

Neonatal and paediatric parenteral nutrition prescription practices in South Africa: a cross-sectional survey

by

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Abstract

Objectives: The objective of this study was to describe the current parenteral nutrition (PN) prescription practices and knowledge of prescribers (paediatric doctors and dietitians) for their neonatal and paediatric patients, in South Africa, and to establish the factors which influence usage and adherence to the available guidelines.

Methods: A descriptive cross-sectional survey was conducted from November 2016 to March 2017 through a self-administered online questionnaire. PN prescription factors were assessed in terms of timing, patient type and diagnosis, use of macronutrients, and fluid allocations. Prescriber knowledge of the ESPGHAN international guidelines was assessed, as well as access to information. Knowledge and practice score competency levels were set, a priori, at 60% and 80% respectively. Respondents were stratified according to work sector (state / private) or professional group (dietitian / paediatric doctor) for statistical comparison. Summary statistics, chi-squared tests and correlation coefficients were used to describe and analyse the data.

Results: A total of 72 survey respondents were included, 58% dietitians and 42% paediatric doctors; 47% private sector and 53% state sector based.

The primary indications for PN use were gut abnormalities and intolerances, prematurity and critical illness. Doctors prioritised fluid calculation in determining their PN prescription. Dietitians were significantly more likely to calculate the patient-specific protein requirements ($p < 0.001$). Only 36% of prescribers commenced PN feeding within the first 24 hours of admission, but the majority (67%) introduced intravenous lipid emulsion (IVLE) from day 1 of PN. The main reasons given for IVLE delay were habit, liver function concerns, and PN bag availability.

The mean practice score was 75% (SD \pm 17). There was no significant difference in mean score between the work sector subgroups (75 \pm 20% state versus 76 \pm 15% private; $p = 0.82$). The dietitians, however, scored significantly higher for practice outcomes compared with the doctors (82 \pm 12% versus 65 \pm 19%; $p < 0.001$).

The main potential factors that influenced the delay or non-use of PN when it was indicated included concerns regarding infectious complications and financial resource constraints. Inadequate access to PN, and a lack of trained staff to administer the PN, also impacted on its use.

Only 64 of the respondents completed the knowledge section of the questionnaire. The mean knowledge score was 74% (SD \pm 12), range 50 – 100%. There was no significant difference in mean score between the work sector subgroups (73 \pm 13% for state versus 76 \pm 12% for private; $p = 0.32$). The mean knowledge score for the dietitians (77 \pm 13%) was however significantly higher than that of the doctors (71 \pm 11%); ($p = 0.04$).

Conclusion: PN prescribing practices in South Africa for neonatal and paediatric patients are not yet optimal in many respects. Prescribers require access to clear PN therapy guidelines, as well as guidance on how to implement these recommendations effectively in daily clinical practice. A multidisciplinary approach to PN feeding is paramount. Our findings emphasise the role of the dietitian as part of the multidisciplinary team in achieving optimal feeding. Additional research is warranted to further assess the PN feeding practices in this vulnerable patient group.

Opsomming

Doelwitte: Die doel van hierdie studie was om pediatriese dokters en dieetkundiges se huidige voorskrifpraktyke en kennis van parenterale voeding (PV) vir neonatale en pediatriese pasiënte in Suid-Afrika te bepaal; asook die faktore wat die gebruik en nakoming van beskikbare riglyne beïnvloed vas te stel.

Metodes: 'n Dwarssnit beskrywende studie is uitgevoer vanaf November 2016 – Maart 2017 deur middel van 'n self-geadministeerde aanlyn vraelys. Faktore wat PV voorskrifte beïnvloed soos tyd geïnisieer, pasiënt tipe en diagnose, gebruik van makronutriënte en vloeistofbehoefte is bepaal. Kennis van die ESPGHAN internasionale riglyne en toegang tot inligting is bepaal onder die voorskrywers. Die vaardigheidsvlakke vir kennis en praktyke is onderskeidelik vooraf vasgestel op 60% en 80%. Vir statistiese vergelykings is respondente stratifiseer volgens werksektor (staat / privaat) en professionele groep (dieetkundiges / pediatriese dokters). Beskrywende statistiek, chi-kwadraat toetse en korrelasie koëffisiënte is gebruik om data te beskryf en analiseer.

Results: 'n Totaal van 72 respondente is ingesluit, 58% dieetkundiges en 42% pediatriese dokters; 47% private sektor en 53% staatssektor gebaseer.

Die hoof indikasies vir PV gebruik was dermkanaal abnormaliteite en intoleransies, prematuriteit en kritieke siekte. Dokters het vloeistof berekeninge geprioriseer in die berekening van hul PV voorskrifte. Dieetkundiges was beduidend meer geneig om pasiënt-spesifieke proteïen behoeftes te bereken ($p < 0.001$). Slegs 36% van respondente het PV begin binne die eerste 24 uur na toelating. Die meerderheid (67%) het egter intraveneuse lipied emulsies begin op dag 1 van PV. Die hoofredes verskaf vir die vertraging van lipied toediening was gewoonte, lewerfunksie bekommernisse en beskikbaarheid van die PV sakke.

Die gemiddelde praktyktelling was 75% (SD ± 17). Daar was geen beduidende verskil in die gemiddelde telling tussen werksektor subgroepe (75 \pm 20% staat versus 76 \pm 15% privaat; $p = 0.82$). Die dieetkundiges het egter beduidende hoër tellings verkry teenoor die dokters (82 \pm 12% versus 65 \pm 19 %; $p < 0.001$).

Bekommernisse oor infektiewe komplikasies en finansiële beperkings was die hoof potensiële faktor vir die vertraging of nie-gebruik van PV in gevalle waar dit aangedui was. Onvoldoende toegang tot PV en 'n tekort aan opgeleide personeel om PV te kan toedien het ook die gebruik beïnvloed.

Slegs 64 van die respondente het die kennisdeel van die vraelys voltooi. Die gemiddelde kennistelling van 74% (SD \pm 12), reikwydte 50-100%. Daar was geen beduidende verskil in die gemiddelde telling tussen werksektor subgroepe nie (73 \pm 13% staat versus 76 \pm 12 % privaat; $p = 0.32$). Die gemiddelde kennistelling van die dieetkundiges (77 \pm 13%) was egter beduidend hoër as die van die dokters (71 \pm 11%); ($p = 0.04$).

Gevolgtrekking: PV voorskrifpraktyke in Suid-Afrikavir neonatale en pediatriese pasiënte is nie optimaal in baie aspekte. Diegene wat PV voorskryf benodig toegang tot duidelike PV terapeutiese riglyne, asook raadgeving oor hoe om die riglyne effektief te implementeer in daaglikse kliniese praktyke. 'n Multidissiplinêre benadering tot PV praktyk is noodsaaklik. Ons bevindinge het die rol van die dieetkundige om optimale voeding te bereik as deel van die multidissiplinêre span beklemtoon. Addisionele navorsing is nodig om die PV voedingpraktyke van hierdie kwesbare pasiëntgroep te bepaal.

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Contributions

Cristen Flint (principal researcher), Professor Renée Blaauw and Dr Evette van Niekerk (supervisors), developed the research idea and study protocol. Cristen Flint performed the data collection and analysis of the results. Professor Daan Nel (CSC) provided additional assistance with statistical analysis of the data. Cristen Flint drafted the dissertation. The results and dissertation were reviewed by Professor Renée Blaauw and Dr Evette van Niekerk. All authors read and approved the final version of the thesis.

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List of Abbreviations and Acronyms

ADSA:	Association for Dietetics in South Africa
ASPEN:	American Society for Parenteral and Enteral Nutrition
CLD:	Chronic Lung Disease
CVC:	Central Venous Catheter
DHA:	Docosahexaenoic Acid
DoH:	Department of Health
EFA:	Essential Fatty Acid
ELBW:	Extreme low birth weight
EN:	Enteral Nutrition
EPA:	Eicosapentaenoic Acid
ESPGHAN:	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
GGT:	Gamma-Glutamyl Transpeptidase
HOD:	Head of Department
HPCSA:	Health Professions Council of South Africa
HREC:	Health Research Ethics Committee
ICU:	Intensive Care Unit
IV:	Intravenous
IVLE:	Intravenous Lipid Emulsion
kCal/ kg:	Kilocalories per kilogram
LBW:	Low Birth Weight
LC-PUFA:	Long-Chain Polyunsaturated Fatty Acid
LFT:	Liver Function Test
MCC:	Medicines Control Council
MCT:	Medium-Chain Triglyceride
MDI:	Mental Development Index
MO:	Medical Officer
NEC:	Necrotising Enterocolitis
PICC:	Peripherally Inserted Central Catheter
PN:	Parenteral Nutrition

RMMSE:	Root Mean Square Standardised Effect
RNI:	Recommended Nutrition Intake
SAPA:	South African Paediatric Association
SBS:	Short-Bowel Syndrome
TE:	Total Energy
UL:	Upper Limit
VLBW:	Very low birth weight

Chapter 1: Literature Review

Chapter 1: Literature Review

1.1 Introduction

Parenteral nutrition (PN) is indicated for the provision of nutrients to neonatal and paediatric patients when it is not possible to feed adequately, or at all, into the gastrointestinal tract.¹⁻⁴ This patient population has high nutritional requirements, both in terms of protein and energy, as well as micronutrients, owing to their ongoing growth and development. In the context of their high nutritional demands, and relatively limited reserves, inadequate feeding during hospitalisation can have a significant influence on both their short- and long-term clinical outcomes.^{1-3,5-7}

Owing to a paucity of standardised recommendations, many decisions related to feeding in this patient population are based on clinical knowledge and experience. The only detailed guidelines to date are those published in 2005 by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).⁸ The successful implementation of these guidelines in actual clinical practice is however fraught with challenges – the vulnerability and complexity of the patient group, the wide variations in PN solutions and availability, the role of the multidisciplinary team, and the setting and context are just a few considerations.^{7,9-13} Research investigating actual clinical practice in terms of the understanding and implementation of these PN guidelines is also still quite limited.¹⁰⁻¹²

In many hospitals worldwide, PN is compounded on a patient-specific basis at hospital level. Fresenius Kabi is currently the sole supplier of neonatal and paediatric PN in South Africa, and all the available components are therefore their registered single units. These single units are combined into standardised formulations at a commercial compounding facility before distribution to hospitals. It is evident from a review of the current literature that the provision of all-in-one standardised PN bags to both neonatal and paediatric patients is unique to the South African context, and is only now being considered and piloted in other sites around the world.¹⁴⁻¹⁶ The use of standardised bags has in a sense simplified and streamlined the process of prescribing PN, but no data yet exists detailing the knowledge and actual practices of PN usage for neonatal and paediatric patients within this context.

1.2 Nutritional risk in critically ill infants and children

Premature neonates, and critically ill infants and children, are a unique patient population in terms of their needs for medical management, including nutritional support. Their high nutrient demands due to ongoing

growth and development, in conjunction with relatively limited energy reserves, place them at high risk of developing malnutrition during hospitalisation.^{1,2,17} The incidence of malnutrition in this group varies between 25% and 70%.¹ Nutrient deficits may negatively impact recovery, but more importantly result in growth faltering and long-term developmental delays. Malnutrition may also contribute to prolonged hospitalisation and elevated health costs.^{1,2,7,17}

Premature infants are a particularly high-risk group and present the additional feeding challenge of attempting to mimic inter-uterine growth and maintain anabolism at foetal rates, as well as achieve a functional outcome similar to that of an infant born at term. The balance between the energy provision and amino acid supply also appears to be important as caloric intake may influence protein accretion. Postnatal growth restriction is a powerful predictor of long-term morbidity and poor neurodevelopmental outcomes in this patient group.^{3,4,6,7,18,19} Stephens et al. (2009) determined that optimising protein and energy intakes within the first week of life in extreme low birth weight (ELBW) infants affected both length growth and the Mental Development Index (MDI) scores at 18 months of corrected age. An increase in calories by 10 kCal/kg per day was independently associated with a 4.6-point increase in the MDI and an additional 1 g/kg per day of protein by a noteworthy 8.2-point MDI increase.²⁰ Yang et al. (2015) demonstrated similar results in their retrospective cohort study of very low birth weight (VLBW) infants – a positive correlation between amino acid provision and neurodevelopmental outcomes at the age of 2 years.¹⁸ The Standardised, Concentrated, Additional Micronutrients, Parenteral (SCAMP) nutrition study was a randomised trial that investigated postnatal head growth (as an indicator of brain growth and later neurodevelopmental outcome), and showed that early, aggressive nutritional intervention in this patient group can improve outcomes.^{6,21}

It is therefore well established in the literature that achieving optimal growth targets as well as long-term developmental outcomes is the ultimate goal of nutrition therapy in premature, and critically ill infants and children. The type and duration of nutrition therapy will vary in each clinical scenario, but PN definitely plays a role in improving the realisation of this goal.

1.3 Indications for parenteral nutrition

PN can be considered an effective yet invasive, and relatively expensive intervention, and as such will always be a secondary choice to commencing with enteral feeding. Enteral nutrition (EN) remains the preferred method of nutritional support for all premature infants, and paediatric patients.^{1,3,4,7} Unfortunately, gut tolerance and physiological and clinical complications are often limiting factors in feeding solely via the enteral route, and supplementary or complete PN is necessary to avoid poor growth and medical outcomes.^{3,8,9} Guidelines vary, but most appear to agree that in premature infants where no significant

enteral feeds can be established within 3 days, that starting early with parenteral feeding is important. In fact, in the ELBW and VLBW neonates, it is beneficial to start PN within 2–6 hours of birth in order to successfully mimic inter-uterine growth conditions.^{3,7–9,22} In older children, depending on their diagnosis and nutritional status, the commencement of PN can be delayed for up to 7 days. As with adults, if the patient presents on admission with malnutrition, particularly underweight or wasting, the introduction of PN more immediately is advisable.²³ The most common indication for PN therapy in paediatric patients is in instances of gut failure and enteral feeding intolerance. Patients with particularly high nutritional requirements, such as those admitted with burns and trauma injuries, may rely on supplementary PN to meet these elevated needs. Many patients with chronic diagnoses, such as those in oncology, renal, and even cardiac units, are at high risk of malnutrition, and may require PN to meet their high nutrient requirements and combat this malnutrition, as well as enable the provision of optimal nutrition in often limited fluid allowances.^{1,8,9,24} Table 1.1 provides a summary of the indications for PN use in children.⁹

TABLE 1.1 INDICATIONS FOR PARENTERAL NUTRITION IN CHILDREN

Gut failure	Other common indications	Patients requiring aggressive nutritional support
Short bowel syndrome	Preterm infants – functional immaturity	Trauma
Necrotising enterocolitis (NEC)	Chemotherapy (resulting in acute damage to the gut)	Burns
Intestinal obstruction	Pancreatitis	Chronic kidney disease
Ischaemia or inflammation of the gastrointestinal tract	Chronic aspiration due to gastro-oesophageal reflux	Liver disease
Gastrointestinal haemorrhage		Cancer
Malabsorption syndromes		Cystic fibrosis
Protracted diarrhoea		
Peritonitis		
Paralytic ileus		
Inflammatory bowel disease		

Source: Adapted from [9]

1.4 Available guidelines for parenteral nutrition

The only international guidelines readily available for the prescription of parenteral nutrition in this patient group are those published in 2005 by ESPGHAN.⁸ There was an intention to revise the guidelines in 2016; however these are not available as yet. The American Society for Parenteral and Enteral Nutrition (ASPEN) also has a brief mention of its recommendations as part of a publication detailing guidelines for both EN and PN therapy in adults and paediatric patients.²⁵ This ASPEN paper is however outdated, and lacks the depth and information required to be clearly applied in clinical practice. An updated version of the ASPEN clinical nutrition guidelines for critically ill patients was published in 2016 but is targeted at the adult population (\geq 18 years of age), and is therefore not applicable as a reference guideline to this study.²⁴ ASPEN has also recently published paediatric-specific guidelines for both PN and EN feeding, but overall the recommendations are quite vague and the evidence grading low. These guidelines do not include neonatal patients, focusing on 1 month to 18 years of age.²³

The paucity of relevant guidelines does lend itself to wide variations in clinical practice and the absence of standard principles of care worldwide. As a result, many healthcare professionals rely on their clinical knowledge and experience, and their own interpretations of the literature, in their daily practice. There are also many opinion papers that tend to refer to the ESPGHAN guidelines, but also highlight the challenges in adhering to the recommendations in a real clinical setting, and although evidence based in most cases, can be subjective and heavily influenced by context.^{4,9,26-29} With the influence of context in mind, it is useful for the purposes of this research to refer to a South African-based review by Velaphi (2011), "Nutritional requirements and parenteral nutrition in preterm infants", in addition to the ESPGHAN guidelines.²⁹

1.5 Nutrient requirements and available parenteral nutrition components

1.5.1 Fluid and electrolytes

As much as protein and calories are the focus in terms of meeting growth and development goals in neonatal and paediatric patients, it is appropriate to first discuss fluid requirements and management. In many instances, it is the fluid allowance that dominates the feeding decisions and achievements. PN is often not given priority when fluid needs to be restricted, which makes optimal feeding a challenge. Also, the amount of each of the nutrients that can practically be included in a stable solution is also often limited by the amount of fluid.^{8,9,26,30}

In preterm and neonatal patients, it is important to be aware of the various phases of insensible water loss, and how these will influence the fluid management, and therefore PN administration. The first week consists of a transition phase, followed by a stabilisation phase as the body adapts to life outside the womb. Finally, in the second week of life, the stable growth phase begins, and marks the turning point in terms of positive fluid and electrolyte balance and weight gain. In the first week, the patient is particularly vulnerable to fluid overload and this may influence the amount of PN given.^{8,9,26,30}

Fluid and electrolyte therapy is influenced by multiple factors – the age, weight, clinical condition and treatment of the patient all contribute. Table 1.2 presents a summary of a guideline for the requirements in neonatal and paediatric patients.^{8,9} It should be noted that this is only a guideline, and that owing to the complexity of influences on fluid and electrolytes, the key message in the literature is the importance of an individualised approach. The administration of optimal feeding with PN within the context of overall fluid goals necessitates discussion between members of the multidisciplinary team to ensure that nutritional goals are not compromised at the expense of fluid goals and vice versa.^{8,9,26}

TABLE 1.2 SUMMARY OF DAILY PARENTERAL FLUID AND ELECTROLYTE REQUIREMENTS

Age/Weight	Fluid (mL/kg/d)	Na ⁺ (mmol/kg/d)	K ⁺ (mmol/kg/d)
<1500g	140 – 180	2.0 – 3.0	1.0 – 2.0
>1500g	140 – 160	3.0 – 5.0	1.0 – 3.0
Preterm to 2 months	140 – 160	2.0 – 5.0	1.5 – 5.0
2 months to 1 yr	120 – 180	2.0 – 3.0	1.0 – 3.0
1 – 2 years	80 – 150	1.0 – 3.0	1.0 – 3.0
3 – 5 years	80 – 100	1.0 – 3.0	1.0 – 3.0
6 – 12 years	60 – 80	1.0 – 3.0	1.0 – 3.0
13 – 18 years	50 – 70	1.0 – 3.0	1.0 – 3.0

Source: Adapted from [8; 9]

1.5.2 Macronutrients

The ESPGHAN guidelines provide detail regarding the determination of, and factors contributing to, energy requirements for neonatal and paediatric patients.⁸ As a general rule the energy requirements for parenteral feeding are 10% lower than those of enteral feeding owing to the elimination of energy required for the process of diet-induced thermogenesis. The life stage and therefore growth velocity, as well as baseline nutritional status and activity levels of the patient, are important contributing factors when calculating

energy requirements. The reason for hospitalisation also needs special consideration, as prematurity, critical illness, and more specific diagnoses such as burns or head injury, will certainly contribute to elevated energy needs.^{8,9}

All the macronutrients are sources of energy in parenteral feeding. It is however important to differentiate between the protein and non-protein (lipid and carbohydrate) energy, as the amino acids are essential for growth and recovery, and should not be considered for their energy contribution to feeding. In spite of this, most current guidelines for energy calculations in paediatric patients seem to refer to total energy (TE). Table 1.3 summarises the current recommended daily intake of PN macronutrients. Given the complex age and weight categories, implementing and adhering to these recommendations can prove challenging.^{8,9,29}

TABLE 1.3 SUMMARY OF DAILY PARENTERAL MACRONUTRIENT REQUIREMENTS

Energy (TE)		Amino Acids		Lipids		Carbohydrate	
Age (yr)	kcal/kg	Age	g/kg	Age	g/kg	Weight (kg)	g/kg
Preterm	110–120	Preterm	1.5–4.0	Preterm	3–4	Up to 3	10–18
0–1	90–100	Term neonates	1.5–3.0	0–12 months	3–4	3–10	16–18
1–7	75–90	2 months to 3 years	1.0–2.5	1–18 years	2–3	10–15	12–14
7–12	60–75	3–18 years	1.0–2.0			15–20	10–12
12–18	30–60					20–30	< 12
						> 30	< 10

Source: Adapted from [8; 9; 29]

The next section describes the current evidence base for the provision of the different macronutrients, and the types of solutions available in the South African PN formulations. The ingredients used in the compounded bags in this country are discussed for the age range of 0 – 12 years. Children aged 12 – 18 years have nutrient requirements more similar to the adult guidelines, and the standardised formulations for adults are therefore used for parenteral nutrition therapy in this group.

