

4. How many neonate's patients are receiving TPN yearly in this hospital? _____
5. How many are VLBW neonate's patients are receiving TPN annually in this hospital? _____
6. Which are the most frequent reasons to begin TPN?

	Sex _____
	Gestational age _____
	VLBW (<1500g) _____
	Intrauterine growth retardation _____
	Digestive intolerance _____
	Restricted enteral output _____
	GI malformations _____
	Necrotizing enteritis _____
	Short intestine _____
	Malabsorption Syndrome _____
	Chylous leak _____
	Esophageal rupture _____
	Other _____

7. Have been any change in the past 5 years? What? _____

IV. HEALTH CARE PERSONNEL

8. Is there a parenteral nutrition team (multidisciplinary team of nutritional support) in this hospital?

Yes	No
-----	----

If your answer is Yes, please answer the following questions

9. Mention which professionals are involved in this parenteral nutrition team and their role (Write the professional degree that they have)

If your answer to question 8 is No, please answer the following questions

10. Mention which professionals are involved in the administration of TPN and their role? (Write the professional degree that they have)

11. Which are the barriers toward having a functional NSTS?

12. Who is the health professional that prepares parenteral nutrition solutions?

Nurse	_____
Dietitian	_____
Pharmacist	_____
Other	_____

13. Have been any change in the past 5 years? What? _____

V. PARENTERAL NUTRITION DESIGN

14. What is the method that you use to make the parenteral nutrition orders?

Paper orders	_____
Electronic orders	_____

15. Do you write this order manually or digital?

16. Could you provide me with a copy of the form that you use order TPN? Yes / No

17. Where is TPN prepared?
 Operating theatre ___
 Pharmacy area ___
 Nutrition area ___
 Neonatology area ___
 Other _____
18. Do you use any TPN calculation software (ABACUS, Baxter) or automated compounding devices (ACDs) to prepare TPN formulations?
19. Do you pack TPN formulations in a single compartment bags or more?
20. Could you provide me with a copy the label that you use for TPN bags?
21. How many days does the TPN unit work? In the case, the TPN unit does not work some days which method do you use to supply TPN those days?
22. If you prepare TPN bags for those days when the TPN unit is not operating, please explain how do you store them?
23. Where is parenteral nutrition delivered?
 Basic Unit Care ___
 Intermediate Unit Care ___
 Intensive Unit Care ___
24. Which kind of in-line filters do you use to deliver TPN?
25. How long does last TPN and how do you proceed when you infuse lipids?
26. Which are the potential errors in TPN practices (order, prepare, storage, labelling, and administration) That you found during your daily practice and which measures do you take to prevent PN-related risks? Please mention the frequency. (Ex. Doble- checking/ triple-chequing on the data entry, gravimetric analysis, visual inspection of each PN bag, sterility testing of isolated rooms/isolators and PN bags)
27. Are you using a publish clinic guide to manage the TPN?
 Yes _____ No _____
28. If your answer to question 27 is YES, please mention which Clinic guide, protocol, or actual recommendations you are using to manage the TPN?
 ESPGHAN & ESPEN ___
 A.S.P.E.N American Society for Parenteral and Enteral Nutrition ___
 British Association for Parenteral and Enteral Nutrition Working Party ___
 British Society of Gastroenterology ___
 Australasian Society for Parenteral and Enteral Nutrition ___
 American Gastroenterological Association ___
 Asociación Española de Pediatría ___
 Other _____
29. If your answer to question 27 is No, please mention which clinic guide or protocol are you using to manage the TPN
30. Is this clinic guide or protocol based on one of the above? What?
31. Could you provide a copy of this clinic guide or protocol? Yes/ No
32. What kind of TPN regimen do you use frequently?
 Always Individualised TPN ___
 Mostly Individualised TPN ___
 Both individualized and Standardised TPN ___
 Mostly Standardised TPN ___
 Always individualised TPN ___
33. What is the method that you are using to estimate the energy requirement of the patient?
 Direct calorimetry ___
 Indirect calorimetry ___
 Prediction formulas ___
34. If you selected prediction formulas, what is the formula you use to calculate the energy requirement of the patient?
35. What is the value of proteins that you use to begin TPN in patients?
 _____%= _____ gr/kg/d in preterm neonates
 _____%= _____ gr/kg/d in term neonates
36. How do you calculate the carbohydrates (D- glucose) intake in patients?
 _____%= _____ gr/kg/d in preterm neonates

_____%=_____ gr/kg/d in term neonates

37. Which type of lipid emulsion do you use?

LCT at 10% ___

LCT at 20% ___

LCT at 30% ___

MCT at 50% ___

What is the value of lipids that you use to begin TPN in patients?

