PHARMACIST’S HANDBOOK OF PARENTERAL NUTRITION
In Neonates and Paediatrics
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In Neonates and Paediatrics

1st Edition
DISCLAIMER

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Perpustakaan Negara Malaysia
Pharmacist's Handbook Of Parenteral Nutrition: In Neonates And Paediatrics
Pharmacy Practice And Development Division
Ministry Of Health Malaysia
2015
ISBN

ISBN 978-967-5570-68-1
Parenteral Nutrition (PN) Service is a life sustaining therapy for patients who cannot eat or tolerate oral feeding via enteral nutrition. PN is important to prevent nutrient deficiencies not only in adults but is also an essential component of care for paediatric patients. In PN service, pharmacists play an important role in ensuring the appropriateness of the PN solution supplied in terms of its composition as well as the quality of the compounded products. In addition to that, the direct involvement of pharmacists in the wards in terms of patient monitoring and decision making process give a great impact to PN service.

Due to the rapidly expanding need for clinical parenteral service, it is timely and essential for the Pharmaceutical Services Division, Ministry of Health to develop and publish this handbook. This Pharmacist’s Handbook of Parenteral Nutrition in Neonates and Paediatrics serves as a guide for pharmacists involved in this service to ensure the standardisation of parenteral nutrition services in all Ministry of Health (MOH) facilities.

It is hoped that the contents of this handbook will serve as a standard reference for pharmacists in managing the service. I am confident that this handbook will also provide useful information in ensuring patients receive optimal and safe treatment based on their individual needs and clinical conditions.

I would like to convey my gratitude to the Clinical Pharmacy Working Committee (Parenteral Nutrition Support Subspecialty) and all parties that have contributed directly or indirectly in the development of this handbook.

Thank you.

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1.0 Introduction

Implementing parenteral nutrition (PN) in paediatric patients could be challenging due to the wide range of patients, ranging from extremely premature infants up to teenagers that could be weighing more than 100 kg. Therefore, it is extremely important to take into account of patient’s age and maturity related changes of the metabolism, fluid and nutrient requirements along with clinical situations in which PN is applied.

Therefore, the substrate requirements of paediatric patients cannot be proportionally derived from adult requirements but are determined according to age-specific and physiological conditions.¹

In comparison to older paediatric patients or adults, term and preterm infants have different energy requirements due to an extremely low body storage of nutrients in many aspects. This includes immature gastrointestinal system, high metabolic rates and the tendency to suffer from evaporative fluid losses, thus requiring a carefully monitored intake to suit their specific requirements.²

The goals of Parenteral Nutrition (PN) in paediatric patients are to:

- Provide sufficient nutrients to prevent negative energy and nitrogen balance.
- Prevent essential fatty acid deficiency.
- Support normal rates of growth without increased significant morbidity.
2.0 Indication for Parenteral Nutrition

Similar to adult, PN is indicated in paediatric patient that cannot be fully fed or contraindicated by oral or enteral route for example severe intestinal failure, malabsorption, short bowel syndrome, etc.

In addition to the above, PN is essential for neonates in the following situation:
- Premature infants < 30 weeks gestation and/or < 1000g.\(^3,4\)
- > 30 weeks gestation but unlikely to achieve full enteral feeds by day 5 of life.\(^3\)
- Severe inter-uterine growth restrictions.\(^5\)
- Birth weight 1000-1500g and anticipated to be not on significant feeds for 3 or more days.\(^4,6\)
- Birth weight more than 1500g and anticipated to be not on significant feeds for 5 or more days.\(^4,6\)
- Necrotising enterocolitis (NEC).\(^5\)
- Gastro-intestinal tract anomalies (tracheo-oesophageal fistula, omphalocele, gastroschisis, malrotation with volvulus, etc.).\(^5\)

3.0 Line Access for Parenteral Nutrition Delivery

PN solution can be infused via central or peripheral vein. The choice of line access for PN delivery is usually influenced by vein availability, concentration and osmolarity of PN solution as well as the length of time the patient will be put on PN as shown on Table 1.

PN solution and intravenous lipid emulsion (IVLE) should be administered using photo-protected tubing set and attached with in-line filter. The recommended in-line filters are 0.2μm filter for aqueous solution and 1.2μm filter for lipid containing solution.
### Table 1: The differences between central and peripheral venous access for PN delivery.