1.5.2.1 Amino acids

The provision of protein in the form of amino acids is often discussed in terms of nitrogen balance in a parenterally fed patient. Achieving a positive nitrogen balance requires providing a minimum daily amount (see Table 1.3 for age-specific values), and usually equates to the provision of 10 – 20% of total energy from

protein. The amino acid solution needs to contain both essential and non-essential amino acids.^{8,9,29} Certain amino acids, such as cysteine, tyrosine and taurine, are considered conditionally essential in children owing to their increased growth demands. Also, owing to immaturity of some metabolic functions, it is necessary for certain levels of amino acids, such as methionine and phenylalanine, to be reduced in paediatric PN solutions to prevent toxicity.^{8,31} In order to achieve the goal of protein accretion and therefore growth, it is important to provide an optimal protein to calorie ratio.^{3,8,9,31}

A Cochrane Review of parenteral amino acid provision in premature infants considered the timing of amino acid provision – early versus late – and concluded that there was insufficient evidence to support the benefit of providing amino acids within the first 24 hours of birth. Although a positive nitrogen balance was achieved in the earlier group, the clinical relevance of this finding could not be determined.³² In spite of this, the ESPGHAN guidelines, and most of the opinion papers and reviews, clearly recommend administering a minimum of 1.5g/kg/day within the first day of life in premature infants.^{4,8,33} Particularly in the ELBW and VLBW premature infants, there seems to be a good body of evidence to support the provision of amino acids as soon as possible, and that this does improve growth outcomes and potentially neurological development in the longer term.^{3,6,8,9,19,20,29,31,32} Interestingly, there is also increasing evidence that early, aggressive amino acid administration can be initiated without risking metabolic complications and acidosis, even in critical patients – the suggestion seems to be achieving at least 3g/kg/day within the first week of life, and thereby more readily mimicking foetal protein accretion rates. Furthermore, commencing amino acid infusion immediately post birth (within 4–6 hours), is associated with improved electrolyte balance and blood glucose control.^{21,28,34}

There is a relative paucity of data for the quantity and timing of protein administration in older children (ages 1–18 years) and much of the ESPGHAN recommendations in this group are graded C or D.⁸ Like in adults, critical illness and surgery result in increased protein catabolism, which may lead to muscle wasting and growth failure if the high protein requirements in the recovery phase are not met.¹ Favez et al. (2016) conducted a randomised clinical control trial comparing early initiation of PN therapy (within 24 hours of admission) in children, newborn to 17 years of age, with waiting for one week, and only commencing PN on day 8. Their conclusion was that starting later was clinically superior, as this patient group had fewer new infections, a shorter reliance on intensive care interventions, and a shorter hospital stay.³⁵ These results should however be interpreted with caution and cannot as yet be applied as a universal guideline. Each ill child's need for PN should be individually assessed by an experienced multidisciplinary team, and appropriate feeding interventions should be initiated as necessary. The study population focused on critically ill children, and the inclusion criteria were quite broad – it is possible that some patients did not require PN intervention and therefore did not show clear benefit as such from the therapy. Also, only 10% of the study participants were classified as high nutritional risk. The vast age range of the study subjects also makes applying a broad recommendation difficult.^{8,26,35}

The type and quality of amino acids provided in PN are important. Much of the evidence for inclusion of certain conditionally essential amino acids is based on their upregulation in breastmilk and focused on the neonatal period.⁹ Owing to the complexity of amino acid interactions and conversions in the body, it is difficult to draw definitive conclusions. The focus on the provision of a balanced, high-quality amino acid solution seems to be more important than individual amino acids at this stage. Blood monitoring of individual amino acids is not routinely performed, and currently available amino acid formulations are based on relatively outdated data, and perhaps assumptions based on the physiological role of certain amino acids to determine need.^{8,9,21,36} The pharmacological stability of individual nutrients also contributes to what can feasibly be included in a solution.³⁷ The role and inclusion of certain amino acids, such as glutamine and arginine, also still need to be more thoroughly investigated in terms of parenteral administration in neonatal and paediatric patients. Currently, Aminoven[®] Infant 10% is the only amino acid solution available for PN use in neonatal and paediatric patients in South Africa.³⁸

1.5.2.2 Lipids

Lipid contributes largely to patient energy intake during parenteral feeding, and should contribute to 25 – 40% of the non-protein calories.⁸ It provides energy density, thereby allowing greater energy provision in a smaller volume – this is particularly important in neonates and paediatric patients, where fluid restrictions often limit the optimal provision of nutrients.²⁶ Lipid is also necessary to prevent the development of an essential fatty acid (EFA) deficiency, which can arise within 72 hours post birth in preterm infants. The provision of 0.5 – 1 g/kg/day of an intravenous lipid emulsion (IVLE) appears to be sufficient to prevent deficiency risk.^{8,28,29,39} IVLE also enables the peripheral administration of PN admixtures as well as being important as the carrier medium for the provision of fat-soluble vitamins.⁸

Table 1.3 provides the goal ranges for lipid infusion based on patient age.^{8,9,29} An IVLE tolerance of 3g/kg/day via a continuous infusion (over 24 hours), is well established in the literature, although special consideration needs to be given in ELBW infants and patients presenting with hyperlipidaemias. There have been concerns about lipid administration in the first few days of PN infusion, mainly owing to pulmonary function (particularly in ELBW infants and patients with acute lung injury or chronic lung disease), but evidence is inconclusive and current administration levels of IVLE do not appear to affect lung function significantly. Some clinicians will still choose to delay lipid administration, but the guidelines state that commencing on day 1 is safe, and that due to EFA deficiency risk, should not be commenced later than day 3.^{4,8,26–30,40} It is also considered safe to administer IVLE in jaundiced infants – concerns have been linked to lipid infusions elevating the plasma free fatty acids, which may displace bilirubin from albumin binding sites, but at recommended administration dosages, free bilirubin does not seem to be affected.⁴⁰

Plasma triglyceride levels should be regularly monitored in patients receiving PN, and a reduction in IVLE infusion should be implemented if levels exceed 250 mg/dl (2.83 mmol/L) in infants, or 400 mg/dl (4.52 mmol/L) in older children.^{8,40}

There are currently two lipid emulsions available in South Africa for parenteral administration in neonates and paediatric patients. Intralipid® 20%, a soybean emulsion, is most commonly used, as it is more readily available, and forms the standard IVLE in the available admixtures.⁴¹ A newer IVLE known as SMOF lipid® 20%, which comprises a combination of soybean, medium-chain triglycerides (MCTs), olive oil and fish oil is only available on special request, so its usage is limited.⁴² The use of SMOFlipid® 20% in preterm and paediatric patients, particularly those receiving long-term PN, is well documented in the literature and appears to offer clinical benefit in terms of liver integrity and function, as well as reduced incidence of sepsis. The main benefit seems attributable to the fish oil which provides docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and is known to have immune-modulatory and anti-inflammatory characteristics.^{8,9,26,40,43–47} The role of long-chain polyunsaturated fatty acids (LC-PUFAs), like DHA and EPA, has been widely researched in the neonatal and paediatric population owing to their high content observed in breastmilk. The main demonstrable benefits link to their presence in the neural tissues, and the associated cognitive and developmental advantage that is achieved through regular dietary availability. The potential benefits of DHA in visual function and development, as well as allergy risk reduction, have also been investigated, although the outcomes are less conclusive to date. Much of the research on LC-PUFAs has involved human breastmilk and supplemented infant formulae, and also focuses on early infancy, but it is an interesting consideration for the inclusion of fish oil in PN formulations.^{9,48}

1.5.2.3 Carbohydrates

Carbohydrates are the major source of non-protein energy in PN therapy, accounting for 60 – 75% of non-protein calories, and are provided in the form of dextrose (D-glucose).⁸ The administration of glucose needs to be carefully monitored due to the risks associated with excessive intravenous (IV) infusion – this is defined as the provision of glucose above the threshold oxidation capability of the body. ESPGHAN classifies the maximal glucose oxidation rate in premature infants as 8.3 mg/kg per minute, and recommends that in critically ill children, the glucose infusion should not exceed 5 mg/kg per minute.⁸ Some of the documented concerns relating to hyperglycaemia (blood plasma glucose > 10 mmol/L or 180 mg/dL) include elevated sepsis risk, liver steatosis and the development of cholestasis, as well as potentially elevated carbon dioxide levels and minute ventilation.^{8,26,29,49} The excessive provision of calories in the form of glucose has also been shown to impair protein metabolism, which could affect growth and development in this patient population. Prolonged hyperglycaemia suppresses the release of insulin, which is required for the effective uptake of

both glucose and amino acids into the cells. Insulin is an anabolic hormone, and as such promotes growth, which is fundamental in neonatal and paediatric patients.^{50,51} The association between hyperglycaemia and increased infectious mortality is well documented in adult patients, and although it appears to be similar in paediatric patients, the studies are less conclusive to date.^{8,50,51}

Velaphi (2011) provided guidelines to commence glucose infusion at the hepatic glucose production rate of 6–8 mg/kg/minute. This can be increased in increments of 0.5–1 mg/kg/minute based on tolerance until the maximum glucose rate of between 12–13 mg/kg/minute is achieved. Tolerance is largely based on blood glucose level monitoring, and the goal is to maintain a level between 2.5 and 8.0 mmol/L (80 and 120 mg/dL), avoiding the risk of hypo- or hyperglycaemia.^{8,28,29}

The use of insulin therapy in infants and children is less common than in adults, as exogenous insulin supply may inhibit protein synthesis and thereby affect growth outcomes. There appears to be a lack of consensus in terms of clinical practice in this regard.^{4,8,9} It is important to adapt IV glucose provision based on each clinical situation – unstable, or critically ill patients, as well as those at risk of refeeding syndrome may need to start at lower rates. It is also vitally important to include non-nutritive glucose supply in total energy provision to avoid hyperglycaemia and overfeeding.^{8,9,29,30} A South African-based study in adult critically ill patients showed that an average of 8% (range 0–29%) of the total energy intake can be attributed to non-nutritional energy sources such as carbohydrate-containing IV fluids.⁵² Neonatalyte, a commonly used IV fluid, contains 10% dextrose.⁵³

The current PN formulations in South Africa provide glucose at a 5 or 10% concentration so that glucose intolerance can be accommodated to a certain extent.

1.5.3 Micronutrients

Micronutrients, although required in comparatively small amounts, are fundamental as co-enzymes and for hormone production in the body, which in turn contribute significantly to normal growth and development. Meeting micronutrient requirements in neonatal and paediatric PN is however complex, owing to a lack of clear evidence on what these exact requirements may be, as well as the challenges in terms of practically including them in the compounded admixtures.^{8,9,30,54}

There is a relative paucity of data on parenteral vitamin and mineral requirements for neonatal and paediatric patients. Very little new research has been done in the last 20 years, and current administration appears to be based on what is available in a certain country or context, and also on historical clinical practice and expert opinion. The absence of deficiency, determined by the blood levels, and also by the lack of clinical signs and symptoms, has led to the assumption that what is currently provided is sufficient.^{8,9,30,54} In fact, some

publications were based on shortages or absence of a certain micronutrient for parenteral use, and the consequent deficiencies and complications that arose in patients, and these provide evidence for their inclusion in PN solutions.^{55,56}

1.5.3.1 Vitamins

There does appear to be consensus that both water- and fat-soluble vitamins should be provided as part of the PN admixture, preferably on a daily basis. Vitamins are susceptible to instability, and it is recommended that whenever possible the vitamin preparations should be added to the lipid emulsion component to facilitate stability in the PN. Another important factor is exposure to direct sunlight, so this should be avoided in order to preserve the vitamin content of the solution.^{8,9,30,57}

In South Africa, vitamins and minerals are currently included in all parenteral admixtures administered to neonatal and paediatric patients. They are provided by Soluvit® Novum and Vitalipid Novum Infant® at the registered dose of 1 mL/kg/day.^{58,59} The inclusion in a commercially prepared all-in-one preparation inhibits the manipulation of the individual micronutrients. Table 1.4 summarises the current ESPGHAN recommendations, based on expert opinion, in comparison with what is provided by the available vitamin preparations. In some instances, the PN is providing significantly more than recommendations, but it should be noted that as documented in the literature, this has not been associated with any adverse effects to date.^{8,30,58,59}

In paediatric oncology patients, the provision of additional vitamins over and above the recommended nutrition intake (RNI) is not currently recommended. Similarly, in burns patients, although the metabolic demand for certain vitamins and minerals may be increased, as demonstrated in adult studies, routine additional supplementation is not advised.^{60,61}

1.5.3.2 Minerals and trace elements

Calcium, phosphorous and magnesium are fundamental for optimal growth and development, particularly in terms of bone mineralisation, but provision in PN is often limited by potential solubility issues. Studies to test compatibility of parenteral nutrients in solution, in the hope of being able to increase the concentration of calcium in compounded admixtures, have shown no advantage over newer lipid emulsions like SMOF Lipid® or increasing the glucose concentration in an attempt to prevent precipitation.^{8,9,62,63} In South Africa, calcium and magnesium are presently included in the standard commercially prepared solutions in the form of calcium gluconate 10% and calcium chloride 10%. Phosphorous is added in the form of potassium

phosphate 20%. Table 1.5 indicates ESPGHAN's guidelines on the provision of these three minerals, although owing to the practical pharmacological limitations discussed, additional calcium, phosphorous or magnesium may need to be supplemented in other ways in certain clinical scenarios.^{8,9,29,62}

TABLE 1.4 SUMMARY OF DAILY PARENTERAL VITAMIN REQUIREMENTS FOR INFANTS AND CHILDREN, AND CURRENT INTRAVENOUS VITAMIN PREPARATIONS AVAILABLE IN SOUTH AFRICA

Vitamin	Infant (Dose/kg/d)	Children (Dose per day)	Soluvit® Novum (per 10mL vial) Dose 1mL/kg/d	Vitalipid® Novum Infant (per 10mL vial) Dose 1mL/kg/d
Vitamin A (µg)	150 – 300	150	0	690
Vitamin D (µg)	0.8 (32 IU)	10 (400 IU)	0	10 (400 IU)
Vitamin E (mg)	2.8 – 3.5	7	0	6.4
Vitamin K (µg)	10	200	0	200
Ascorbic acid (mg)	15 – 25	80	100	0
Thiamine (mg)	0.35 – 0.50	1.2	2.5	0
Riboflavin (mg)	0.15 – 0.2	1.4	3.6	0
Pyridoxine (mg)	0.15 – 0.2	1.0	4.0	0
Niacin (mg)	4.0 – 6.8	17	40	0
B12 (µg)	0.3	1	5.0	0
Pantothenic acid (mg)	1.0 – 2.0	5	15	0
Biotin (µg)	5.0 – 8.0	20	60	0
Folic acid (µg)	56	140	400	0

Source: Adapted from [8; 58; 59]

TABLE 1.5 SUMMARY OF DAILY PARENTERAL CALCIUM, PHOSPHOROUS AND MAGNESIUM REQUIREMENTS

Age	Calcium mg (mmol) / kg	Phosphorous mg (mmol) / kg	Magnesium mg (mmol) / kg
0 – 6 months	32 (0.8)	14 (0.5)	5.0 (0.2)
7 – 12 months	20 (0.5)	15 (0.5)	4.2 (0.2)
1 – 13 years	11 (0.2)	6 (0.2)	2.4 (0.1)
14 – 18 years	7 (0.2)	6 (0.2)	2.4 (0.1)

Source: Adapted from [8; 9]

Iron is not currently included in neonatal and paediatric PN, mainly because of concerns of overload and its potential to increase the risk of developing gram-negative septicaemia. Current guidelines do however

recommend iron supplementation in long-term PN patients (receiving PN for longer than 3 weeks).^{8,9,54,57} In VLBW infants, the usage remains controversial, as the need exists, but the risks of infection are a concern.^{29,30} ESPGHAN reported a grade B recommendation for supplementation of iron in this patient group, but the dose is not clearly defined – suggested doses are provided in Table 1.6.⁸ Many critically ill paediatric patients, such as burns and cancer patients, receive multiple blood transfusions which is another reason why parenteral iron should not be routinely administered.^{60,61} Monitoring of iron status in this patient population as a whole is recommended to prevent toxicity and ensure that deficiencies can be avoided.⁹

The suggested requirements from the ESPGHAN guidelines for chromium, copper, iodine, manganese, molybdenum, selenium and zinc are also summarised in Table 1.6, together with the quantities present in Peditrace[®], the trace element preparation presently available and included in all standard compounded PN solutions in South Africa.^{8,64}

TABLE 1.6 SUMMARY OF DAILY PARENTERAL TRACE ELEMENT REQUIREMENTS AND THE CURRENT INTRAVENOUS TRACE ELEMENT PREPARATION AVAILABLE IN SOUTH AFRICA