_____ gr/kg/d in preterm neonates

_____ gr/kg/d in neonates

38. Which vascular line do you use most frequently to deliver the TPN?

	Always	Most	Sometimes	Never
Peripheral line				
Central line				
Peripherally inserted central catheter				
Umbilical				

39. Have been any change in the past 5 years? What?

VI. PATIENT MONITORING

Before to begin TPN

40. Do you assess biochemistry measures before beginning TPN in the patient?

Yes

No

41. If your answer is Yes, please tell us which biochemistry measures you assess most frequently before Beginning TPN in the patient

	Always	Most times	Sometimes	Never
Hemogram				
Urea/creatinine				
Electrolytes				
Hepatic function test				
Blood glucose Level				
Total proteins/Albumin				
Vitamins and minerals status				
Cholesterol				
Triglycerides				
Others _____				

42. Do you assess anthropometric measures before beginning TPN in the patient?

Yes

No

43. If the answer is Yes, please point out which anthropometric measures you use most frequently

	Always	Most times	Sometimes	Never
Weight				
Length				
Cephalic perimeter				
Other				

Patient on TPN

44. How frequently do you assess fluid balance, blood glucose levels?

	At least one per day	Every 12 hours	Every 8 Hours	Other
Fluid balance				
Blood glucose levels				
Temperature				
Heart rate				
Respiratory Frequency				

45. How frequently do you assess anthropometric parameters?

	Once per day	Twice per week	Other
Weight			
Length			

46. Have been any change in the past 5 years? What?

VII. MANAGE OF COMPLICATIONS

47. Regards to some complications such as hyperglycemia, hypoglycemia, hyperbilirubinemia, cholestasis, and sepsis, which lab test and symptoms do you use to define them? Or do you base the diagnosis of these complications in any international classification (ex. ICD)?

48. If you observe possible complications of TPN, what do you do?

49. Do you have a clinic guide protocol to manage complications of TPN? If your answer is Yes, what is this clinic guide or protocol?

	Yes	No	What?
--	-----	----	-------

50. Could you provide a copy of this clinic guide or protocol?

51. Have been any change in the past 5 years? What?

VIII. CEASING TPN

52. Who decides to cease TPN?

53. What is the reason to cease TPN? (At least half of a patient's requirements are met, as the patient commences on an oral diet or enteral feeds, referring medical team makes the decision)

54. Do you have a protocol to cease TPN? If your answer is Yes, what is this clinic guide or protocol?

	Yes	No	What?
--	-----	----	-------

55. Do you have a follow-up protocol for patients following the termination of PN? If your answer is Yes, what is this clinic guide or protocol?

	Yes	No	What?
--	-----	----	-------

56. If your answer is yes in questions 55 or 56 Could you provide a copy of this clinic guide or protocol?

57. Have been any change in the past 5 years? What?

58. Did you face any difficulty, problem, or challenge during the period that you have been involved in TPN administration? What?

Figure A. 1 Survey of health professionals delivering PN treatment at four neonatal intensive care unit (NICU)s.

Appendix B

ESTABLECIMIENTO	NOMBRE	APELLIDO	SEXO (M/F)	N° HOJA	N° HISTORIA CLÍNICA
0	0	0	0	0	0

REGISTRAR EN ROJO LA ADMINISTRACION DE FARMACOS Y OTROS PRODUCTOS (EN ENFERMERIA)

1 EVOLUCIÓN		2 PRESCRIPCIONES	
FECHA (DIA/MES/AÑO)	HORA	NOTAS DE EVOLUCIÓN	
0/01/00	00.00	Paciente requiere NPT	
		Peso (Kg)	0,000
		Edad (d)	-
		Liq. Tot.	0,0
		Flujo Dx (mg/Kg/min)	0,0
		% D/A	<input type="text"/>
		Lípidos 20%	0,0
		Aminoácidos 10%	0,0
		Na mEq	0,0
		Ac Na mEq	0,0
		Kcl mEq	0,0
		Funda	0,0
		Ca Mg	0,0
		Mg	0,0
		Acido ascorbico	0,0
		MTE4	0,0
		Medicación	0,0
		Leche materna	0,0
		Formula	0,00
		Osmolalidad	<input type="text"/>
		cal/kg/d	<input type="text"/>
		cc Kg/d alim enteral	<input type="text"/>
CALCULADA POR: PREPARADA POR: ENTREGADA POR:		FIRMAR AL PIE DE CADA PRESCRIPCIÓN ADMINIST. R. FARMAC. OS	
		FÁRMACOTERAPIA E INDICACIONES (PARA ENFERMERIA Y OTRO PERSONAL)	PREPARACION
			ml
			peso con funda <input type="text"/>
			peso real
		Aminoácidos 10% 100 ml	0,0
		Cloruro de sodio 3.4mEq	0,0
		Cloruro de potasio 2 mEq	0,0
		<input type="text"/>	<input type="text"/>
		<input type="text"/>	<input type="text"/>
		Sulfato de Magnesio 20%	0,0
		Gluconato de calcio 10%	0,0
		Oligoelementos 2ml	0,0
		Lípidos al 20%	0,0
		Acido ascorbico 500mg	0,0
		Heparina 5000 UI	0,0
		Pasar Intravenoso a <input type="text"/>	ml/hora
		INSUMOS	
		Bolsa de nutrición parenteral	
		Equipo para bomba Ambar	
		Jeringa 50 ml	
		Jeringa 10 ml	
		Jeringa 3 ml	
		Jeringa 5 ml	
		Llave de 3 vias con extension	
		Agua hipodérmica 18	