<table>
<thead>
<tr>
<th>Central Access</th>
<th>Peripheral Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>• For initiation of full parenteral nutrition.</td>
<td>• For short term venous access to provide partial nutritional supplementation.</td>
</tr>
<tr>
<td>• Insert the catheter into the superior/inferior vena cava or outside the right atrium.</td>
<td>• Placement of needle/short catheter into a subcutaneous vein.</td>
</tr>
<tr>
<td>• Percutaneously insert the CVC directly through a deep vein (Eg. subclavian, internal jugular or femoral vein)</td>
<td></td>
</tr>
<tr>
<td>• Peripherally inserted central catheter (PICC) – the catheter is inserted peripherally via a subcutaneous vein to reach the central vein.</td>
<td></td>
</tr>
</tbody>
</table>

In neonates, the umbilical vessels can also be used:

- The umbilical artery catheter (UAC) has an increased risk of complications with > 5 days of use.  
- The umbilical venous catheter (UVC) has an increased risk of complications with more than 14 days of use.

| • Route of choice in delivering solutions with >1000mOsm/L. | • Osmolarity of PN solution is limited to 600mOsm/L to lower risk of phlebitis due to infiltration. |
| • Dextrose concentration up to 20% is used centrally. PN with 25% dextrose is usually reserved for severely malnourished patients. | • Dextrose concentration above 10% is associated with increase in phlebitis. The peripheral dextrose use of 12.5% dextrose containing PN is discouraged. However, 12.5% dextrose containing PN is sometimes used in patients who require higher calories. |
| • In general, the amino acid concentration in peripheral veins should not exceed 2.5% as it may increase solution osmolarity. | • In general, the amino acid concentration in peripheral veins should not exceed 2.5% as it may increase solution osmolarity. |

**Note:**
Admixtures of lipid emulsion together with amino acid and dextrose solution offer additional protection to the peripheral venous endothelium against phlebitis.
4.0 Energy Requirements

PN is supplied as an energy fuel to cover nutritional needs of the patient for basal metabolic rate, physical activity, growth and to correct pre-existing malnutrition. Generally, infants require less calorie when fed parenterally than during enteral feeding because there is no energy lost in stools and there is less thermogenesis.\textsuperscript{4,7} Infants require greater calories per kg bodyweight compared to children and adults due to increased cellular growth and physical activity and higher heat loss.\textsuperscript{8}

Table 2: Parenteral energy requirements.

<table>
<thead>
<tr>
<th>Age (Year)</th>
<th>Kilocalories (kcal)/kg bodyweight per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASPEN 2002</td>
</tr>
<tr>
<td>Pre-term</td>
<td>-</td>
</tr>
<tr>
<td>0-1</td>
<td>90-120</td>
</tr>
<tr>
<td>1-7</td>
<td>75-90</td>
</tr>
<tr>
<td>7-12</td>
<td>60-75</td>
</tr>
<tr>
<td>12-18</td>
<td>30-60</td>
</tr>
<tr>
<td>&gt;18</td>
<td>25-30</td>
</tr>
</tbody>
</table>
5.0 Components of PN

Nutrition provided by intravenous formulation consists of fluids, carbohydrates, proteins, fats, electrolytes, vitamins and trace elements. PN can be supplied as:

- Aqueous solution that contains water, proteins, carbohydrates, electrolyte, vitamins and trace elements.
- All in one solution that contains water, carbohydrates, proteins, fats, electrolytes, vitamins and trace elements. All in one solution can be obtained commercially or compounded tailored to the patients’ requirements.

5.1 Fluid

Fluids are generally supplied as water that acts as a carrier for nutrients and metabolites. Water and electrolyte requirements per unit body mass are generally very high in neonate and decrease with age until adulthood.\(^4\)

Most of researches described on the adaptation processes of water and electrolyte metabolism related to the preterm neonate or adults, unfortunately limited knowledge of these processes in older children.\(^4\) Most of the recommendations are generally based on extrapolations from data on neonates and adults.\(^4\)

Fluid requirements as shown in the tables below are for general guideline. Fluids may need to be adjusted specific to patient’s clinical condition. For an example, if a patient is suffering from Patent Ductus Arteriosus (PDA), fluids may need to be restricted to prevent worsening of the PDA.
i. First postnatal week