Trace element	ESPGHAN Guideline (2005)	Peditrace [®] (µg/1 mL)	Peditrace [®] (µmol/1 mL)
Iron	Preterm: up to 200 µg/kg/d Infant & child: 50 – 100 µg/kg/d	0	0
Zinc	Preterm: 450 – 500 µg/kg/d Infant <3 months: 250 µg/kg/d Infant >3months: 100 µg/kg/d Child: 50 µg/kg/d (UL 5 mg/kg/d)	250	3.82
Copper	20 µg/kg/d	20	0.315
Manganese	1 µg/kg/d (UL 50 µg/kg/d)	1	0.0182
Chromium	0.2 µg/kg/d (UL 5 µg/kg/d)	0	0
Selenium	2 – 3 µg/kg/d	2	0.0253
Iodine	1 µg/d	1	0.0079
Fluoride	No recommendation	57	3.0
Molybdenum	Preterm: 1 µg/kg/d Infant & child: 0.25 µg/kg/d (UL 5 µg/kg/d)	0	0

Source: Adapted from [8; 64]

UL, Upper Limit

With many of the trace elements, it is a balancing act between preventing deficiencies and avoiding toxicity. Of particular concern in terms of toxicity are copper and manganese, as excess amounts are usually excreted

in bile, a process which is obviously inhibited during parenteral nutrition feeding. It is common practice to reduce or exclude copper in cases of cholestasis, and ESPGHAN also recommends monitoring copper intake closely in long-term PN. In terms of manganese, elevated blood values above normal levels, and associated deposition in the central nervous system with or without symptoms, have been reported in the literature, and it is recommended that especially in long-term PN administration, the quantities of manganese are reduced.^{8,9,54,65-67} It is worth noting, however, that in the South African context this approach is currently not possible, as both copper and manganese are included routinely in all available admixtures.⁶⁴

In preterm infants and paediatric burns patients, as well as those experiencing high gastrointestinal losses, additional copper and zinc may need to be supplemented, but blood levels then need to be closely monitored.^{8,9,30} In oncology patients, some of the chemotherapy medications can result in excess losses of magnesium, potassium, phosphate, and calcium – these electrolytes therefore need to be closely monitored, and additional supplementation initiated if necessary.⁶⁰ Although chromium and molybdenum are recommended in the ESPGHAN guidelines, they are currently not included in the Peditrace[®] preparation as indicated in Table 1.6.^{8,64}

1.6 Challenges associated with parenteral nutrition in neonatal and paediatric patients

Unfortunately, PN therapy in neonatal and paediatric patients is not without its challenges. There are complications associated with this route of feeding, the risk of infection is a real concern, and actual clinical practice often differs greatly from what is stipulated in the guidelines and literature. Feeding prescriptions also are often based on what is available, as opposed to what is considered optimal nutrition for the patient. Some of these issues are discussed in this section to highlight the complexity of PN feeding practices in this patient population worldwide.^{8,10,12,13,29,34,68-73}

1.6.1 Clinical complications

Of the most prominent challenges, particularly for patients reliant on long-term PN support, are the effects on the liver. Cholestasis can be caused by multiple factors, but there is evidence to suggest that duration of PN therapy, the quantity of glucose administered, elevated levels of certain trace elements, as well as the type of IVLE, all play a role in its development.^{9,28,29,40,46,49,74,75} It is important to ensure, where possible, in high-risk patients, that these nutrition-related factors are properly managed. High-risk patients include those that receive PN for a prolonged duration (longer than 2 weeks), for example, ELBW infants, and children with short-bowel syndrome (SBS).⁶⁶ The initiation of early enteral feeding, even at minimal trophic levels, is beneficial for maintaining gut integrity, as well as reducing cholestasis risk. Also, where possible, the use of

third-generation lipid emulsions (IVLE containing a fish oil component), such as SMOFlipid® should be implemented.^{9,29,43,66,75–78} The main hepato-protective effect seems to be attributed to the fish oil component of the SMOFlipid® emulsion. Tomsits et al. (2010) investigated the safety and efficacy of SMOFlipid® in premature infants requiring PN therapy, and noted the potential beneficial role of this IVLE in cholestasis management.⁴³ Pichler et al. (2014) compared a soybean / MCT combination lipid, Lipofundin®, with SMOFlipid® in patients aged 0–16 years with intestinal failure receiving PN for at least two weeks, and who were already showing signs of liver complications. The Lipofundin® resulted in improved liver parameters over time, but the addition of olive and fish oil in the IVLE resulted in the most notable reversal of liver abnormalities, as well as less inflammation.⁴⁷ Goulet et al. (2010) noted improvements in plasma bilirubin levels in long-term home PN paediatric patients (aged 5 months to 11 years) receiving PN containing SMOFlipid® when compared with Intralipid®.⁴⁵ Finally, Hoffmann et al. (2014) investigated SMOFlipid® usage in paediatric oncology patients undergoing chemotherapy treatment, and although cholestasis incidence did not differ between the two groups, possibly owing to the relatively short duration of PN therapy (14 days), the SMOFlipid® resulted in lower gamma-glutamyl transpeptidase (GGT) levels. GGT can be considered an early marker of the development of cholestasis and the authors suggested there is therefore early evidence for the liver protective effect of SMOFlipid® in this patient group.⁴⁶

Hyperglycaemia is also a common problem related to PN therapy, and is directly related to glucose infusion. Critically ill and preterm patients are most at risk owing to their relative instability and the presence of sepsis. Inhibition of insulin release in these stressed patients exacerbates the elevated blood glucose levels further.^{8,9,29} The early provision of amino acids may promote insulin release, and in many instances the amount of glucose in the PN solution may need to be reduced.⁸ In South Africa, there are lower glucose admixtures available for this purpose. Insulin therapy in neonatal and paediatric patients is not common practice, but may be considered if hyperglycaemia persists.^{8,29,30}

The challenge of feeding optimally is a complex issue, and nutrient deficits place this patient group at risk of developing malnutrition.² Achieving growth and development targets is often hindered by the disease process, as well as medical interventions and a lack of adherence to feeding guidelines. These outcomes should be closely monitored, and changes to prevent and treat malnutrition, and promote growth, should be implemented if necessary.^{7,9,28,29}

Another concern in long-term patients is metabolic bone disease associated with PN. This presents in a similar form to rickets, and may be caused by the relative inactivity and the underlying pathology, but also by suboptimal calcium and phosphorous provision and utilisation. These biochemical parameters should be closely monitored in patients that are identified as high risk.^{8,9,29}

In light of these potential clinical complications, regular monitoring of the patient is imperative. Table 1.7 summarises the recommended tests and measurements that should be done in parenterally fed neonatal and paediatric patients.^{8,29}

TABLE 1.7 RECOMMENDED MONITORING IN NEONATAL AND PAEDIATRIC PATIENTS ON PARENTERAL NUTRITION

Test / Measurement	Frequency
Glucose	6 – 8 hourly while increasing glucose infusion rate Once or twice daily once on a stable glucose infusion
Serum electrolytes & urea	Twice a week while increasing fluid rate, then weekly
Serum Ca, Mg, PO ₄	Weekly
Liver function tests (LFTs)	Weekly
Serum triglycerides	Weekly
Urinary glucose	Daily for first 5 days and then weekly
Weight, length & head circumference	Weekly

Source: Adapted from [8;29]

1.6.2 Line access and infection risk

The high nutrient content of PN provides an ideal medium for bacterial and fungal growth, and it is therefore imperative that the compounding and administration of PN are completed under strict aseptic conditions. In South Africa, compounding is not done at hospital level at all. Commercially prepared solutions are compounded by Fresenius Kabi at a single site, using barrier isolator technology, producing standardised regimens that have been terminally sterilised. They are then transported under strict cold-chain conditions to five distribution dispensaries throughout the country. The bags are dispensed daily on a patient-specific basis, and maintaining the cold chain and rigorous quality measures throughout, are transported to hospital dispensaries and finally to the ward to be administered to the patient.^{8,29,79}

PN requires suitable venous access, and good line care is essential for minimising infection risk. Where possible, particularly if parenteral nutrition therapy is going to exceed 7 days, a peripherally inserted central catheter (PICC) or central venous catheter (CVC) should be inserted. There is evidence to support either the use of the jugular or subclavian site, as well as no additional mechanical or infectious risk associated with femoral access. In neonates, it is also considered acceptable practice to utilise the umbilical line initially; usage of this access site should however not exceed 5 days or 14 days for arterial and venous catheters respectively. The guidelines are clear that PN solutions containing a lipid emulsion should not hang for longer than 24 hours. Healthcare professionals handling and prescribing the PN should practise good hygiene, and

also monitor the access site for signs of infection and compromise, in order to minimise the risk of complications.^{8,9,80}

Donnell et al. (2002) suggested in their findings that the predominant cause of septicaemia in surgical neonates and infants was due to bacterial translocation, but this appears to be a controversial result, as their methodology in determining translocation was challenged in a subsequent editorial.⁶⁸ A study by Fizez et al. (2016) in critically ill children also investigated PN initiation and the link to infectious complications. They concluded that delaying PN therapy by one week was superior in terms of infection outcomes.³⁵ These results should however be interpreted with caution, as the goal of nutrition therapy is to promote growth and development, and prevent malnutrition, and it should not be delayed based on a single finding. The key message in the literature remains that the safe, appropriate administration of PN can minimise infection risk in neonatal and paediatric patients.⁸¹⁻⁸³

1.6.3 Parenteral nutrition availability

Although a seemingly obvious concept, it is worth noting the role which accessibility to PN may play in feeding practices.^{14,73} In South Africa, the health system is split between a private and state sector. The state hospitals tend to have a more restricted procurement process, and more limited funds, and this has the potential to influence the availability of certain drugs, including PN. Also, as mentioned previously, Fresenius Kabi is currently the sole supplier of neonatal and paediatric PN in the country, and distributes the compounded bags from a single central compounding facility to five dispensaries located in the major city centres. It seems logical that areas considered further away from these dispensaries, may potentially experience delays and therefore the ability to commence PN therapy, in comparison with hospitals in the direct vicinity.^{84,85}

In any country, the product registration of a drug will also determine its availability – the current standard PN formulations that are available in South Africa consist of preparations that are approved and registered with the Medicines Control Council (MCC) and the Department of Health (DoH).^{84,86}

Finally, the pharmacology involved in producing a stable product may be a limiting factor in terms of what feasibly can be provided in a PN solution. Amino acids, electrolytes, and minerals such as calcium and phosphorous, present particular challenges in terms of compounding a nutritionally optimal admixture that is also stable.^{8,37,57,62,63,67}

1.6.4 Adherence to guidelines in clinical practice

The current available guidelines have been discussed in detail in Section 1.5, but it is evident from surveys and audits conducted in neonatal and paediatric intensive care units (ICUs) worldwide, that knowledge of guidelines does not necessarily translate into actual clinical practice.^{10-13,87} Moreno et al. (2016) reported notable differences between predicted requirements for the nutrition therapy administration, intended prescription, and actual protein and energy delivery in a single paediatric ICU in Brazil. In this single-centre, prospective cohort study, they noted that actual energy and protein provision comprised half of the estimated requirements and that 68% of the patients were underfed. The main reasons for this finding appeared to be suboptimal prescription as well as recurrent interruptions to the administration of feeds.¹³ Turpin et al. (2013) described similar findings in their medical chart review in German neonatal ICUs. The results from survey studies suggest that although the PN guidelines are often known by the healthcare professionals, the intention to treat differs greatly from what is achieved. They noted that only 30% of their preterm patients received amino acids within the first day of life, and 34% received IVLE by day 3, despite apparent knowledge of the guidelines.⁸⁷ Lapillonne et al. (2013) conducted a large survey including 74% of the neonatal units in Germany, France, Italy, and the United Kingdom, to investigate adherence of the unit protocols to international guidelines, and also the factors that influence compliance. They found large variations in parenteral feeding protocols and feeding practices, and that the size of the hospital, number of neonatal beds, and location did not have a significant influence on prescribing patterns. Amino acids were often not administered within the first day of life, and both amino acids and IVLE were commenced at lower doses than recommended by the ESPGHAN international guidelines. The authors noted that the variation in lipid administration may be due to a lack of clear scientific evidence and guidance for clinicians in this regard. Interestingly, the academic institutions in this study were more likely to introduce lipid earlier in their preterm infants, as well as administering higher glucose infusions at PN initiation. This study also highlighted that the international guidelines may be too theoretical, and therefore difficult to implement in clinical practice, and that some units relied more heavily on clinical practice protocols than the ESPGHAN publication.¹²

There is a relative paucity of literature examining the knowledge of doctors and dietitians in relation to PN in neonatal and paediatric patients. Most of the studies that have considered healthcare professionals' knowledge of the international guidelines have only focused on knowledge of the protein targets in this patient group, as the primary objectives of the studies have been to assess prescribing practices. Ahmed et al. (2004) conducted telephonic interviews with physicians, and noted that 65% of respondents did not know the target dose for parenteral amino acid provision in VLBW infants. It should however be noted that this study was prior to the publication of the ESPGHAN guidelines in 2005.⁸⁸ Grover et al. (2008) found that only 27% of the pharmacists surveyed knew the target dose for amino acids.¹⁷ Lapillonne et al. (2009) showed

improved knowledge of protein targets, with 92% of physician respondents knowing the target should be ≥ 3 g/kg/day on commencement of parenteral feeding, and 44% aiming for the 3.5 – 4 g/kg/day recommendation in their VLBW patients.¹¹

There appears to be high variability in terms of the healthcare professionals involved in making PN feeding decisions, as well as their application of the knowledge and guidelines in clinical practice. The literature does highlight the importance of and need for ongoing training and education in this regard, and there is evidence that improved awareness, as well as implementing standardised clinical protocols, can have beneficial results for improved practice.^{10–12,72,88–91} Jadcherla et al. (2016) examined the impact of implementing a feeding quality improvement programme involving a standardised feeding strategy for premature infants. Although the focus was more on EN feeding, their findings highlight that with clear feeding guidelines, the progression of feeds and thereby achievement of growth goals can be significantly improved.⁹¹

Currently, in the South African context, only two studies have been conducted to survey the feeding practices in preterm infants. The focus of both was on EN, and only premature and low birth weight (LBW) infants, so although different, their findings are useful in providing insight into response rates, overall approaches to feeding in this patient group, and feeding practice within the South African healthcare environment. Raban et al. (2013) targeted paediatricians and described the commencement of enteral feeds within the first 24 hours of life. Only a quarter of the neonatal patients (< 25 weeks gestational age) received EN feeds on day 1. The research also provided insight into access to fortification and donor milk, as well as feeding goals in this patient group. Bradfield et al. (2016) investigated EN practices of doctors and dietitians in both the private and state sectors. They noted significant differences in the initiation of feeding between the state and private hospital setting – the prescribers working in state hospitals were more likely to commence EN nutrition therapy earlier than those in private hospitals. Dietitians were also significantly more likely to calculate protein requirements for their patients, than the doctors.^{85,92}

1.7 Standardised versus individualised parenteral nutrition

The way in which PN for neonatal and paediatric patients is compounded and prescribed differs greatly around the world. Some units rely on individualised preparations done by their hospital pharmacy on site; others have a combination of standardised formulations and individualised compounding; and others, as in South Africa, rely on commercially prepared standardised bags. The debate in favour of either is ongoing, but overall the literature seems to suggest that the use of standardised all-in-one PN solutions is feasible and safe; minimises the risk of errors and misuse (for prescribing and compounding); and can assist in optimising nutrient delivery. It also appears to be a cost-effective approach, and increases the availability of parenteral nutrition without the need for onsite compounding facilities and trained staff. Contamination, and therefore

the associated infection risk, also seem to be minimised through the use of premixed PN solutions.^{14,15,73,79}
The stability of standardised formulations can also be more readily achieved and maintained.^{37,93}

The challenge with standardised solutions seems to lie mainly in their lack of flexibility. Certain patient groups, such as the VLBW and ELBW neonates, and critically ill children, may require a solution that is tailor-made for their biochemical and nutritional needs. The main concern appears to be the need to manipulate the electrolytes and overall fluid in certain clinical situations. Perhaps the best solution is having access to a combination of standardised and individualised admixtures.^{14-16,79,94}

The context in which PN feeding is done will likely dictate whether standardised or individualised PN is the best option – in South Africa, the commercially prepared formulations suit the economic, and environmental climate in which healthcare is currently provided.^{79,84}

1.8 Motivation for research study

PN has a fundamental role to play in the nutritional management of many neonatal and paediatric patients, and it is evident from the literature that its use may be influenced by several factors. The paucity of data describing PN use in this patient group within the South African health context, motivated the research study.

Chapter 2: Research Design and Methodology

Chapter 2: Research Design and Methodology

In this chapter, the research methodology is described in detail. The research question, study aim and objectives, as well as the complete study plan that was followed, are provided.

2.1 Research question

What are the current paediatric and neonatal PN prescribing practices in South Africa, and what factors influence and guide these practices, with special emphasis on knowledge?

2.2 Aim of the investigation

The aim of the investigation was to identify the current paediatric and neonatal PN prescribing practices in South Africa.

2.3 Objectives of the investigation

The study objectives were designed to be achieved through the use of a questionnaire and included the following (see Figure 2.1 for conceptual framework):

- i. To determine the prescribing practices of PN by paediatric medical specialists and dietitians in South Africa.
- ii. To determine the factors that influence PN usage by paediatric medical specialists for their patients in South Africa.
- iii. To determine where PN prescribers access PN information and guidelines.
- iv. To determine PN prescribers' knowledge of the ESPGHAN international guidelines (referred to as the ESPGHAN guidelines going forward) and recommendations on feeding practices relating to PN in paediatric and neonatal patients.
- v. To compare the subgroups (work sector – state/private) in terms of PN prescribers' feeding practices and factors related to their PN use.
- vi. To compare the subgroups (profession – dietitian/paediatric doctor) in terms of PN feeding practices and knowledge of international guidelines.