SNS-MSP / HCU-form.005 / 2008 EVOLUCIÓN Y PRESCRIPCIONES (1)

Figure B.1 Parenteral nutrition order form

Appendix C

Raw data from the interviews

Table C.1 Description of the neonatal units

	Places of basic care	Places of intermediate care	Places of intensive care	Total (n=16)	Another places
HGONA (n=5)	8±2 (3) Do not know (2)	20±5.29 (3) Do not know (2)	17±3.6 (3) Do not know (2)	5	0
HGOIA (n=4)	24.37±29.03 (4)	33±14.14 (4)	12 (4)	4	Isolation area 2 places (2)
HGDC (n=4)	0 (3) Do not know (1)	7.67±1.15 (3) Do not know (1)	6.67±1.15 (3) Do not know (1)	4	0
HGEG (n=3)	4 (3)	4(3)	5 (3)	3	Infectiology 8 places (2) Infectiology 6 places (1)
	(n=16)	(n=16)	(n=16)	16	

Table C.2 Presence of laminar flow hood

Laminar flow hood	Yes	No	Do not know	Didn't answer	Total (n=16)
HGONA (n=5)	0	4	1	0	5
HGOIA (n=4)	4	0	0	0	4
HGDC (n=4)	1	2	1	0	4
HGEG (n=3)	0	2	1	0	3
Total	31.25% (n=5)	50% (n=8)	18.75% (n=3)	0	100% (16)

Table C.3 Existence of nutritional support team

Existence of NST	Yes	No	Do not know	Didn't answer	Total (n=16)
HGONA (n=5)	2	2	1	0	5
HGOIA (n=4)	1	3	0	0	4
HGDC (n=4)	0	4	0	0	4
HGEG (n=3)	0	3	0	0	3
Total	18.8% (n=3)	75% (n=12)	6.3% (n=1)	0	16

Table C.4 Parenteral nutrition compounding process

Place of PN compounding	Pharmacy unit	NICU	Operating theater	TPN unit	Do not know	Total (n=16)
HGONA (n=5)	1	0	0	1	3	5
HGOIA (n=4)	0	4	0	0	0	4
HGDC (n=4)	2	0	2	0	0	4
HGEG (n=4)	0	3	0	0	0	3
	18.8% (n=3)	43.8% (n=7)	12.5% (n=2)	6.3% (n=1)	18.8% (n=3)	16

Table C.5 Parenteral nutrition calculation process

Method of calculations	Software in excel	manually	Software/manual	Total (n=16)
HGONA (n=5)	5	0	0	5
HGOIA (n=4)	2	1	1	4
HGDC (n=4)	4	0	0	4
HGEG (n=3)	3	0	0	3
	87.5% (n=14)	6.3% (n=1)	6.3% (n=1)	16

Table C.6 Parenteral nutrition storing process

Storing PN	Not stored (prepare daily)	Kept in Refrigeration (standard TPN)	Total (n=16)
HGONA (n=5)	2	3	5
HGOIA (n=4)	4	0	4
HGDC (n=4)	4	0	4
HGEG (n=3)	3	0	3
	81.3% (n=13)	18.8% (n=3)	16

Table C.7 Regimen of parenteral nutrition

Regimen of PN	Always individual (n=16)	Mostly individual	Both individual & standard	Mostly standard	Always standard soon after birth(n=16)
HGONA (n=5)	5	0	0	0	4
HGOIA (n=4)	4	0	0	0	0
HGDC (n=4)	4	0	0	0	0
HGEG (n=3)	3	0	0	0	0
Total	100% (n=16)	0	0	0	25% (n=4)

Table C.8 Published guideline to manage parenteral nutrition treatment

Use of published guideline	Yes	No	Do not know	Total (n=16)
HGONA (n=5)	1	3	1	5
HGOIA (n=4)	4	0	0	4
HGDC (n=4)	1	3	0	4
HGEG (n=3)	0	3	0	3
	37.5% (n=6)	56.3% (n=9)	6.3% (n=1)	16

Table C.9 Unpublished guideline to manage parenteral nutrition treatment

Use of unpublished guideline	Consensus or protocol of the neonatology area	MSP protocol	Protocol in process	Do not know	N/A	Total (n=16)
HGONA (n=5)	2	0	0	2	1	5
HGOIA (n=4)	0	0	0	0	4	4
HGDC (n=4)	0	2	1	0	1	4
HGEG (n=3)	3	0	0	0	0	3
	31.3% (n=5)	12.5% (n=2)	6.3% (n=1)	12.5% (n=2)	37.5% (n=6)	16

Table C.10 Professional that prepares parenteral nutrition formulations

Professional who prepares PN	Pharmacist	Nurse	Do not know	Total (n=16)
HGONA (n=5)	4	0	1	5
HGOIA (n=4)	4	0	0	4
HGDC (n=4)	3	0	1	4
HGEG (n=3)	0	3	0	3
	68.8% (n=11)	18.8% (n=3)	12.5% (n=2)	16