**Table 3: Parenteral fluid intake during the first postnatal week according to ESPGHAN 2005.**

<table>
<thead>
<tr>
<th>Days after birth</th>
<th>Recommended fluid intake (mL/kg body weight per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; day</td>
</tr>
<tr>
<td>Term neonate</td>
<td>60-120</td>
</tr>
<tr>
<td>Preterm neonate</td>
<td>60-80</td>
</tr>
<tr>
<td>&gt;1500g</td>
<td></td>
</tr>
<tr>
<td>Preterm neonate</td>
<td>80-90</td>
</tr>
<tr>
<td>&lt;1500g</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5: Parenteral fluid intake for term infants after the first month of life and for children according to ESPGHAN 2005.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Fluid intake (mL/kg body weight per day)</th>
<th>Maximal volumes in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term infants from the 2&lt;sup&gt;nd&lt;/sup&gt; months of life</td>
<td>120-150 (180)</td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>80-120 (150)</td>
<td></td>
</tr>
<tr>
<td>3-5 years</td>
<td>80-100</td>
<td></td>
</tr>
<tr>
<td>6-12 years</td>
<td>60-80</td>
<td></td>
</tr>
<tr>
<td>13-18 years</td>
<td>50-70</td>
<td></td>
</tr>
</tbody>
</table>

ii. First month of life and beyond

**Table 5: Parenteral fluid intake for term infants after the first month of life and for children according to ESPGHAN 2005.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Fluid intake (mL/kg body weight per day)</th>
<th>Maximal volumes in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term infants from the 2&lt;sup&gt;nd&lt;/sup&gt; months of life</td>
<td>120-150 (180)</td>
<td></td>
</tr>
<tr>
<td>1-2 years</td>
<td>80-120 (150)</td>
<td></td>
</tr>
<tr>
<td>3-5 years</td>
<td>80-100</td>
<td></td>
</tr>
<tr>
<td>6-12 years</td>
<td>60-80</td>
<td></td>
</tr>
<tr>
<td>13-18 years</td>
<td>50-70</td>
<td></td>
</tr>
</tbody>
</table>
5.2 Carbohydrates

Carbohydrates are one of the major contributors of energy in parenteral nutrition. Ideally, it should constitute 60-75% of the total non-protein calories in the TPN regimen. Dextrose, the monohydrated form of glucose is used in PN solution and provides 3.4kcal/g. However, in general practice, 4kcal/g glucose is widely used in Malaysia. There is no essential amount of carbohydrate needed because the human body is capable of forming carbohydrates from lipids and amino acids. Nonetheless, its presence is still important to prevent breakdown of somatic protein sources.

Carbohydrate requirements are shown below (Table 6&7). It is worth to note that maximum dextrose concentration of the final concentration for peripheral PN solution is 10-12.5% while for the central PN solution is 25%. However, glucose intake of 10% on day 1 of postnatal life for both preterm and newborn infants is commonly practise in the government hospitals of Malaysia setting.

In preterm infants glucose infusion should be started with 4-8mg/kg/min. Maximal glucose administration in preterm infants is 16mg/kg/min (23g/kg/day) after birth. Maximal glucose administration in term infants is 13mg/kg/min (18g/kg/day). In critically ill children glucose intake should be limited to 5mg/kg/min (7.2g/kg/day).

### Table 6: Recommended parenteral glucose supply (g/kg/BW and day).

<table>
<thead>
<tr>
<th>Weight</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3kg</td>
<td>10</td>
<td>14</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>3-10 kg</td>
<td>8</td>
<td>12</td>
<td>14</td>
<td>16-18</td>
</tr>
<tr>
<td>10-15 kg</td>
<td>6</td>
<td>8</td>
<td>10</td>
<td>12-14</td>
</tr>
<tr>
<td>15-20 kg</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>10-12</td>
</tr>
<tr>
<td>20-30 kg</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>&lt;12</td>
</tr>
<tr>
<td>&gt;30 kg</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>
Table 7: Recommended parenteral glucose supply according to percentage of dextrose.4

<table>
<thead>
<tr>
<th>Patient Age Group</th>
<th>Initial Concentration</th>
<th>Advanced By</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature infants, Newborn</td>
<td>5%</td>
<td>2.5% dextrose every other day</td>
</tr>
<tr>
<td>infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older infants, Children</td>
<td>5%</td>
<td>2.5% dextrose per day</td>
</tr>
<tr>
<td>Teenagers, Adults</td>
<td>5%</td>
<td>5% dextrose per day</td>
</tr>
</tbody>
</table>

Potential complications and risks of carbohydrate infusion:
- Hyperglycaemia or hypoglycaemia.
- Glycosuria and potential osmotic diuresis.
- Cholestasis and/or hepatic steatosis (from prolonged high glucose concentration infusion).