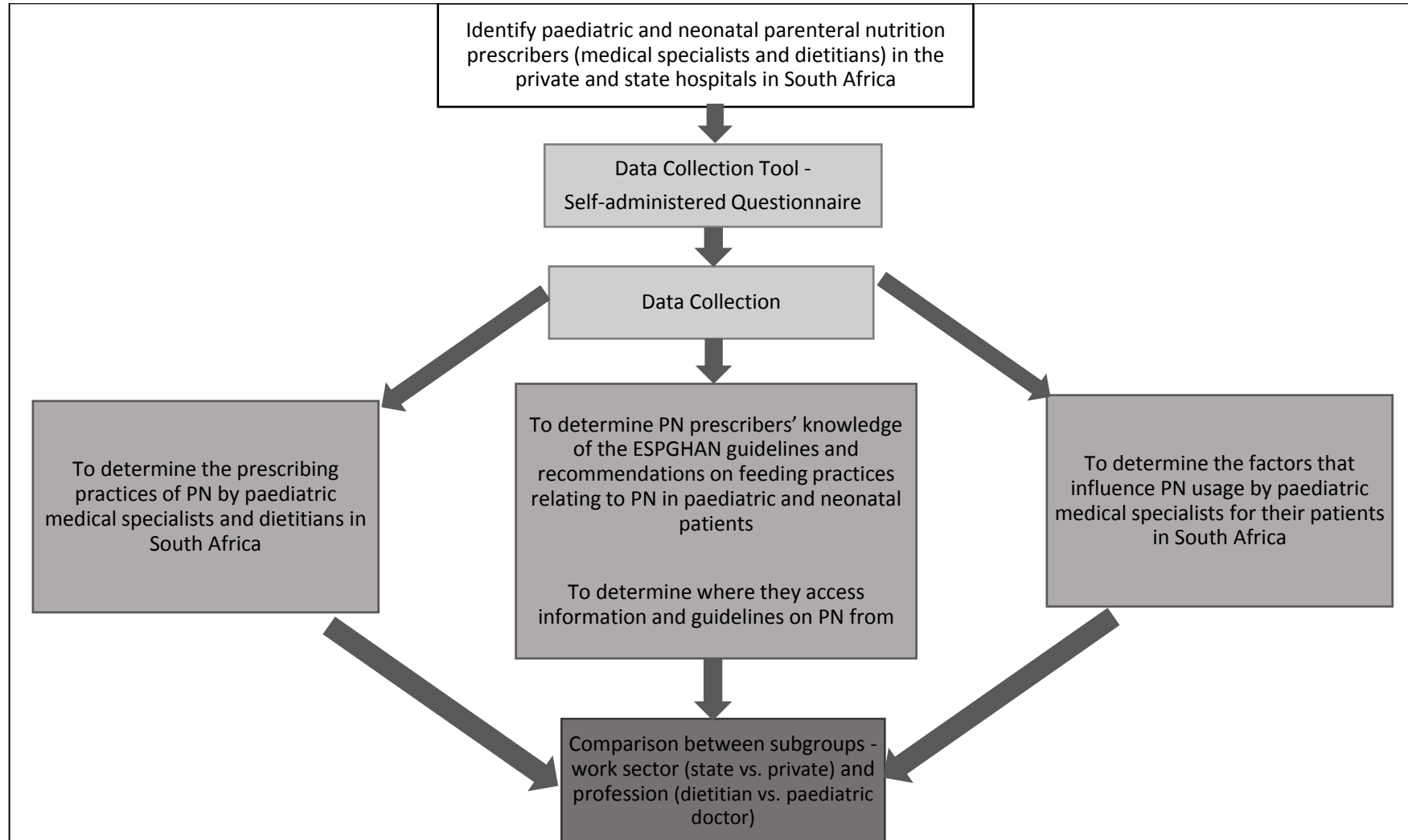


FIGURE 2.1 CONCEPTUAL FRAMEWORK FOR ACHIEVING STUDY AIMS AND OBJECTIVES

PN: Parenteral Nutrition; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition

2.4 Null hypothesis

H₀: There is no difference in the PN prescribing practices and knowledge of the ESPGHAN guidelines between the work sector subgroups (state and private hospital sectors).

H_{0L}: There is no difference in the PN prescribing practices and knowledge of the ESPGHAN guidelines between the profession subgroups (dietitians and paediatric doctors).

2.5 Study design

This was an observational, descriptive, cross-sectional study (questionnaire survey) with an analytical component.

2.6 Study population

The study population consisted of all paediatric medical specialists and dietitians working with neonatal and/or paediatric PN in South Africa. The targeted study population was a relatively small group of specialist dietitians and medical specialists (estimated based on the number of neonatal and paediatric units in both private and state hospitals in South Africa). As Fresenius Kabi is the sole supplier of PN to this patient group in the country, the company was able to provide insight into usage in the hospitals. There are 197 hospitals ordering neonatal and paediatric PN bags regularly, 69 (35%) state, and 128 (65%) private sector institutions.⁹⁵

Inclusion criteria:

Identified neonatal and/or paediatric PN prescriber. For the purposes of this study, the 'prescriber' was defined as a registered dietitian or medical specialist (medical officer training in paediatrics/paediatrician/paediatric specialist/neonatologist) assisting with the prescription of, or prescribing PN in neonatal or paediatric patients on a weekly basis.

Exclusion criteria:

Paediatric medical specialist or registered dietitian not currently working in a neonatal and/or paediatric intensive care unit in South Africa, or prescribing PN in this patient group less frequently than on a weekly basis.

Sampling:

The sample size calculation was based on the primary objective. To describe paediatric PN prescription practices in South Africa with a precision of 17%, 83% power and a 95% confidence interval, 70 participants needed to be included.

For sub-group analyses, Objective (v) and (vi), a minimum of 30 participants per group was required for hypothesis testing. This was calculated with a power of 85% and a small–medium effect size of RMSSE=0.55.

Purposive sampling was used, as all identified prescribers, as defined by the inclusion criteria, were included in the study. The final study sample consisted of all the respondents to the questionnaire from this target group.

The study population was stratified according to work sector (state / private) or professional group (dietitian / paediatric doctor) for the purposes of the analytical component of the study.

2.7 Data collection

2.7.1 Recruiting of study participants

The potential study participants were accessed via the organisations and societies that communicate regularly with them. For the dietitians, the Association for Dietetics in South Africa (ADSA) was used as a means of inviting the prescribers to participate in the survey. ADSA sent out an advertorial as part of their regular communication with their members, providing details of the research and inviting dietitians involved in neonatal and paediatric parenteral nutrition prescription to follow the online survey link and complete the questionnaire. The paediatric medical specialists were reached via the South African Paediatric Association (SAPA). SAPA sent an email with the research information and a link to the survey to its members, but the initial contact process yielded no response from this target group.

A second round of contacts was initiated with the potential study participants in order to improve questionnaire response rates. This involved another advertorial via ADSA. The medical specialists were then recruited by the researcher contacting them directly. For state hospitals, the heads of paediatric departments were emailed with information on the study and a link to the questionnaire to distribute to

their individual teams of doctors. For the private sector hospitals, the main hospital groups were identified – Life Healthcare, Mediclinic, Netcare and Independent. The Life Healthcare and Independent hospitals had little information available on their websites so had to be excluded from this recruiting process. The Mediclinic and Netcare websites had detailed lists of all their paediatric healthcare professionals, and in most cases included a contact email address. These email addresses were used to send the study information and a survey link directly to the medical specialists.

2.7.2 Questionnaire development and composition

No validated questionnaire tool for this study was available, so related questionnaires were used as a guide to develop a new questionnaire based on the study objectives. The questionnaire consisted of 35 questions, including questions linked to relevant demographic information; PN prescription practices; the potential factors related to PN usage; information access; and overall knowledge of the PN guidelines.

PN prescription factors were assessed in terms of timing, patient type and diagnosis, use of macronutrients (protein, glucose and lipid), and fluid allocations. Previous studies have focused predominantly on the dosage and timing of macronutrients in PN prescription, so this was included as a key component of the prescription factor assessment.^{10,12,72} The ESPGHAN Guidelines have a dedicated chapter for fluid in terms of PN management, so the decision was made to include fluid practices in the questionnaire.⁸ Prescriber knowledge of the ESPGHAN guidelines was assessed, as well as access to information.⁸ The decision to use the ESPGHAN guidelines as a gauge of knowledge was based on the availability of the information and the fact that they were currently the only concise, clear, defined guidelines for parenteral nutrition in this patient group that could be found after extensive searches. They represent a collective opinion for nutrition in this patient population based on the clinical evidence available, and were viewed as ‘best practice’ at the time of questionnaire development and distribution. No previous questionnaire assessing knowledge in this way was available, so the knowledge questions were developed with the guidance and assistance of expert opinion, and refined during the validation process. Factors that may influence PN prescribing practices such as resource availability, years of practice, frequency of scripting, provincial location, work sector (state/private), and experience with PN were also included. If the participant was involved in both state and private sector hospitals, he/she was asked to complete the questionnaire based on the work sector in which the majority of prescriptions was completed. Please refer to Addendum A for the questionnaire.

The content validity of the developed questionnaire was reviewed by a selected panel of five clinical dietitians and neonatologists before implementation. The panel adjusted the wording of some of the questions, ensured that both the neonatal and paediatric patient feeding practices were addressed, and that the knowledge questions were clear and easy to understand, and covered the main aspects of PN feeding. The

face validity was assessed by conducting the questionnaire with 3 identified dietitians and medical specialists with previous experience in neonatal and paediatric PN, but who did not meet the inclusion criteria for the study as they were not actively prescribing PN at the time. A few minor amendments to the questionnaire were necessary to improve question understanding as well as content. An additional 2 identified prescribers who also met the criteria of the pilot group were then asked to test the finalised, online survey system for face validity, ease of use, and time to complete the questionnaire (10 minutes). This pilot and test were completed before the questionnaire was made available for completion by the identified study participants.

2.7.3 Questionnaire administration

The data was collected by means of a self-administered online questionnaire via SurveyMonkey®. Each participant was allocated a code to ensure anonymity during the data-collection and analysis processes. A cover letter and informed consent document were included in the electronic system. Completion of the survey online was viewed as providing consent. An incentive, in the form of entrance into a 'lucky draw' for a relevant academic conference sponsorship (to the value of R3500.00) was offered for completion and submission of the questionnaire. Participants were allowed to choose to participate in this draw by submitting their contact email after completing the questionnaire.

As this was a self-administered questionnaire, the need for training and standardisation was eliminated, and inter-observer variation was not a concern. The pilot process helped to ensure that the questions were well formatted and phrased, thereby improving the quality of the data captured. Incomplete questionnaires were used for the relevant completed sections. The participants that failed to conform to the inclusion criteria were excluded and did not form part of the study. These were identified as survey respondents who do not actively prescribe or recommend PN feeding in neonatal or paediatric patients (they answered 'no' to both Questions 6 and 8; see Addendum A).

2.8 Analysis of data

2.8.1 Data capture

The data was captured using Microsoft Excel 2013, and based on the pre-established coding system.

2.8.2 Statistical analysis

Statistical analysis was done using STATISTICA™ version 13.2 (StatSoft Inc. 2016 STATISTICA data analysis software system, www.statsoft.com). Basic analyses for the descriptive data included the summary of the data into categories, and pivot table representations of this information. General frequency responses from the questionnaire data were calculated and used to assess potential associations between the categorical variables (e.g. primary reasons for use of PN; duration of practice; frequency of PN use). The chi-squared (χ^2) test was used for analyses between nominal variables (e.g. calculation of the various nutrient requirements; profession; work sector); the Mann–Whitney U Test for comparisons between not normally distributed nominal and continuous variables (e.g. commencement of PN; practice score; knowledge score); and Spearman's rank correlation coefficient for continuous variable analysis. The significance level was set at 95% ($p < 0.05$). This process was completed with the assistance of the statistician from the Centre for Statistical Consultation at Stellenbosch University.

The practice scores were determined by combining several of the questions related to clinical practice. The commencement of PN, introduction of lipid, and calculation of patient-specific requirements were considered. Best practice was allocated the highest score – commencing PN within 24 hours (3 points); introducing lipid from day 1 (3 points); and always calculating requirements for protein, energy, glucose oxidation rate and fluid (2 points each). A maximum score of 14 was achievable, and the combined scores were reflected as a percentage of this total. The PN practices assessment was analysed based on a competency of 60%. Owing to no references for practice scores being available, it was decided a priori to use 60%.

The analysis of the knowledge assessment was based on a comparison with the 2005 ESPGHAN Guidelines on Parenteral Nutrition in Paediatrics.⁸ The relevant questions (Numbers 21 to 35, see Addendum A: Questionnaire) were marked for correctness and one point allocated for each correct answer. These points were collated to form the knowledge score, and a maximum of 15 points was achievable. The knowledge scores are reflected as a percentage. Once again, owing to the lack of available references for knowledge assessment scoring, it was decided a priori to use an 80% competency.

2.9 Financial disclosure

The research was self-funded.

2.10 Ethics approval

In accordance with the National Health Act, No. 61 of 2003, ethics approval was obtained from the Stellenbosch University Health Research Ethics Committee (HREC) – S14/10/252. The use of communication channels via the established dietetic and paediatric organisations, and readily available information online, also ensured the voluntary nature of study participation and protection of the participants' personal contact information.

Coding was used throughout the data-collection and analysis process to ensure that answers could not be linked to a specific name on the sample population list. The use of an online survey system also allowed the anonymity of the participants to be maintained during the data-collection process.

The online survey included a cover letter informing the participants about the proposed research and their involvement, and an informed consent document. Their agreement to participate in the survey was included in this consent process.

Data management was overseen by the primary researcher, and data was stored on an external hard drive as well uploaded to an online 'cloud'. All access to this data was password protected to ensure limited access to the information.

Chapter 3: Results

Chapter 3: Results

In this chapter the study findings are presented and summarised.

3.1 Demographic characteristics

A total of 83 respondents commenced with the questionnaire. Based on the estimated targeted sample population, this is a response rate of 42%. Figure 3.1 depicts the flow of participation in the survey. Four respondents (5%) were excluded from the data analysis due to their only completing the first question in the survey; and one (1%) did not conform to the inclusion criteria as he/she did not prescribe PN in this patient group at all. A further six (7%) were excluded as they exited the survey after answering only the first five questions (providing basic demographic data). The final sample consisted of 72 respondents. A further eight (10%) respondents did not complete the knowledge section of the questionnaire (Questions 25 – 35), and a sample of 64 was therefore utilised for data analysis in this component.

The first section of the questionnaire explored the demographic characteristics of the study respondents. Table 3.1 provides an overview of these findings. There was a relatively even split between those working in the private and state health sectors. If the respondents worked in both sectors, they were asked to specify where they were predominantly based, and answer the survey based on these experiences and setting. Interestingly, the split within the state sector between the smaller regional and secondary hospitals, and the larger academic institutions, was equal. The majority of the respondents worked in units with more than 6 beds for neonatal or paediatric patients.

There were more dietitians than paediatric doctors that completed the survey, but a relatively good distribution of specialists within the latter group. Unfortunately, no paediatric surgeons or paediatric cardiologists responded to the survey. The respondents had variable years of experience, but overall there was good representation across the group.

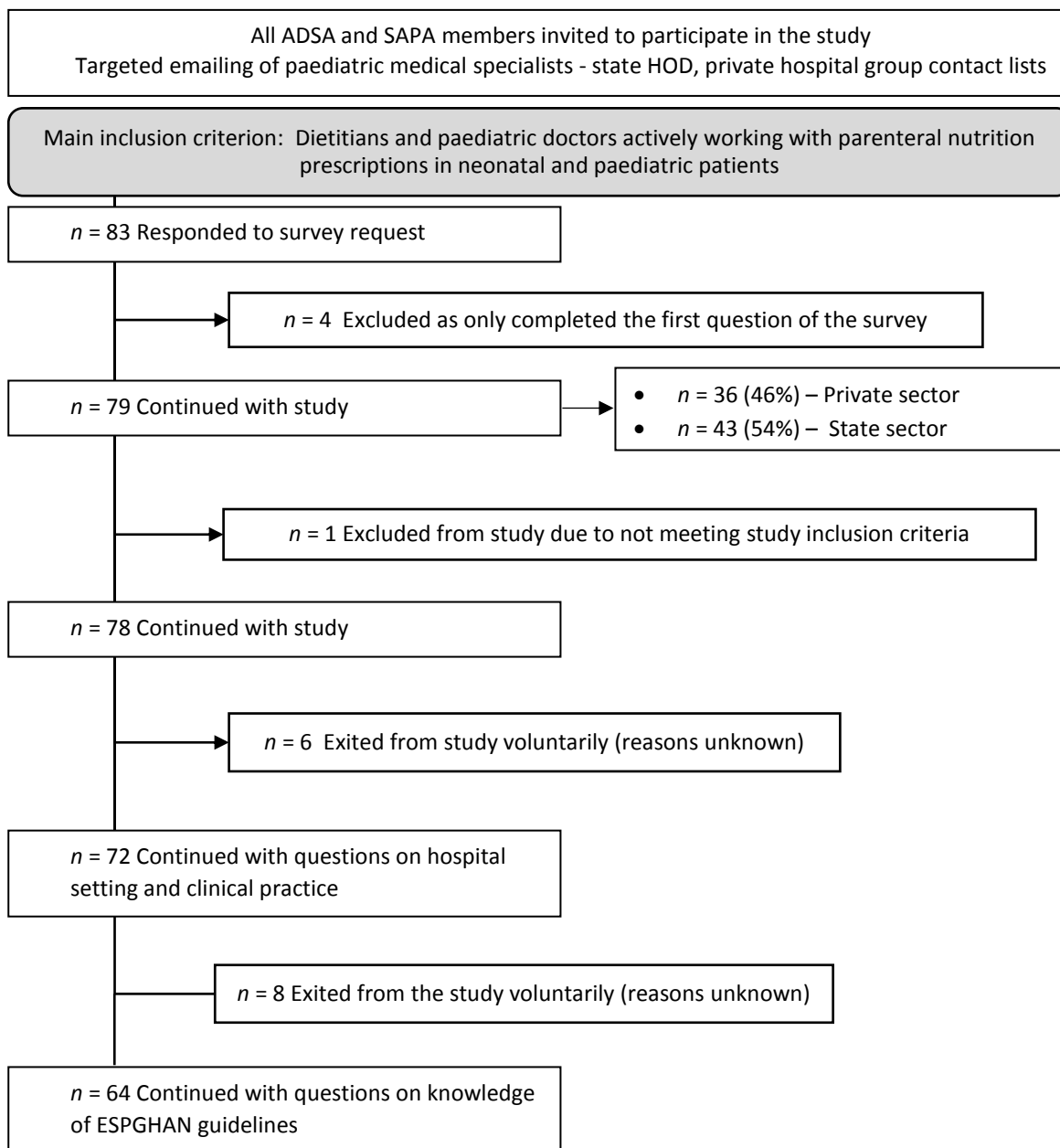


FIGURE 3.1 FLOW CHART INDICATING PARTICIPATION IN THE STUDY

ADSA: Association for Dietetics in South Africa; SAPA: South African Paediatric Association; HODs: Heads of Department; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition

The survey also noted the provincial location of the study participants. The provincial distribution is shown in Figure 3.2. The survey responses were based predominantly in the Gauteng province (51%), followed by KwaZulu-Natal (18%) and the Western Cape (14%). There was no representation from Limpopo and the Northern Cape.

TABLE 3.1 SUMMARY OF THE DEMOGRAPHIC CHARACTERISTICS OF THE SURVEY RESPONDENTS

Hospital sector (n = 72)	n	%
Private	34	47
Exclusively private hospital	32	94
Both – predominantly private hospital	2	6
State	38	53
Regional / secondary hospital	16	42
Academic / tertiary hospital	16	42
Both – predominantly state hospital	6	16
Number of beds in neonatal / paediatric unit (n = 72)	n	%
1 – 5 beds	10	14
6 – 10 beds	32	44
> 10 beds	30	42
Profession (n = 72)	n	%
Dietitian	42	58
Doctor	30	42
- Medical Officer (MO)	1	3
- Neonatologist	2	7
- Paediatrician	19	63
- Paediatric Intensivist	7	23
- Paediatric Pulmonologist	1	3
Duration of practising and working with PN prescriptions (n = 72)	n	%
0 – 2 years	12	17
3 – 5 years	21	29
6 – 10 years	16	22
11 – 20 years	19	26
> 20 years	4	6

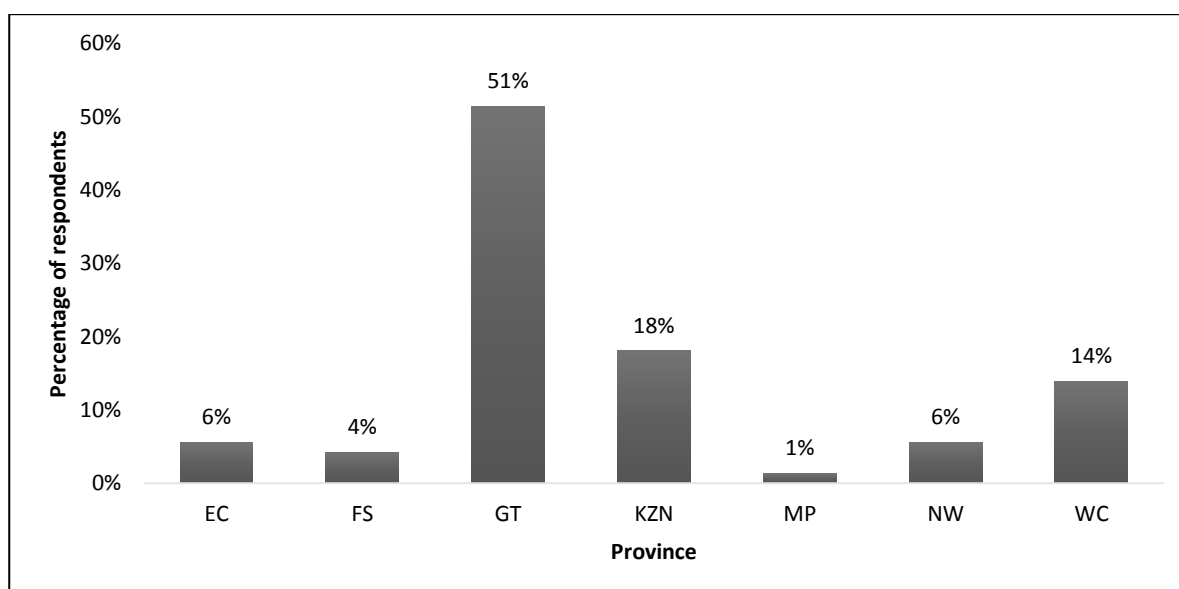


FIGURE 3.2 PROVINCIAL DISTRIBUTION OF THE SURVEY RESPONDENTS

EC: Eastern Cape; FS: Free State; GT: Gauteng; KZN: KwaZulu-Natal; MP: Mpumalanga; NW: North-West;

WC: Western Cape

3.2 Parenteral nutrition feeding practices

3.2.1 Parenteral nutrition usage and nutrient calculations

The survey respondents were asked to rank their reasons for PN usage in their neonatal and paediatric patients. The primary reasons for prescribing or recommending PN feeding were determined by combining the frequencies of a 1–3 ranking for each category. Figure 3.3 provides a graphical summary of these findings. Gut anomalies and intolerances, prematurity, critical illness, and post-operative need were the main clinical indications for PN usage. Unfortunately, the respondents who chose other reasons as their main reason, did not specify which conditions these might be. The more specialised categories, oncology and burns, were far less common as a predominant reason to utilise PN.

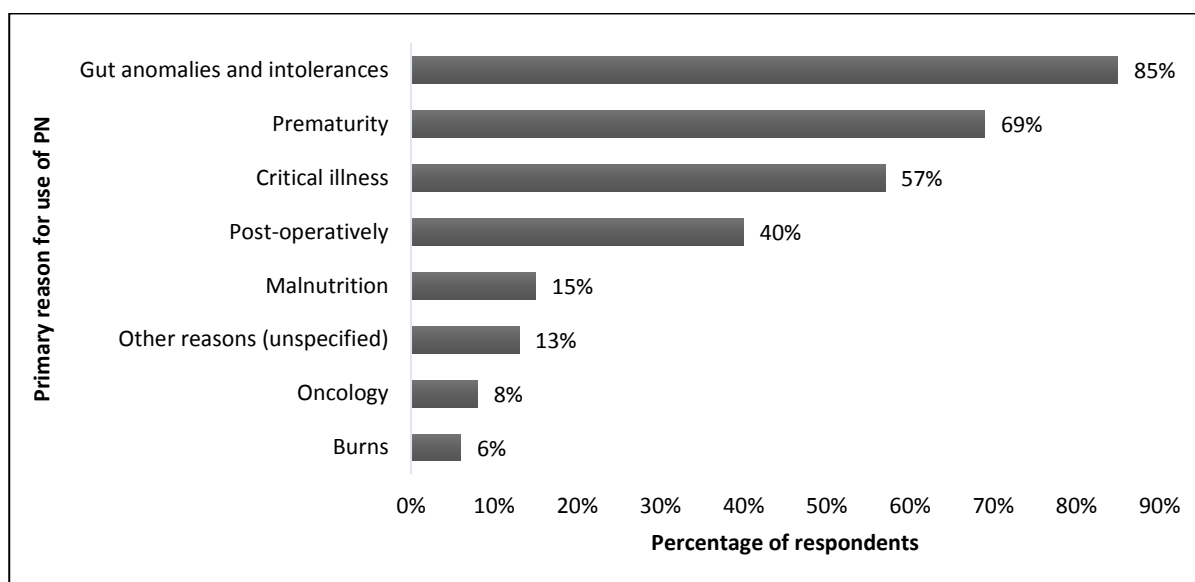


FIGURE 3.3 PRIMARY REASONS FOR USE OF PARENTERAL NUTRITION IN NEONATAL AND PAEDIATRIC PATIENTS

In addition to the clinical indications linked to PN usage, the questionnaire investigated the type of patient (neonates and/or paediatric patients) and frequency of PN prescription. These findings are summarised in Table 3.2. Usage of PN was slightly more prevalent in neonatal patients. When asked how often they prescribed or recommended PN in their patients, the majority of the respondents only used PN once a week.

TABLE 3.2 SUMMARY OF THE PATIENT TYPE AND FREQUENCY OF PARENTERAL NUTRITION USAGE

Neonatal and paediatric PN use (n = 72)	n	%
Dietitians	42	58
- Neonatal PN use	38	90
- Paediatric PN use	31	74
Doctors	30	42
- Neonatal PN use	19	63
- Paediatric PN use	17	57
Frequency of PN use (n = 72)	n	%
Neonatal PN use	57	79
- Daily	13	23
- 2 – 3 times per week	12	21
- Once a week	32	56
Paediatric PN use	48	67
- Daily	5	10
- 2 – 3 times per week	11	23
- Once a week	32	67

The questionnaire also asked respondents to indicate how often, if at all, they calculated the various macronutrient requirements for their patients. Responses were categorised as ‘always’, ‘sometimes’ or ‘never’. Table 3.3 shows the frequency of patient-specific calculation for the group as a whole, but also stratified by profession. In general, the dietitians were more likely to calculate requirements for energy and protein, as well as the glucose oxidation rate. It was found that the doctors prioritised fluid calculation in determining their PN prescription.

TABLE 3.3 SUMMARY OF CALCULATION OF PATIENT-SPECIFIC MACRONUTRIENT REQUIREMENTS

Calculation of requirements (n = 72)	Total group		Dietitians		Paediatric doctors	
	n	%	n	%	n	%
Energy	72	100	42	58	30	42
- Always calculate patient energy requirements	42	58	33	79	9	30
- Sometimes calculate patient energy requirements	23	32	8	19	15	50
- Never calculate patient energy requirements	7	10	1	2	6	20
Glucose oxidation rate						
- Always calculate the glucose oxidation rate	24	33	18	43	6	20
- Sometimes calculate the glucose oxidation rate	23	32	19	45	4	13
- Never calculate the glucose oxidation rate	25	35	5	12	20	67
Protein	44	61	35	83	9	30
- Always calculate patient protein requirements	21	29	7	17	14	47
- Sometimes calculate patient protein requirements	7	10	0	0	7	23
- Never calculate patient protein requirements						
Fluid	60	83	32	76	28	93
- Always calculate patient fluid requirements	9	13	7	17	2	7
- Sometimes calculate patient fluid requirements	3	4	3	7	0	0
- Never calculate patient fluid requirements						

Of particular interest, were the differences between the two professions in terms of protein and fluid calculation. The dietitians were significantly more likely to calculate the protein requirements for their patient ($n = 35, 83\%$) compared with the doctors ($n = 9, 30\%$); ($p < 0.001$, chi-squared 26.49). Only one-third of the doctors ($n = 9, 30\%$) always calculated protein requirements. Although not significant, the doctors were definitely more likely to calculate fluid ($n = 28, 93\%$) in comparison with the dietitians ($n = 32, 76\%$); ($p = 0.069$, chi-squared 5.36). These findings are graphically represented in Figures 3.4 and 3.5 respectively.

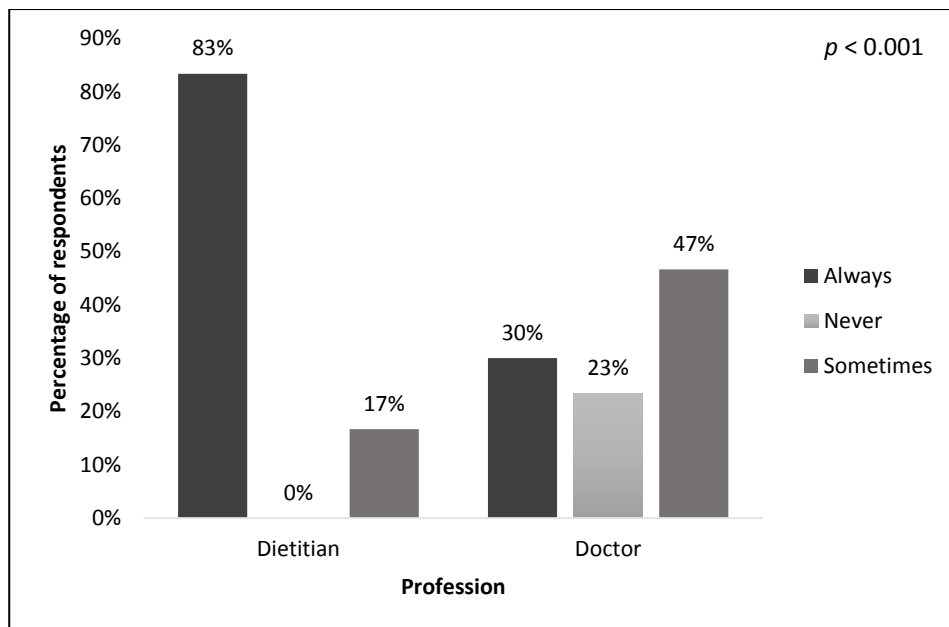


FIGURE 3.4 CALCULATION OF PROTEIN REQUIREMENTS BASED ON PROFESSION

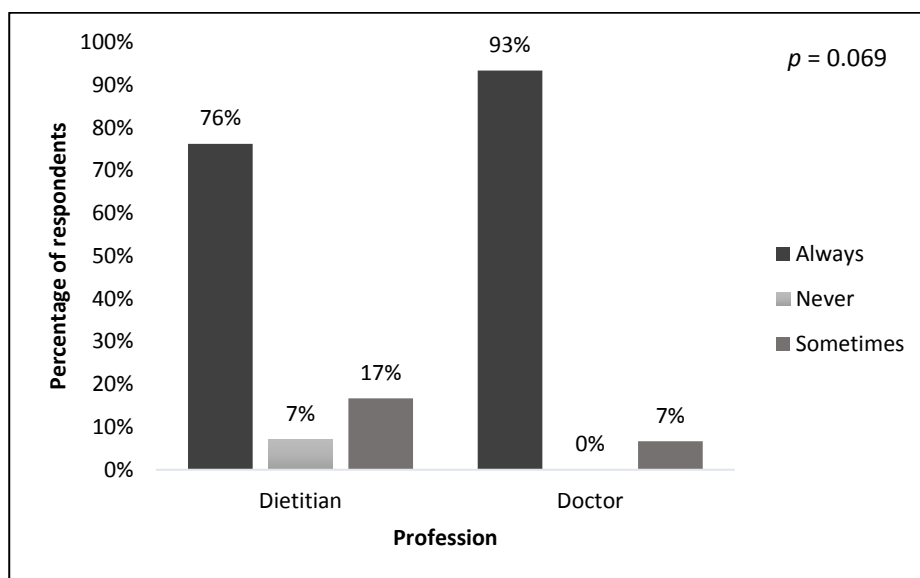


FIGURE 3.5 CALCULATION OF FLUID REQUIREMENTS BASED ON PROFESSION

3.2.2 Timing of parenteral nutrition commencement and lipid introduction

Prescription practices include not only the calculation of requirements, but also the practical implementation of PN feeding. The questionnaire investigated the timing of both PN commencement, as well as lipid introduction to the PN prescription.

Figure 3.6 shows the timing of PN feeding commencement for the total respondent group, as well as per hospital sector. Just over a third of the survey respondents commenced PN feeding of their neonatal or paediatric patients within the first 24 hours; the majority, about half, started on day 2 (24 – 48 hours), and some started on day 3 (49 – 72 hours). One of the respondents started with PN feeding later, only commencing with PN in their patients by day 7. Private hospital respondents were more likely to start earlier with PN than state hospital respondents – the majority of private sector respondents started within the first two days. State hospital respondents started predominantly on day 2. There was, however, no significant difference between the private and state sector subgroups ($p = 0.644$).

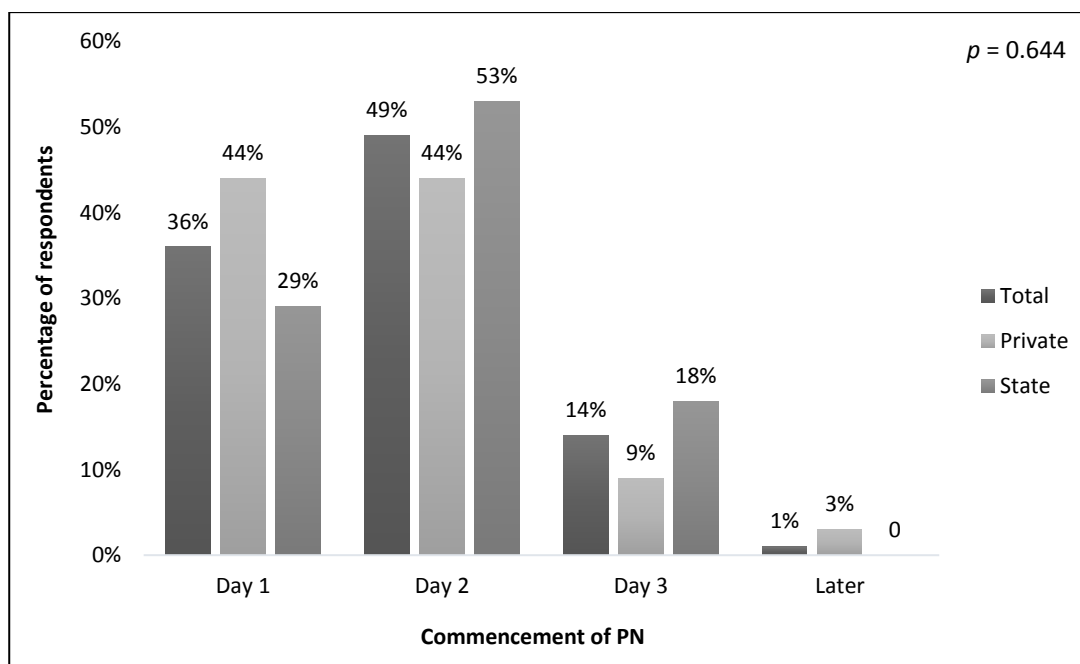


FIGURE 3.6 TIMING OF PARENTERAL NUTRITION COMMENCEMENT IN NEONATAL AND PAEDIATRIC PATIENTS BASED ON HOSPITAL SECTOR

Day 1: Within 24 h; Day 2: Within 24 – 48 h; Day 3: Within 49 – 72 h; Later: Specified Day 7; PN: Parenteral Nutrition.

The questionnaire asked the respondents to specify how soon they included lipid as part of their PN prescription. The majority of the survey respondents actually did introduce lipid from day 1 of PN feeding ($n = 48, 67\%$), some commenced with lipid as part of the PN from day 2 ($n = 21.29\%$), and the remainder introduced lipid after day 3 ($n = 3.4\%$). There was no significant difference between the practices in the state and private sectors for the timing of lipid introduction (1.39 ± 0.75 days state versus 1.44 ± 0.66 days private; $p = 0.783$).

The respondents that delayed lipid ($n = 24.33\%$), defined as starting after day 1 of PN feeding, were asked to indicate the main reason for this practice. Figure 3.7 provides a graphical summary of the results. The predominant reason for this practice was habit, followed by concerns about liver function, and also PN availability. Respiratory function, line tissing, and metabolic acidosis appeared to be less of a concern to the respondents in relation to lipid introduction. Only one of the two respondents that stated other reasons for lipid delay gave additional information, stating that it is was the paediatrician's preference to do so.

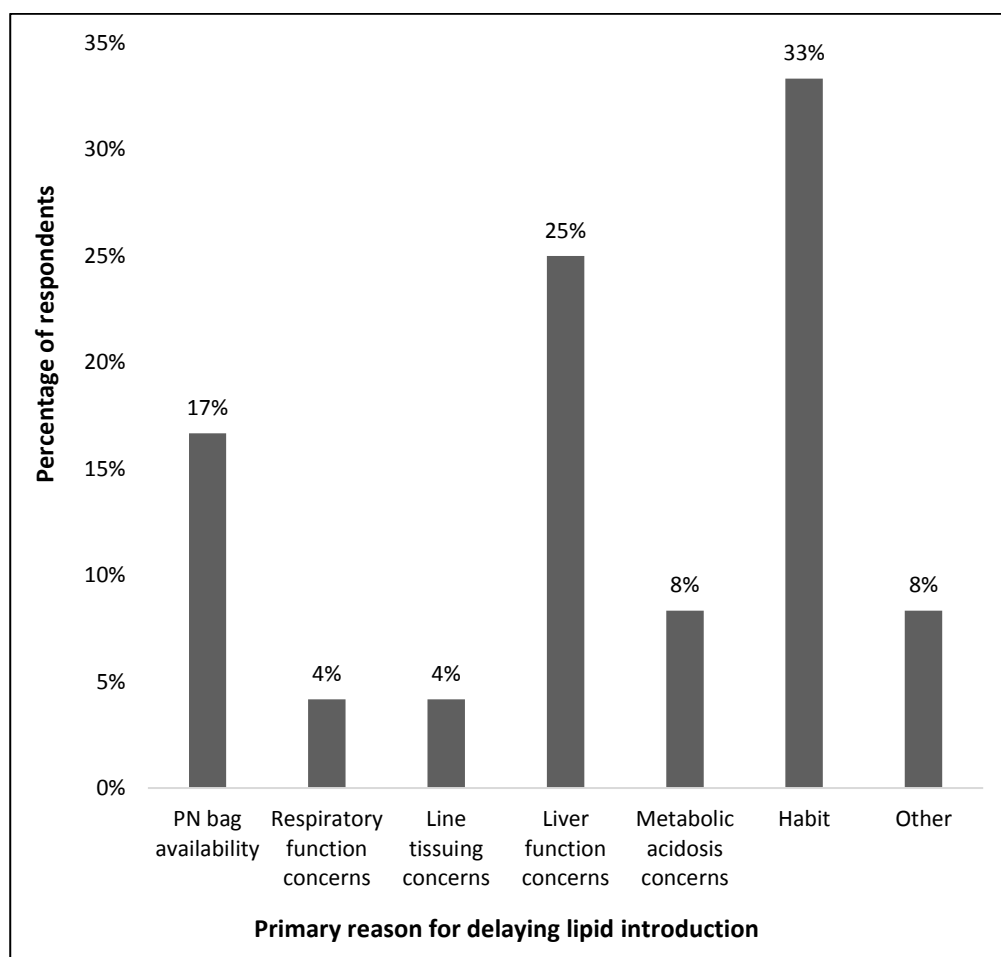


FIGURE 3.7 SUMMARY OF THE REASONS LIPID INTRODUCTION IS DELAYED

PN: Parenteral nutrition

3.2.3 Practice scores

In order to quantify the practices of the respondents in relation to their PN feeding prescriptions, a practice score was generated. The practice score was determined by combining several of the questions related to clinical practice. The commencement of PN, introduction of lipid, and calculation of patient-specific requirements were considered. A maximum score of 14 was achievable, and the combined scores were reflected as a percentage of this total. Figure 3.8 illustrates the percentage of respondents achieving best practice by question, as well as indicating the baseline competency of 60%.