5.3 Proteins
Proteins play vital roles in maintaining structural integrity and functional components of cells in the body. It is provided in PN solution to prevent catabolism and to achieve positive nitrogen balance in patients. In fact, the infusion of amino acid is recommended to be given to neonates from day 1 of life because the presence of amino acid in the bloodstream can stimulate endogenous insulin secretion, hence reduce the frequency and severity of neonatal hyperglycaemia.5,11 At least 1-1.5g/kg/day is needed to prevent negative nitrogen balance in the first week of life.12 However, higher intakes are needed to achieve physiological protein deposition. When no growth faltering has occurred in the period before, aiming for 3.5 – 4.0g protein/kg/day is advised for extremely low birth weight and very low birth weight infants.
5.3 Proteins

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Studies using high protein allotments of 4-6g/kg/day have been associated with adverse effects such as azotemia, metabolic acidosis and neurodevelopmental abnormalities.13

Potential complications and risks of protein infusions:

- Acidosis
- Elevated blood urea nitrogen (BUN)
- Hyperammonia
- Cholestasis with prolonged administration

<table>
<thead>
<tr>
<th>Table 8: General protein requirements for initiation and advancement of PN.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Year)</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Preterm</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2 months – 3 years</td>
</tr>
<tr>
<td>3 years – 18 years</td>
</tr>
<tr>
<td>Critically ill (3 years – 12 years)</td>
</tr>
</tbody>
</table>

Studies using high protein allotments of 4-6g/kg/day have been associated with adverse effects such as azotemia, metabolic acidosis and neurodevelopmental abnormalities.13

Potential complications and risks of protein infusions:
Sources of protein in PN solution:

- Protein is administered as a solution of amino acids.
- 1g of protein yields 4kcal of energy.
- Vaminolact® contains amino acids composition similar to human breast milk.

**Table 9: Relative concentrations of amino acids in Vaminolact® and human milk.**

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Content (g/100g)</th>
<th>Human Breast Milk</th>
<th>Vaminolact®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>4.7</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>Arginine</td>
<td>4.6</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Aspartic Acid</td>
<td>10.1</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Cysteine</td>
<td>1.6</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Glutamic Acid</td>
<td>18.1</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>3</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>3</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Isoleucine</td>
<td>4.8</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Leucine</td>
<td>10.4</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Lysine</td>
<td>8.1</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>1.9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>4.1</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Proline</td>
<td>8.5</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Serine</td>
<td>5.5</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>Taurine</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Threonine</td>
<td>5.3</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2.2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>3.9</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td>5.4</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>
5.4 Lipids

Lipid emulsions are the major source of non-protein calories in the PN solution. The presence of lipid emulsions in PN solution improves the NPC:N ratio of the PN regimen, allowing protein to be utilised efficiently for anabolic processes, hence improving net nitrogen balance in the body. The inclusion of lipids in PN regimen also enable less carbohydrate to be given and thus decreases carbon dioxide production formed from excessive concentration of carbohydrates. Lipid intake is recommended to provide 25-40% of non-protein calories in fully fed parenterally.15

Lipids contain polyunsaturated fatty acids such as linoleic acid and alpha linolenic acid which are essential components of neurodevelopment. Lipids infusion should be initiated within the first 3 days of life to prevent essential fatty acid deficiencies. Minimum amount of linoleic acid is 0.25g/kg/day for preterm and 0.1g/kg/day for infants and children.4

Table 10 above shows the lipid requirements according to age.4,16

<table>
<thead>
<tr>
<th>Age</th>
<th>Initial (g/kg body weight/day)</th>
<th>Daily Increase (g/kg body weight/day)</th>
<th>Maximum (g/kg body weight/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonates</td>
<td>0.5-1</td>
<td>0.5-1</td>
<td>3-4</td>
</tr>
<tr>
<td>Term neonates, infants &amp; children</td>
<td>1</td>
<td>0.5-1</td>
<td>3-4</td>
</tr>
<tr>
<td>Critically ill children</td>
<td>1</td>
<td>0.5-1</td>
<td>2-4</td>
</tr>
</tbody>
</table>