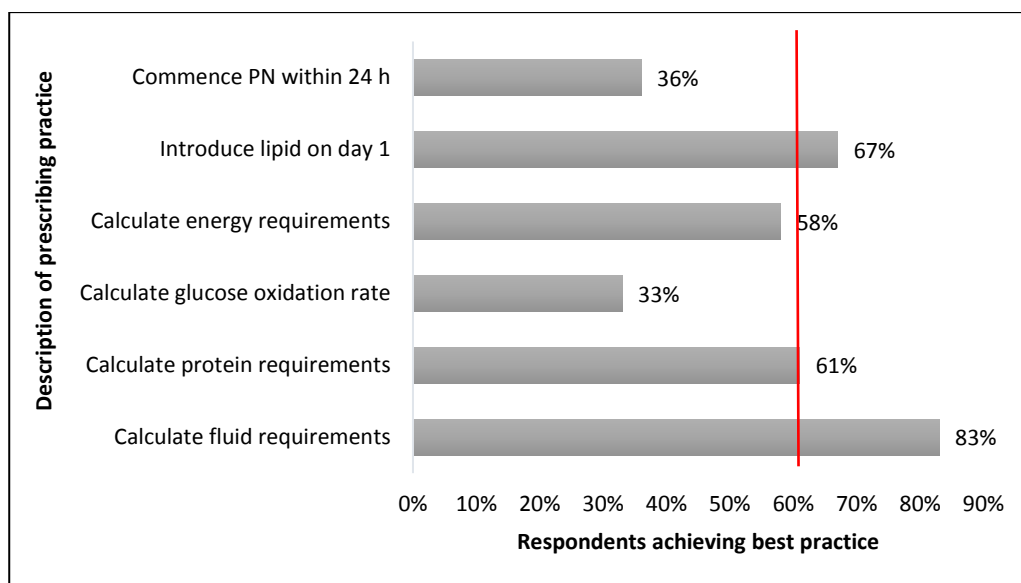


FIGURE 3.8 SCORES FOR BEST PRACTICE FOR PARENTERAL NUTRITION USAGE IN NEONATAL AND PAEDIATRIC PATIENTS

PN: Parenteral Nutrition; h: hours

60% considered baseline competency for clinical practice score

The mean practice score was 75% (SD ± 17). The survey respondents achieved competencies for three of the aspects assessed. Calculation of fluid requirements was the most optimal practice, followed by the timing of lipid introduction and calculation of patient-specific protein requirements. Calculation of energy requirements was just below competency, at 58%. The final two factors were almost half of the baseline competency level – commencement of PN within 24 hours of admission, and calculation of the glucose oxidation rate were rarely achieved to best practice standards. Interestingly, there was a significant negative correlation between the timing of PN feeding commencement and the overall practice score achieved – the group of survey respondents that did commence PN feeding within the first day were significantly more likely to achieve a high overall practice score, as shown in Figure 3.9 ($r = -0.48$; $p < 0.001$).

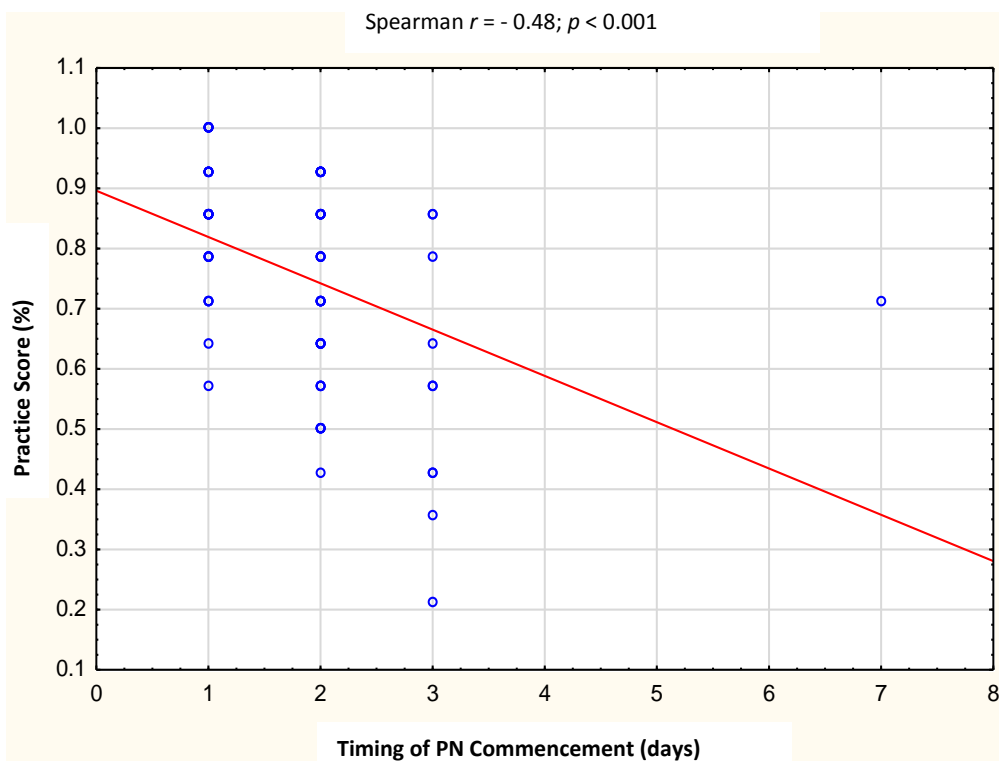


FIGURE 3.9 CORRELATION BETWEEN THE TIMING OF PARENTERAL NUTRITION COMMENCEMENT AND PRACTICE SCORE ACHIEVED

Comparison of the mean scores for the state and private sector showed no significant difference between the two subgroups ($75 \pm 20\%$ state versus $76 \pm 15\%$ private; $p = 0.82$). As shown in Figure 3.10, the mean practice score for the dietitians was however significantly higher than for the doctors ($82 \pm 12\%$ versus $65 \pm 19\%$; $p < 0.001$). Surprisingly, a weak negative association was found between the number of years of clinical experience and the practice score ($r = -0.17$; $p = 0.16$).

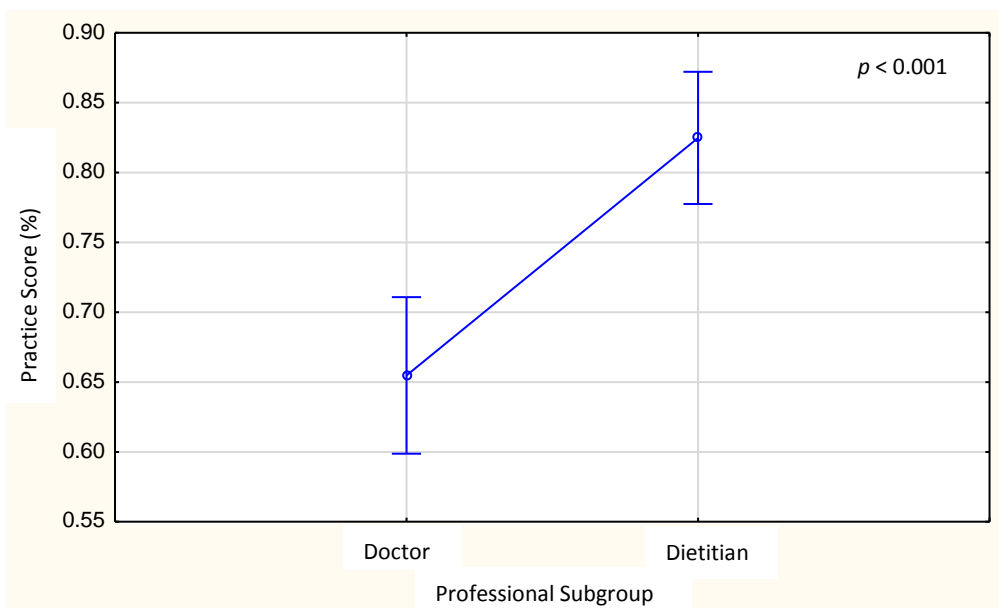


FIGURE 3.10 COMPARISON OF THE MEAN PRACTICE SCORES BY PROFESSIONAL SUBGROUP

3.3 Factors affecting parenteral nutrition usage

The questionnaire aimed to investigate potential factors that might influence clinical practice in terms of PN feeding. The survey respondents were asked to rank the reasons they might not use PN or delay the use of PN when it was indicated (rank from 1 – 8, blank if not applicable). Table 3.4 summarises the frequency of a number 1–3 ranking for each factor, indicating the primary reason for non-use or delay of PN feeding. Concern relating to infectious complication risk was the most predominant factor influencing PN usage. The high cost of PN also played a major role in avoidance of PN feeding. The lack of access to neonatal and paediatric PN, as well as a lack of trained staff to administer the PN to patients, also featured quite highly as factors influencing PN prescription practices. Unfortunately, those that selected ‘other’ as their main reason for non-use or delay, did not provide further explanation. This was also quite a predominant factor, so elaboration by respondents on these additional reasons would have been interesting. Budget limitations of the institution, medical aid limitations, and a lack of PN knowledge appeared less important in influencing the utilisation of PN.

TABLE 3.4 FACTORS AFFECTING THE NON-USE OR DELAYED USE OF PARENTERAL NUTRITION IN NEONATAL AND PAEDIATRIC PATIENTS

Main reason for not using or delaying PN (<i>n</i> = 72)	<i>n</i>	%
High cost of PN	24	33
Budget limitations in the institution	8	11
Concerns regarding infectious complications	42	58
Lack of trained staff	16	22
Lack of access to PN	18	25
Lack of knowledge	9	13
Medical aid limitations*	11	15
Other (unspecified)	18	25

*Medical aid limitations only applicable to the private hospital sector in South Africa

PN: Parenteral Nutrition

3.4 Respondent knowledge assessment

3.4.1 Access to information

The survey respondents were asked to indicate which potential sources of information they utilised, by ranking them from 1 – 7, or leaving the question blank if not applicable. Table 3.5 provides a summary of the frequency of use as a primary information source (ranked number 1–3). Published guidelines (65%) and journal articles (63%) were the most frequently accessed information sources. Interestingly, published guidelines were listed by almost half of the respondents as their number 1 resource. Congress and

conference lectures, study notes and discussions with company representatives were also utilised quite readily as sources of information on PN feeding. Only 18 (25%) of the respondents listed journal clubs, ward rounds and internal meetings as their main sources of information. Unfortunately, those that selected 'other' as their main information source, did not elaborate on the additional resources they accessed.

TABLE 3.5 SUMMARY OF INFORMATION SOURCES UTILISED BY SURVEY RESPONDENTS

Information source (<i>n</i> = 72)	Primary source of information	
	<i>n</i>	%
Journal articles	45	63
Congress and conference lectures	33	46
Journal clubs, ward rounds and internal meetings	18	25
Company representatives	24	33
Lecture notes from their studies	23	32
Published guidelines	47	65
Other (unspecified)	4	6

3.4.2 Knowledge scores

Sixty-four (89%) of the survey respondents completed the knowledge section of the questionnaire: 28 (44%) from the private sector, and 36 (56%) from the state sector. Similarly, for the profession subgroups, 28 (44%) doctors and 36 (56%) dietitians answered this section and were included in the analysis.

The questionnaire assessed knowledge of the ESPGHAN international guidelines.⁸ There were 15 questions, with one point allocated to each correct answer. The knowledge scores were reflected as a percentage of the total. Figure 3.11 shows frequency of correct answers for the knowledge scores for each individual questions.

The respondents only achieved the baseline competency of 80% for five of the questions. The highest scores related to the practicalities of PN usage (hanging time of the bag, dedicated line access and filter usage), as well as the link between hyperglycaemia and mortality risk, and the inclusion of lipids in PN infusions to avoid EFA deficiency. All the respondents knew that PN should hang for 24 hours. Interestingly, the two lowest correct scores were related to knowledge of patient-specific requirements. Less than half of the respondents (*n* = 27, 42%) knew the correct range of protein (amino acids) per kilogram body weight to use when calculating their PN prescription, while only 53% (*n* = 34) knew the recommended patient-specific energy ranges. Knowledge of the importance of micronutrients in the PN infusion (the recommendation to include both fat-soluble vitamins and trace elements daily) was also below baseline competency. Only 70% (*n* = 45)

of the survey respondents knew to gradually increase the fluid volume of the PN infusion over time. With regard to the cause of liver steatosis in PN-fed patients, 38% ($n = 24$) incorrectly thought that the IVLE was the primary cause, as opposed to the glucose.

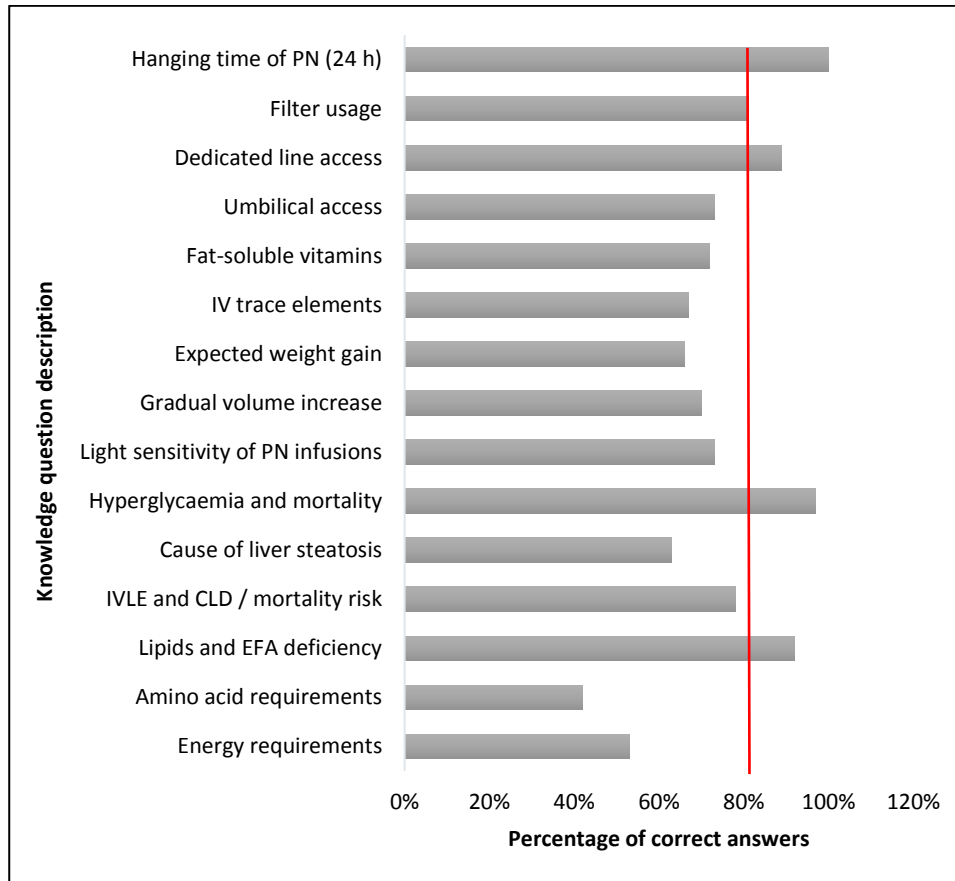


FIGURE 3.11 STUDY RESPONDENT KNOWLEDGE SCORES PER QUESTION

PN: Parenteral Nutrition; h: hours; IV: Intravenous; IVLE: Intravenous Lipid Emulsion; CLD: Chronic Lung Disease; EFA: Essential Fatty Acid

80% considered baseline competency for knowledge score

The mean knowledge score for the study respondents was 74% (SD \pm 12), range 50 – 100%. Comparison of the mean scores for the state and private sector showed no significant difference between the two subgroups (73 \pm 13% for state versus 76 \pm 12 % for private; $p = 0.32$). The mean knowledge score for the dietitians (77 \pm 13%) was however significantly higher than that of the doctors (71 \pm 11%); ($p = 0.04$) as shown in Figure 3.12.

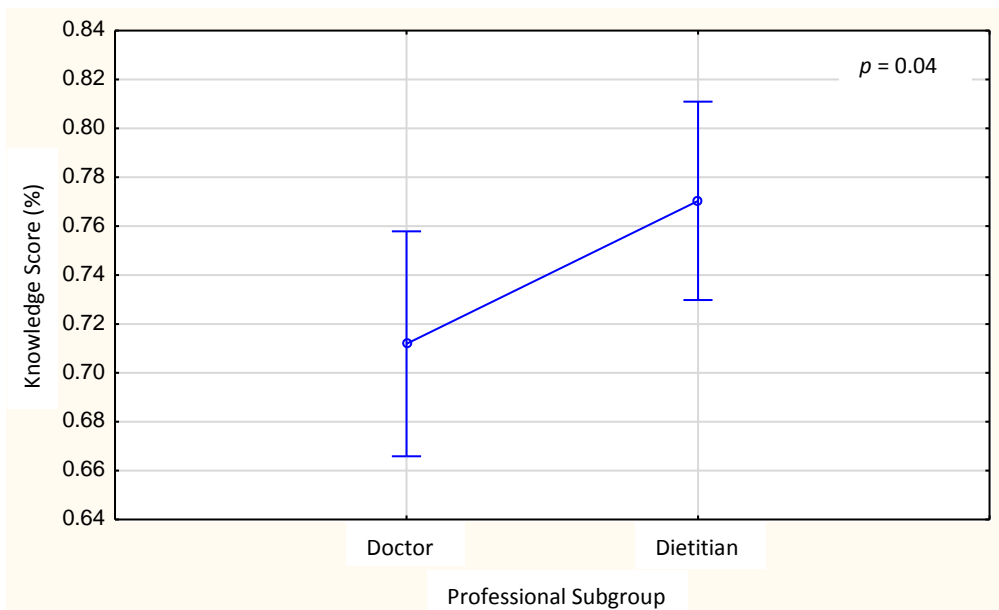


FIGURE 3.12 COMPARISON OF THE MEAN PRACTICE SCORES BY PROFESSIONAL SUBGROUP

The study respondents that utilised published guidelines as one of their sources of information achieved significantly higher knowledge scores versus those that did not access published guidelines as an information source at all ($77 \pm 2\%$ for published guidelines accessed versus $70 \pm 13\%$ for published guidelines not accessed; $p = 0.04$). Similar to practice scores, a weak negative association between the number of years of clinical experience and the knowledge scores of the study respondents was found ($r = -0.06$; $p = 0.66$).