Table 10 above shows the lipid requirements according to age. It is recommended to monitor patients’ triglyceride level and the rate for infusion of IVFE should not exceed 0.125g/kg/hour. IVFE should be infused at rates to avoid serum triglyceride levels of more than 200mg/dL. Fat oxidation for term infants is 4g/kg/day and for preterm infants is 3g/kg/day.4,16
Potential complications and risks of lipid infusions:

- Hypertriglyceridemia in preterm infant with physiologic jaundice and hyperbilirubinemia (>18mg/dL) is associated with kernicterus.
- Potential risk of kernicterus at low levels of unconjugated bilirubin due to displacement of bilirubin from albumin binding sites by free fatty acids. As a general rule, lipids should not be increased beyond 0.5g/kg/day until bilirubin is below threshold for phototherapy.
- Increased risk of exacerbation of chronic lung disease.
- Exacerbation of persistent pulmonary hypertension.
- ‘Lipid overload syndrome’ with coagulopathy and liver failure.
- Hypersensitivity reaction (chills, fever, cyanosis, rash, nausea, vomiting).
- The clinical consequences associated with hypertriglyceridemia in neonates include increase risk of pancreatitis, immunosuppression and altered pulmonary haemodynamic.

Generally, 1g of fat yields 9kcal of energy. Lipid emulsion preparation can be provided by a variety of product options such as Intralipid®, Lipofundin®, SMOFlipid® and Lipidem®. Table 11 below shows the composition comparison of the lipid sources that can be found in the market. Lipid emulsion is isotonic to human blood and thus when infused as one of the components in PN solution, it can reduce osmolarity of the overall solution and minimise the risk of thrombophlebitis. Standard 20% lipid emulsion contains a lower ratio of phospholipid emulsifier/ triglycerides than standard 10% lipid emulsion, and should preferably be used for intravenous PN to decrease the risk of hyperlipidemia. Direct exposure to ultraviolet rays especially during phototherapy, can cause the formation of harmful hyperoxides in the lipid emulsion.
Table 11: Composition of Intralipid 20%, SMOFlipid®20%, Lipofundin®20% and Lipidem® 20% per 1000mL.17-20

<table>
<thead>
<tr>
<th>Contents</th>
<th>Intralipid® 20%</th>
<th>SMOFlipid® 20%</th>
<th>Lipofundin® 20% MCT/LCT</th>
<th>Lipidem® 20% (Above 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soybean oil (g)</td>
<td>200</td>
<td>60</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Omega-3-acid triglycerides</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>Medium chain triglycerides</td>
<td>-</td>
<td>60</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Olive oil</td>
<td>-</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fish oil, rich in omega-3-acids</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Energy content (kcal)</td>
<td>2000</td>
<td>2000</td>
<td>1908</td>
<td>1910</td>
</tr>
<tr>
<td>Osmolarity (mOsm/L)</td>
<td>350</td>
<td>380</td>
<td>380</td>
<td>410</td>
</tr>
</tbody>
</table>

To ensure the safety and effective use of lipids in PN, the following recommendations should be adhered to during lipid administration in neonates:

- Lipids should be infused over 24 hours to improve lipid clearance. Premature and term newborns have low lipoprotein lipase activity compared to adults. Hence, their fats clearance are less efficient.
- Vitamin E supplementation as an antioxidant. Lipid metabolism results in lipid peroxidation which leads to free radical formation. Free radicals can damage cell membranes during vitamin E deficiency.
- Lipid emulsions should be infused in light protective tubing.
5.5 Electrolytes

Electrolytes requirements are shown below (Table 12). There are limitations to amount of calcium and phosphate that can be supplied in PN. Calcium and phosphate are able to form precipitate depending on the amounts added into the PN solution. One method of avoiding the risk of calcium-phosphate precipitation is to use organic phosphate and calcium salts. A recommended ratio (mol/mol) of 1.3:1 to 1.7:1 by weight calcium to phosphate in PN allows for the highest absolute retention of both minerals and simulates the in utero accretion of calcium and phosphate. Providing 1.7 mmol/dL of calcium and 2mmol/dL of phosphorus in PN solution has been shown to improve mineral retention and bone mineral content. It is not recommended to routinely adding magnesium in the PN for infants whose mothers have received therapeutic dose of magnesium (i.e for tocolysis or as a prophylaxis).

Table 12: Electrolytes requirements in neonates, infants & children.

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Neonate</th>
<th>Infants/ Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mEq/kg/day)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>2-5</td>
<td>2-5</td>
</tr>
<tr>
<td>Potassium</td>
<td>2-4</td>
<td>2-4</td>
</tr>
<tr>
<td>Calcium</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.3-0.5</td>
<td>0.1-0.3</td>
</tr>
<tr>
<td>Phosphate</td>
<td>-</td>
<td>1-2mmol/kg</td>
</tr>
</tbody>
</table>

Factors that can affect calcium and phosphate compatibility are:

- pH
- Temperature
- Presence of light
- Concentration of calcium and phosphate
- Amino acid concentration
- Calcium salt
- Presence of lipid
5.6. Vitamins

Vitamins are essential and should be an integral part of PN whenever PN is administered. However, the vitamins requirement of neonates and older children has not been extensively studied. Table below show the estimation of vitamins intake in children.

**Table 13: Recommended intakes for parenteral supply of water soluble vitamins for infants and children.**

<table>
<thead>
<tr>
<th>Water Soluble Vitamin</th>
<th>Best Estimate (preterm infant) (Amount/d)</th>
<th>Content in 1mL Soluvit® N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine</td>
<td>0.35mg</td>
<td>0.25mg</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>0.15mg</td>
<td>0.36mg</td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td>0.18mg</td>
<td>0.4mg</td>
</tr>
<tr>
<td>Cyanocobalamin (B12)</td>
<td>0.3μg</td>
<td>0.5μg</td>
</tr>
<tr>
<td>Niacin</td>
<td>6.8mg</td>
<td>4mg</td>
</tr>
<tr>
<td>Panthothenic Acid</td>
<td>2.0mg</td>
<td>1.5mg</td>
</tr>
<tr>
<td>Biotin</td>
<td>6μg</td>
<td>6μg</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>56μg</td>
<td>40μg</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>25mg</td>
<td>10mg</td>
</tr>
</tbody>
</table>

**Table 14: Recommended intakes for parenteral supply of lipid soluble vitamins for infants and children.**

<table>
<thead>
<tr>
<th>Fat Soluble Vitamin</th>
<th>Best Estimate (preterm infant) (Amount/d)</th>
<th>Content in 4mL Vitalipid® N Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol (A)</td>
<td>1643 IU</td>
<td>920 IU</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>160 IU</td>
<td>160 IU</td>
</tr>
<tr>
<td>Alpha-Tocopherol (E)</td>
<td>2.8 IU</td>
<td>2.84 IU</td>
</tr>
<tr>
<td>Phytomenadione (K)</td>
<td>80 μg</td>
<td>80 μg</td>
</tr>
</tbody>
</table>

** Note:
500μg = 1643 IU
1mg = 1 IU
5.7 Trace Elements

Recommended intakes of trace elements mostly cannot be achieved through the use of a single paediatric trace element product. For those paediatric patients with renal dysfunction and impaired biliary excretion or cholestatic liver disease, trace elements should be excluded from the formulation. However, trace elements are indicated for use in long term PN patients.23

<table>
<thead>
<tr>
<th>Trace Elements</th>
<th>Recommended Daily Requirements</th>
<th>Contents in 1mL Peditrace®24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>Preterm: 450–500 μg/kg/day</td>
<td>250μg</td>
</tr>
<tr>
<td></td>
<td>Infant less 3 months: 250 μg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infant aged 3 months or older: 100 μg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Term infant: 200μg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: 50 μg/kg/day - 5 mg/day</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td>Preterm: 1 μg/kg/day</td>
<td>1μg</td>
</tr>
<tr>
<td></td>
<td>Term: 1 μg/kg/day</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>Infant and children: 20 μg/kg/day</td>
<td>20μg</td>
</tr>
<tr>
<td>Fluoride</td>
<td>-</td>
<td>57μg</td>
</tr>
<tr>
<td>Iodide</td>
<td>Infant and children: 1μg/day</td>
<td>1μg</td>
</tr>
<tr>
<td>Selenium</td>
<td>Preterm (LBW): 2μg/kg/day</td>
<td>2μg</td>
</tr>
<tr>
<td></td>
<td>Children: 2-3 μg/kg (≥ 3 mo to ≤ 5 years)</td>
<td></td>
</tr>
</tbody>
</table>
6.0 Monitoring

The aim of monitoring is to avoid complications such as metabolic and mechanical complications, line-related sepsis, etc. Through careful monitoring, complications can be minimised without diminishing the overall benefit of PN.