Chapter 4: Discussion

4. Discussion

4.1 Purpose and objectives of the research

Nutrition plays an important role in achieving good clinical outcomes, as well as optimal growth and development in this vulnerable patient group.^{1,3,5,20} PN therapy is often required to achieve feeding goals, when EN is insufficient or contraindicated.^{8,9} In spite of this, the nutritional management of neonatal and paediatric patients is highly variable, and knowledge and access to available guidelines do not always translate into clinical practice.^{10,12,87,88} This study was the first in South Africa to examine the prescribing practices and knowledge with regard to PN nutrition therapy in neonatal and paediatric patients. Previous questionnaire-based studies for this patient group in South Africa have focused on EN feeding practices.^{85,92} This research set out to investigate the current approaches to PN feeding of neonatal and paediatric patients in the South African hospital context. It aimed to examine prescribing practices and the potential factors that could influence nutrition decisions. It also aimed to consider where dietitians and paediatric doctors working in this field access information on PN, and to gauge their knowledge of the standardised recommendations in the ESPGHAN PN Guidelines.⁸

The healthcare structure in South Africa is divided into two main sectors. The state sector is government funded, and services the majority of the population. The private sector however predominates in terms of both funding and staff resources, despite servicing a much smaller percentage of the population.⁹⁶ It was hypothesised that despite the notable difference in context between both sectors, there would not be a difference in the clinical practice approaches and knowledge outcomes between the two subgroups.

For the purposes of this research, it was beneficial to target the healthcare professionals known to work actively with the prescription of PN in neonatal and paediatric patients. In South Africa, the paediatric doctors, which include paediatricians, as well as paediatric specialists, are registered to prescribe PN. Dietitians are also trained in this field, and as per registration with the Health Professions Council of South Africa (HPCSA), can make recommendations on the scripting of PN to neonatal, paediatric and adult patients, but owing to the Schedule 3 registration status of the product, may not prescribe in the absence of a doctor.⁹⁷ In the context of these different roles, it seemed worthwhile to compare the practice and knowledge outcomes between the professional subgroups. It was hypothesised that there would be no difference between the healthcare professionals in terms of their PN feeding practices and knowledge of the guidelines.

4.2 Demographic characteristics

The final response rate for this questionnaire was comparable with that of previous South African survey-based studies related to feeding practices in this patient group.^{85,92} International studies in this field have achieved response rates of between 23 and 100%.¹⁰

There are nine provinces in South Africa. These vary in terms of population density and economic stability, and consequently hospital infrastructure. Gauteng is the economic and political hub and as such is the most densely populated with the largest number of hospitals, both large state academic institutions and private facilities. KwaZulu-Natal is one of the bigger provinces, and therefore has a large number of smaller state and private facilities distributed throughout. The Western Cape has a relatively stable economic climate and is the third largest province in terms of hospital infrastructure.⁹⁸ The survey respondents were based predominantly in these three provinces. There was no representation from Limpopo and the Northern Cape. Although this does raise the concern of under-representation, the overall responses stratified by province are relatively in line with the distribution of hospitals, as well as neonatal and paediatric PN use in South Africa.^{84,99}

The state and private hospital sector subgroups were both well represented in this study (53% and 47% respectively), and allowed for comparison in the analytical component of the study. There were slightly more dietitians (58%) than paediatric doctors (42%) represented in the sample population. Within the doctors group, there was varied representation of the specialties – the majority were paediatricians (63%), but also paediatric intensivists (23%), two neonatologists (7%), one paediatric pulmonologist (3%) and a paediatric registrar (3%). Unfortunately, there were no paediatric surgeons or cardiologists. Previous survey-based research investigating PN practices in neonates has focused on the doctors.¹⁰ Only one study, based in North America, included dietitians in their respondent group.⁷² Within the South African context, Bradfield (2016) is the only similar study in its target of both doctors and dietitians regarding their feeding practices in this patient group. As mentioned previously, the focus of this survey was, however, on EN feeding.⁹²

The majority of the respondents (86%) indicated that there were more than 6 beds in their unit. This is consistent with the study setting for previous research conducted on neonatal feeding in South Africa –Raban et al. (2013) found most respondents were based in a medium-sized (6–10 bed) unit.⁸⁵ This does also seem to be consistent with the European-based surveys.¹²

The experience levels of the respondents were relatively well distributed. The majority had worked in the field for between 3 and 20 years (78%). Four (6%) had more than 20 years of clinical experience. There was a weak negative correlation between the years of experience and the practice and knowledge outcomes. This could be indicative of the more experienced paediatric doctors and dietitians not adjusting their

practices over time, or keeping up to date with changes in the guidelines. They perhaps rely more on their practical clinical experience to guide their prescription and patient-management decisions. Practitioners who qualified more than 20 years ago would also potentially have had less exposure to PN during their training. None of the previous studies has investigated the years of experience in relation to prescription factors and outcomes.

4.3 Parenteral nutrition feeding practices

4.3.1 Parenteral nutrition usage

PN is indicated for the provision of nutrients to neonatal and paediatric patients when it is not possible to feed adequately, or at all, into the gastrointestinal tract.¹⁻⁴ When asked to indicate the main reasons for PN usage in their patients, the most common indications were gut anomalies and intolerances, and prematurity, which is consistent with current recommendations in the literature. Gut failure includes SBS, NEC, intestinal obstruction, and malabsorption syndromes, and is a clear indication for commencing PN feeding.^{8,9} The use of PN feeding in prematurity is also well documented as a means of maintaining growth trajectories and improving long-term neurodevelopmental outcomes in this patient group.^{3,5,20,29} Malnutrition was also indicated as a reason for PN usage. South Africa has a high prevalence of paediatric malnutrition due to poor socioeconomic circumstances and poor household food security.¹⁰⁰ The use of PN therapy in this diagnosis, although not common practice in the literature, is therefore not surprising in the South African context. Oncology and burns are relatively specialised fields, and as such, the lower incidence of use in these types of patients is to be expected. Unfortunately, the survey respondents that indicated 'other reasons' for PN use, did not elaborate. It would be interesting to explore what other reasons the prescribers feel are necessary indications for the use of PN therapy in their patients.

This study was unique in its focus on PN therapy for both the neonatal and paediatric patient groups. The majority of survey-based research in this field to date, both in South Africa and abroad, has focused on neonatal and particularly premature patient feeding.^{10-12,85,92} The emphasis on this patient group could in part be due to the more definitive feeding guidelines available for premature and neonatal patients, as well as related to the higher prevalence of these patients admitted to neonatal and paediatric ICUs.^{4,8,27-30,34,101-103} Kruger (2014) investigated the admissions in a paediatric ICU setting in South Africa, and found that the majority of patients were under the age of 1 year. Within this group, most of the patients were premature infants and neonates.¹⁰⁴ With this in mind, as well as NEC and prematurity being common indications for PN feeding, it does make sense that neonatal PN use was slightly higher than paediatric prescriptions in our study findings.^{9,29}

More than half the survey respondents were only involved in PN prescription once a week. This might be due to EN remaining the preferred method of nutritional support for all premature infants and paediatric patients. PN is often considered an effective yet invasive but relatively expensive intervention, and as such is usually a secondary choice to commencing with enteral feeding.^{1,3,4,7} The relatively low frequency of PN usage could also relate to the various factors attributed to the delay or non-use of PN feeding when it is indicated.

4.3.2 Calculation of parenteral nutrition requirements

ESPGHAN's Guidelines for Paediatric Parenteral Nutrition is an extensive document that has dedicated chapters for each nutrient, discussing the evidence base for its inclusion in PN therapy, but also providing recommendations on how to calculate requirements on a patient-specific basis.⁸ Of particular relevance to PN feeding in neonatal and paediatric patients is the calculation of energy (TE), the glucose oxidation rate, amino acid (protein) requirements, and the fluid allowance.^{8,9,26,29,30} The study survey investigated the frequency with which the respondents were likely to calculate these parameters for their patients. The paediatric doctors definitely prioritised fluid calculation and were less likely than the dietitians to consider the energy and protein calculations. Perhaps the most noteworthy finding in this regard was the difference in protein calculation between the two professional subgroups. The dietitians were significantly more likely to calculate patient-specific amino acid requirements than the paediatric doctors ($p < 0.001$). Bradfield et al. (2016) found that this was also the case for EN feeding protein calculation.⁹² None of the other studies in this field examined the calculation of requirements. Their focus was more on nutrient targets and achievement of these goals in patient feeding.^{10,12,72}

4.3.3 Timing of parenteral nutrition commencement and lipid introduction

The focus in the guidelines for the timing of PN commencement tends to be on the provision of amino acids. In premature infants in particular, recommendations are that PN feeding be started almost immediately after birth, or at least within the first 2 – 6 hours.³ ESPGHAN recommends starting with protein supply on the first postnatal day.⁸ In older paediatric patients, the guidelines are less clear. The results from the PEPaNIC trial implied that commencement of PN should be delayed for the first week, but this does not take individual diagnosis or nutritional status of the patient into account.³⁵ As with adults, the recommendation stands that when EN therapy is contraindicated or inadequate, if the child is malnourished or considered at high nutritional risk, or has a diagnosis associated with high nutrient demands, PN feeding should commence on

day 1.^{23,25} Our results showed that only 36% of the survey respondents commenced PN feeding within the first 24 hours. The majority (49%) started on day 2. This finding is consistent with a chart review conducted by Turpin et al. (2013) – only one-third of the preterm patients received amino acids within day 1.⁸⁷ A review by Lapillone et al. (2013) also indicated that PN initiation on day 1 was between 24 and 54%, and that most prescribers (67–94%) started PN by day 2.¹⁰ Their multicentre European-based survey conducted in the same year did however indicate a more optimal practice – 63% of the doctors aimed to commence amino acids within the postnatal day.¹² Hans et al. (2014) also found that the majority of healthcare professionals started PN therapy within the first 24 hours in very preterm patients.⁷² In the older paediatric patients, starting early with PN is far less likely. Fizez et al. (2016) favoured day 7, which was the same as one respondent in our study.³⁵ Moreno et al. (2016) noted that only 10% of paediatric patients received PN therapy within the first day.¹³

The timing of PN commencement was one of the areas in which the respondents scored the lowest on the practice score assessment. Interestingly, there was a significant correlation between achieving an optimal best practice score and the timing of PN initiation. Those dietitians and paediatric doctors that started feeding early, seemed to have more optimal overall clinical practices in terms of their PN feeding approach.

The use and timing of IVLE is possibly one of the most researched aspects of PN therapy in neonates and paediatric patients. There still appears to be controversy in terms of the timing of IVLE, as well as the reasons for stopping, delaying, and avoiding IVLE administration.^{4,8,26–30,40} The ESPGHAN Guidelines recommend commencement of lipid within the first 3 days in newborn infants receiving insufficient EN feeding, and note that it is safe to commence from day 1. The guidelines in paediatrics are less definitive, but minimum provision in all patients is recommended to avoid an EFA deficiency.⁸ This was an area of practice in which the survey respondents actually did quite well compared with findings in previous studies. Two-thirds (67%) included IVLE from day 1. A review of various practice-related surveys showed that 46 – 96% of healthcare professionals introduced lipids before day 3.¹⁰ In a French-based study, more than half of the prescribers only commenced with IVLE after day 3.¹¹ Turpin et al. (2013) noted that only 34% of patients were receiving IVLE as part of their PN by day 3.⁸⁷ In the survey examining practices across European neonatal units, Lapillone et al. (2013) found excellent compliance with the ESPGHAN Guidelines in this regard – 90% of their physicians aimed to initiate lipid within the first 3 days of PN feeding.¹²

The 24 (33%) respondents that did delay IVLE introduction to their PN prescription were asked to elaborate on their reasons for this clinical practice decision. It was quite alarming that the predominant reason given was habit. This has not been noted in previous studies. The finding alludes to the honesty of the respondents, but also highlights that sometimes feeding decisions are made based on a preference or routine, rather than on evidence-based practice. Six (25%) of the respondents highlighted liver function concerns as their reasoning for IVLE delay. This is consistent with previous study findings as a common reason for clinicians to stop or decrease IVLE infusion.¹⁰ Four (17%) of the respondents stated PN bag availability as their main

reason. Interestingly, these responses were split between the private and state hospital settings, and were also not based in the more remote provincial regions. This finding could therefore be interpreted as having less to do with access to PN bags containing lipid, and perhaps more to do with a need for different lipid-containing formulations. This would need to be explored further in future research. Other reasons given included metabolic acidosis, respiratory function, and line-tissuing concerns. Our findings are consistent with the literature, which in addition to the reasons we found, also included confirmed or suspected sepsis, low platelet count and elevated triglycerides as reasons for stopping or decreasing the IVLE dose.^{10,11,72,88} One respondent who selected 'other' did not elaborate – perhaps his/her reasoning was in line with one of these additional noted concerns.

4.3.4 Practice scores

In line with the study objectives, the practice score outcomes gave some indication of how well the healthcare professionals are doing in their adherence to the guidelines and recommendations for PN feeding in their neonatal and paediatric patients. Our finding of a mean practice score of 74% is consistent with findings in previous studies. Although these studies did not assess clinical practice in exactly the same way, they have all highlighted that implementation of recommended guidelines in clinical practice is not being readily and optimally achieved.^{11-13,72,87}

The respondent group met the set baseline competency level for fluid and protein calculation, as well as the timing of IVLE initiation. The initiation of PN within the first 24 hours and calculation of the patient-specific glucose oxidation rate were notably suboptimal. There was no significant difference in clinical practice between the private and state sector subgroups. This finding is consistent with the EN feeding survey conducted by Raban et al. (2013). The comparison between the profession subgroups, however, yielded a thought-provoking outcome. The dietitians achieved a significantly higher mean practice score than the paediatric doctors. As so few studies have looked at dietitians in relation to PN feeding practices to date, this is a unique and interesting finding. In the South African context, where dietitians are not allowed to prescribe PN due to its Schedule 3 status, but rather make recommendations on the prescription in conjunction with the doctor, it is noteworthy that their adherence to the guidelines is more optimal in clinical practice.⁹⁷

4.4 Factors affecting parenteral nutrition usage

In line with Objective (ii) of the study, the survey respondents were asked to indicate the potential factors that influence their decision to delay or avoid PN therapy for their neonatal or paediatric patients. The most common reason given was concern regarding the risk of infectious complications. Fizez et al. (2016) highlighted the benefit of delaying PN feeding in paediatric patients for the first week, particularly in terms of infection-related outcomes.³⁵ The high nutrient content of PN does provide an ideal medium for bacterial and fungal growth, so this concern is not unfounded. Much of this perceived infection risk, however, may be unfairly attributed to the PN therapy. The CVC and line access, as well as the handling of the PN during administration, are the critical factors associated with infection risk.⁸ Patients receiving PN feeding are usually the more critically ill patients, and are therefore more prone to complications overall. Adult studies have shown that in comparison with EN feeding interventions, PN does not necessarily pose a higher infection risk. In fact, in some instances the incidence of infections was found to be lower in PN therapy groups.^{105,106} In the South African context, PN is compounded in a single, centralised commercial facility. This method, in comparison with hospital-based compounding, has been shown to help minimise the infection risk associated with the actual PN solution by providing a sterile, standardised end product.⁷⁹ The key message in the literature remains that the safe, appropriate administration of PN can minimise infection risk in neonatal and paediatric patients.⁸¹⁻⁸³ Our finding, however, indicates that dietitians and paediatric doctors still have concerns in this regard.

PN is often associated with a high cost, and several factors related to this were stated as reasons for delay or non-use of PN. The high cost of PN in comparison with other feeding modalities was another frequent reason given. Interestingly, there is evidence to suggest that central compounding of PN is a more cost-effective approach than hospital mixing.⁷⁹ Our findings do however highlight that the perception of high cost may be enough to influence PN feeding practices. A small number of the respondents (11%) also listed budget limitations in their institutions as a primary reason for avoiding PN therapy for their patients. Not surprisingly, the majority of the respondents who highlighted this as a main issue, were based in state facilities. The budget limitations in the public health sector are well documented in the literature, and are a concern for overall healthcare provision and medical care in state hospitals.^{84,96,99} Eleven (15%) of the private-based doctors and dietitians stated that medical aid limitations influenced the use of PN for their patients. It is interesting that regardless of the work sector setting, the cost of PN was a relevant factor in determining feeding decisions for this patient group. Healthcare professionals may feel that they cannot compromise on costly medical interventions, but that nutrition is an area where they can reduce costs when necessary.

A lack of access to PN also appears a frequent reason for PN delay or non-use. This factor could be linked to the delivery of PN, as well as ordering restrictions within the facility. The proximity to PN distribution centres

may play a role here. This is a potential limitation of having only commercially available PN solutions in South Africa. In both the state and private sectors, weekend ordering is sometimes restricted by the availability of a hospital pharmacist to process the script. The state facility access to PN may also be limited by tender availability of a product.^{86,96}

A lack of trained staff to administer the PN to patients was also a concern for the study respondents, and is a factor that might negatively impact on PN use, even when it is indicated for patients. This is not a surprising outcome, as PN requires both trained doctors and nurses for its safe and successful administration. Placement of a CVC or PICC line requires a competent doctor, and the correct hanging of the PN bag relies on nursing staff who are properly trained in aseptic techniques, as well as neonatal and paediatric critical care. The paucity of healthcare professionals, especially doctors and nurses, in the South African health sector is well documented in the literature. Understaffing, combined with an inadequate skill set in the existing staff, may certainly influence the willingness of a paediatric doctor or dietitian to commence PN therapy for his or her patients.^{107,108}

A lack of knowledge was noted by nine (13%) of the respondents as a factor that may affect their delay or non-use of PN. There was no significant difference between the knowledge scores of those who perceived their inadequate knowledge to be a factor influencing their PN use and those who did not. Interestingly, however, three of the respondents that listed lack of knowledge as a concern, did not complete the knowledge assessment component of the questionnaire. Few studies have assessed knowledge in relation to PN prescription. Ahmed et al. (2004) noted that two-thirds of the doctors they interviewed (specialist registrars working in neonatal units) had no idea how much protein to prescribe for their patients, and also no knowledge of the amount of nitrogen available in the PN solutions.⁸⁸

Finally, a large proportion of the survey respondents (25%) selected 'other' as their primary reason for avoiding PN feeding. Unfortunately, none elaborated on their responses. It would have been really useful for the purposes of this study to gain insight into additional factors that may influence the way in which PN feeding is implemented in neonatal and paediatric patients.

These results highlight some interesting factors that influence the use of PN for neonatal and paediatric patients in South Africa. The prescription of PN is not only determined by patient need, but also by clinical factors such as infection risk, economic considerations, staff and medical resource availability, overall access to the PN solutions, and the prescriber's knowledge.

4.5 Respondent knowledge assessment

The knowledge aspect of this study incorporates two of the study objectives. The first investigated where the survey respondents access the information they use to guide their PN feeding practices, and the second consisted of an actual assessment of their knowledge of the ESPGHAN Guidelines.⁸

Our findings highlight the use of literature by both the dietitians and the paediatric doctors as the main resource used to guide their PN feeding decisions. Also, those prescribers that accessed the published guidelines as a resource achieved a significantly higher knowledge score than those not utilising the guidelines at all. Lapillone et al. (2013) is the only other study to have considered awareness of PN guidelines. Their European-based survey noted that 80% of the senior physicians working in neonatal units made use of published guidelines – this included the ESPGHAN International Guidelines⁸, national (country-specific), as well as in-house guidelines. Although they did not conduct a knowledge assessment of the guidelines, they noted that awareness of the guidelines did not necessarily translate into clinical practice.¹²

The smallest number of respondents (25%) made regular use of journal clubs, ward rounds and internal meetings to guide their clinical nutrition practices. As could be expected, the majority of this group were based in the academic and tertiary level state institutions. The five private hospital-based doctors and dietitians were all from Gauteng and the Western Cape. This suggests that access to this type of forum is dictated by the location of the hospital, as well as the teaching focus of the institution.

The four respondents (6%) that stated other sources of information as their main resource did not elaborate. It would have been interesting to gain insight into what other forms of information on PN therapy are available and considered important in guiding clinical practice.

For the knowledge assessment component of the study, it was unfortunate that eight of the participants withdrew from the survey at this point, and could not be included in this section of the analysis. The reasons for withdrawal are unknown. One could speculate that they felt their knowledge was inadequate, but it could also have been survey fatigue or some other reason.

The mean knowledge score for the group was suboptimal, and only 5 of the 15 questions in the knowledge section achieved a correct score above the baseline competency of 80%. The questionnaire did not specifically ask the respondents if they are aware of the ESPGHAN guidelines. The knowledge component of the questionnaire was also developed based predominantly on expert opinion as no previous validated questionnaire was available. These two factors could have contributed to the suboptimal knowledge scores.

In spite of these potential limitations, our findings highlight that healthcare professionals may lack knowledge of the patient-specific PN nutrient requirements, the recommended content of the PN solutions, and even the practicalities of increasing feeding volumes and line access routes in their patients. There was also a deficiency in knowledge regarding the causes of some of the potential clinical complications associated with PN feeding.

It is of concern that the prescribers scored poorly on the patient-specific requirement questions. This finding suggests that although dietitians and paediatric doctors may claim to be calculating the nutrient needs of their patients, these calculations are either based on the incorrect values, or they are not actually doing the calculations in daily practice. Our finding that less than half the respondents knew the correct amino acid range is consistent with that of Ahmed et al. (2004) – two-thirds of the doctors they interviewed did not know the protein requirements of their patients or the amino acid content of the PN solutions they were administering.⁸⁸

It is encouraging that the practical aspects of PN usage were well known by most of the respondents. All the participants knew the correct hanging time of 24 hours. Most knew about the importance of dedicated line access, as well as the use of a filter to administer the PN to the patient. The correct handling of PN solutions is known to minimise the infectious complication risk, and filter usage prevents the occurrence of a fat embolus.^{8,9}

As with the practice score outcomes, the dietitians performed significantly better than the paediatric doctors in their knowledge scores. This finding again emphasises that although dietitians are currently only involved in an advisory capacity regarding PN prescription, they have a sound knowledge base and training in this field.

Chapter 5:

Conclusion and

Recommendations

5. Conclusion and Recommendations

5.1 Conclusion

Our study provided insight into the use of PN therapy in neonatal and paediatric patients in South Africa. Neonatal and paediatric patients are a vulnerable patient group, and their nutritional needs should be carefully considered and achieved to maintain both growth and optimal clinical outcomes. Despite clear guidelines, particularly in the neonatal group, PN feeding was seldom initiated within the first 24 hours of admission. The inclusion of IVLE in PN prescriptions was relatively well accepted and implemented, but it was of concern that the predominant reason for delay of lipid was attributed to habit. The calculation of patient-specific requirements, as well as knowledge of what these requirements are, was also suboptimal.

Our findings also highlighted the complexity of adhering to optimal PN feeding practices in the South African healthcare environment. Concerns relating to infectious complications, the perceived high cost of commercially prepared PN solutions, as well as limited financial and human resources, all influenced clinicians' decisions to implement PN therapy for their patient.

Also, access to information did not necessarily translate into 'best practice' and sound knowledge of the PN guidelines. The need for updated, concise, well-defined PN feeding recommendations for neonatal and paediatric patients is evident. The necessity of ongoing education and training on PN feeding is also fundamental to improving clinical practice and knowledge in this regard.

In South Africa, the dietitian's current role in PN prescription is limited to an advisory service. In our study the dietitians performed significantly better than the paediatric doctors in both the practice and knowledge assessments. Our findings emphasise the role of the dietitian as part of the multidisciplinary team in achieving optimal feeding.

In conclusion, PN prescribing practices in South Africa for neonatal and paediatric patients are not yet optimal in many respects. Dietitians and paediatric doctors require access to clear PN therapy guidelines, as well as guidance on how to implement these recommendations effectively in daily clinical practice. A multidisciplinary approach to PN feeding is paramount. Additional research is warranted to further assess the PN feeding practices in this vulnerable patient group.

5.2 Subgroup analysis comparison outcomes

Based on the study findings, we accept the null hypothesis (H_0) that there is no difference in the prescribing practices and knowledge of international guidelines between the work sector subgroups (state and private). Considering the dietitians scored significantly higher for both the practice and knowledge score assessments in the questionnaire, we can however reject the null hypothesis (H_{0L}) for the professional subgroup comparison.

5.3 Strengths and limitations

This is the first study of its kind in South Africa to investigate the PN prescribing practices in neonatal and paediatric patients. This study is also unique in its assessment of the prescriber knowledge of the international PN feeding guidelines and recommendations, as well as in comparing the different hospital sectors (state and private) and professional groups (paediatric doctors and dietitians) within this context.

There were limitations to the current study. Questionnaire-based surveys are challenging in terms of achieving an optimal response rate. One of the major limitations of our study was the low participation rate. Although a targeting sampling process was conducted, there is no database available in South Africa to determine which paediatric doctors and dietitians specifically work with PN, and would therefore have met the inclusion criteria. We relied on the relevant associations to guide us in targeting the survey respondents. The subgroup analyses were also limited by the relatively small sample size. For particular analyses where a notable difference in the guidelines exists, it would also have been beneficial to further separate the groups into paediatric and neonatal groups had the respondent numbers allowed.

The absence of respondents from Limpopo and the Northern Cape also raises concerns regarding under-representation. Responses from Limpopo and the Northern Cape would potentially have been useful, as these two provinces are based relatively far from the established PN distribution centres, and also are considered comparatively resource poor, and could therefore potentially have had a slightly different PN usage pattern as well as different factors influencing clinical practice. This is, however, speculation and would need to be explored through additional research.

There were slightly more dietitians than paediatric doctors who participated in the study. The concern of under-representation could also be related to the absence of some paediatric specialties responding to the survey. There were no paediatric surgeons or paediatric cardiologists in the sample.

As the questionnaires were self-administered, the study design relied on the honesty and transparency of the respondents. Although a pilot and validation process was conducted to minimise ambiguity,

misinterpretation of a question could have influenced the responses. Unfortunately, for those questions with an option for 'other', the respondents did not elaborate further. This limited the ability of the research team to fully interpret the responses in some cases. For the section on factors influencing PN usage especially, it would have been useful to gain insight into additional issues the respondents felt affected their PN prescription practices.

The information access section of the questionnaire was also quite limited and could possibly have explored the presence of unit protocols and how these related to PN prescription and the guidelines.

The practice score was composed of quite a limited range of prescription-related questions. It would have been useful to explore clinical practice in more detail, perhaps also incorporating the choice of line access (central versus peripheral, as well as the use of umbilical lines in neonates); monitoring practices (such as frequency of blood glucose and electrolyte monitoring, LFT and serum triglyceride testing, utilisation of urinary glucose and anthropometrical measurements); as well as the use of insulin therapy in relation to PN feeding.

Finally, the knowledge score could have been impacted by the choice of questions selected to assess the respondent knowledge of the ESPGHAN guidelines.

5.4 Recommendations

In terms of answering the research question, it would be beneficial to conduct additional survey-based research with a larger sample size and more equal representation in the subgroups. This would enable further analyses, and perhaps additional statistical inferences could be achieved.

A multicentre chart review to analyse the actual feeding practices in relation to the guidelines in neonatal and paediatric patients is also recommended in order to gain further insight into prescribing practices and adherence to guidelines and protocols.

Further research could be extended to include nursing staff and investigate their role and practices in terms of neonatal and paediatric PN usage in South Africa.

South Africa is relatively unique in the way in which PN feeding is conducted, and it would be useful to explore how other African countries, and their prescribers, are faring in terms of both their knowledge and practices, as well as access to PN for their patients.

The ESPGHAN Guidelines are relatively outdated, and new guidelines are due for publication shortly. It is recommended, post publication of the new guidelines, to assess if there are changes, and perhaps improvements, in both clinical practice and knowledge outcomes.

Finally, if additional PN products, such as SMOFlipid[®], were to become readily available in the South African context, it would be useful to investigate prescribers' experiences and use of lipid in neonatal and paediatric patients further. Adequately powered, randomised clinical trials researching the use of a new lipid in relation to clinical outcomes in this patient group are also recommended.

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Addenda

Addendum A

Questionnaire

PARTICIPANT NUMBER

Neonatal and paediatric parenteral nutrition prescription practices in South Africa: a cross-sectional survey

Thank you for agreeing to participate in this research study.

Instructions:

- Please answer the questions honestly. Remember your identity is kept completely confidential.
- If you are unsure of the meaning of any question, you may ask the researcher for assistance.
- Please tick the most relevant box.

Demographic and Background Information:

1. Please indicate which province you are currently working in:

		Tick (v)
A	Eastern Cape	
B	Free State	
C	Gauteng	
D	KwaZulu-Natal	
E	Limpopo	
F	Mpumalanga	
G	Northern Cape	
H	North-West	
I	Western Cape	

2. I currently work and prescribe parenteral nutrition at:

		Tick (v)
A	State – regional / secondary hospital level	
B	State – academic / tertiary hospital level	
C	Private	
D	Both – but predominantly private	
E	Both – but predominantly state	

3. I am qualified as (please indicate the highest qualification):

		Tick (v)
A	Neonatologist	
B	Paediatric pulmonologist	
C	Paediatric surgeon	
D	Paediatric cardiologist	
E	Paediatrician	
F	Medical Officer	
G	Dietitian	
H	Other ... please specify _____	

4. I have been actively practising and prescribing in the field of neonatal / paediatric medicine or nutrition for:

		Tick (v)
A	0 – 2 years	
B	3 – 5 years	
C	6 – 10 years	
D	11 – 20 years	
E	> 20 years	

Prescribing Practices:

If you work in both the private and state sectors, please answer the following questions for the unit in which you do most of your parenteral nutrition prescribing.

5. The unit/s in which I prescribe parenteral nutrition in neonatal and/or paediatric patients has a total of:

		Tick (v)
A	1 – 5 beds	
B	6 – 10 beds	
C	> 10 beds	

6. I currently prescribe parenteral nutrition in neonatal patients:

		Tick (v)
A	Yes	
B	No	

7. If yes, please indicate how often you prescribe parenteral nutrition in this patient group (please select the most correct answer from the list below):

		Tick (v)
A	Daily	
B	2 – 3 times per week	
C	Once a week	

8. I currently prescribe parenteral nutrition in paediatric patients:

		Tick (v)
A	Yes	
B	No	

9. If yes, please indicate how often you prescribe parenteral nutrition in this patient group (please select the most correct answer from the list below):

		Tick (v)
A	Daily	
B	2 – 3 times per week	
C	Once a week	

10. The main reason I use parenteral nutrition in my neonatal / paediatric patients is for the following conditions:

Please rank your answer in order of predominant usage, with 1 being the main reason, etc. If not applicable to your prescription of parenteral nutrition, please leave the block next to that option blank.

		Tick (v)
A	Prematurity	
B	Gut anomalies or intolerances	
C	Post-operatively	
D	Oncology	
E	Burns	
F	Malnutrition	
G	Critically ill patients	
H	Other ... please specify _____	

11. In my patients, where it is clear that enteral feeds will not be tolerated or possible, I start parenteral nutrition:

		Tick (v)
A	Within < 24 hours (day 1)	
B	Within 24 – 48 hours (day 2)	
C	Within 49 – 72 hours (day 3)	
D	If later, please specify By day _____	

12. In my patients requiring parenteral nutrition, I introduce lipid (fat) to the prescription from:

		Tick (v)
A	Day 1	
B	Day 2	
C	Day 3	
D	After day 3	

13. If you answered B, C or D for question 12, and do not use lipid (fat) containing parenteral nutrition in your patients from the initiation of parenteral nutrition (i.e. **day 1**), is it **predominantly** due to (please select one answer):

		Tick (v)
A	Parenteral nutrition bag availability	
B	Concerns regarding respiratory function	
C	Concerns regarding tissing of the line	
D	Concerns regarding liver function	
E	Habit of administering clear (fat-free) TPN initially	
F	Concerns regarding metabolic acidosis	
G	Other ... please specify _____	

14. When prescribing parenteral nutrition in my patients, the prescription (dosage and rate) is mainly based on (please only select one answer):

		Tick (v)
A	The fluid allocation for my patient	
B	The protein requirements for my patient	
C	The energy requirements for my patient	
D	The volume size of the parenteral nutrition bag	
E	The parenteral nutrition code I am most familiar with	
F	Other ... please specify _____	

15. When prescribing parenteral nutrition, I calculate patient-specific **energy** requirements?

		Tick (v)
A	Always	
B	Never	
C	Sometimes	

16. When prescribing parenteral nutrition, I calculate and consider the glucose oxidation rate of my patient?

		Tick (v)
A	Always	
B	Never	
C	Sometimes	

17. When prescribing parenteral nutrition, I calculate patient-specific **protein** requirements?

		Tick (v)
A	Always	
B	Never	
C	Sometimes	

18. When prescribing parenteral nutrition, I calculate patient-specific **fluid** requirements?

		Tick (v)
A	Always	
B	Never	
C	Sometimes	

Factors Influencing Prescription:

19. The main reason I do not prescribe parenteral nutrition, or may delay prescribing PN in my neonatal / paediatric patients when it is indicated, is due to:
 Please rank your answer in order of the most predominant reason, with 1 being the main reason, etc. If not applicable to your setting or situation, please leave the block blank.

		Tick (✓)
A	My concerns about the high cost of parenteral nutrition	
B	Budget restrictions in my institution	
C	Concerns regarding the infectious complications associated with parenteral nutrition	
D	A lack of trained staff to administer PN	
E	A lack of access to parenteral nutrition (delayed ordering and delivery)	
F	Inadequate knowledge	
G	Medical aid limitations	
H	Other ... please specify _____	

Knowledge of Guidelines:

20. I get most of my information on parenteral nutrition from:

Please rank your answers in order of the most relevant reason, with 1 being the main source of information, etc. If not applicable as a source of information for you, please leave the block blank.

		Tick (v)
A	Journal articles	
B	Congress and conference lectures	
C	Journal clubs, ward rounds and internal meetings	
D	Company representatives	
E	Lecture notes from my studies	
F	Published guidelines	
G	Other ... please specify _____	

21. According to the international guidelines on parenteral nutrition in paediatric patients, an infant (0–1 year), but not preterm, on parenteral nutrition requires:

		Tick (v)
A	30 – 60 kcal/kg/day	
B	60 – 75 kcal/kg/day	
C	75 – 90 kcal/kg/day	
D	90 – 100 kcal/kg/day	
E	110 – 120 kcal/kg/day	
F	I do not know	

22. According to the international guidelines on parenteral nutrition in paediatric patients, a minimum of _____ and maximum of _____ amino acid intake is recommended:

		Tick (v)
A	1 g/kg/day; 5 g/kg/day	
B	1.5 g/kg/day; 4 g/kg/day	
C	0.5 g/kg/day; 2.5 g/kg/day	
D	2 g/kg/day; 3 g/kg/day	
E	I do not know	

23. Patients who do not receive lipid as part of the parenteral nutrition prescription are at risk of developing an essential fatty acid deficiency.

		Tick (v)
A	True	
B	False	

24. Early administration of intravenous lipids in the first days of life increases the incidence of chronic lung disease or death in premature infants when compared with late administration of intravenous lipids.

		Tick (v)
A	True	
B	False	

25. Feeding a patient high amounts of lipid (fat) in parenteral nutrition is the primary cause of liver steatosis ("fatty liver").

		Tick (v)
A	True	
B	False	

26. Hyperglycaemia (elevated blood glucose levels) is associated with increased infectious-related mortality.

		Tick (v)
A	True	
B	False	

27. Parenteral nutrition infusions are light sensitive and should be protected during phototherapy.

		Tick (v)
A	True	
B	False	

28. A gradual increase of fluid volume when administering parenteral nutrition in neonatal and paediatric patients is not necessary.

		Tick (v)
A	True	
B	False	

29. Please select the correct answer to complete the following statement: Expected weight gain in preterm and term infants is _____ body weight per day.

		Tick (v)
A	2 – 5 g/kg	
B	8 – 12 g/kg	
C	10 – 20 g/kg	
D	25 – 30 g/kg	

30. Parenterally fed infants and children should receive an intravenous supply of trace elements such as copper and zinc as part of the infusion.

		Tick (v)
A	True	
B	False	

31. The fat-soluble vitamins (A, D, E and K) do not need to be included in a parenteral nutrition infusion daily.

		Tick (v)
A	True	
B	False	

32. In neonates, the umbilical vessels can be used for parenteral nutrition infusion, but the risk of complications increases if the umbilical artery catheters are left in place for more than 5 days.

		Tick (v)
A	True	
B	False	

33. The catheter port used for parenteral nutrition administration may also be safely used for blood sampling and medication administration.

		Tick (v)
A	True	
B	False	

34. The use of a terminal filter for the administration of parenteral nutrition in neonatal and paediatric patients is not essential.

		Tick (v)
A	True	
B	False	

35. The parenteral nutrition bag and administration line of lipid-containing infusions should be changed after no more than 24 hours in order to minimise infectious complications.

		Tick (✓)
A	True	
B	False	

Thank you for offering your time to participate in this research study!