In addition to above statement, careful monitoring of infusion line such as leakage and incorrect infusion rate due to problem arise from infusion pump errors is important.

For long term PN administration, measurement of trace elements and vitamins, at the intervals of 6 months is recommended. Bone mineral density assessment is recommended at yearly interval.

Table 16: Recommended laboratory and clinical monitoring.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unstable Patients</th>
<th>Stable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Blood Count</td>
<td>Daily</td>
<td>3 times a week</td>
</tr>
<tr>
<td>Na, K, Cl, Urea, Serum Creatinine</td>
<td>Daily</td>
<td>3 times a week</td>
</tr>
<tr>
<td>Mg$^{2+}$, Ca$^{2+}$, PO$_4^{2-}$</td>
<td>Twice weekly</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Serum Triglyceride</td>
<td>Twice weekly</td>
<td>Once weekly unless complications arise</td>
</tr>
<tr>
<td>Liver Function Test</td>
<td>For long term PN (&gt; 2 weeks duration)</td>
<td></td>
</tr>
<tr>
<td>Blood Sugar (Dextrostix)</td>
<td>4-6 hourly for the first 3 days</td>
<td>Twice daily once stable</td>
</tr>
<tr>
<td>Weight</td>
<td>Daily</td>
<td></td>
</tr>
</tbody>
</table>
7.0 Complications

Complications may arise during PN supplementation and can be grouped as follows:

a) Stability of the PN solutions and drug-PN interactions.
b) Catheter related infections.
c) CVC related mechanical complications.
d) Metabolic or nutritional.

7.1 Stability of the PN Solutions and Drug-PN Interactions

7.1.1 Compatibility\textsuperscript{4,25}

- Admixture formulation for preparing PN solution should be validated whenever possible by a licensed manufacturer or suitably qualified institution.
- The formulation detailing permissible limits for additions of electrolytes and other additives should be sought from the suppliers that are supplying the raw materials.
- Alternative ingredients are not recommended to be substituted without expert advice or repeat validation.
- Organic bound form of phosphate is preferred over inorganic phosphate to prevent the risk of calcium-phosphate precipitation.
- If any inorganic phosphate to be used in the formulation, strict order of mixing PN components must be followed and maximum calcium-phosphate concentration must be taken into consideration. However, occasional precipitates may still occur due to various factors.
- A terminal filter should be used whenever administering PN admixtures.
- The standard for filter size is 0.2micron filter can be used if no lipids are administered through the filter. 1.2microns filter should be used for the administration of lipids emulsion and 3 in 1 PN solutions.
7.1.2 Drug Interactions

- PN mixed with medications should be avoided whenever possible unless validated by the manufacturer or accredited laboratory.
- Medications known to affect plasma protein binding of bilirubin should be avoided in parenterally fed newborn patients with severe hyperbilirubinaemia.

7.2 Catheter Related Infections

- PN solution should be prepared aseptically in a suitable environment according to Good Preparation Practise (GPP).
- The infusion sets and extensions should be used no more than 72 hours and changed as recommended by the manufacturers.
- For lipid infusion sets, they need to be changed 24 hours after usage or as recommended by the manufacturers.¹
- CVC blood cultures should be taken for any unexplained fever or if patient develops other clinical signs of catheter-related sepsis (CRS).
- Broad spectrum or empirical intravenous antibiotics should be commenced promptly whenever CRS is suspected.
- Once the infecting microorganism has been identified, a narrower spectrum antibiotic therapy should be given and duration of therapy should be guided by the organism identified.
- CVC is recommended to be removed if blood culture is positive of fungal growth or if persistent pyrexia with positive blood cultures after 48 hours of appropriate antibiotics.⁴
7.3 CVC Related Mechanical Complications

7.3.1 Occlusion

- Occlusion of the CVC can be originated from:
  
  i. Within the CVC lumen due to blood, drug or PN fluid precipitate.
  
  ii. In the vein due to clot or fibrin sheath.
  
  iii. External to the CVC due to the tip resting against a vein wall or due to external compression such as clavicle, or patient positioning.

- CVC should be flushed with sodium chloride 0.9% between all therapies. Whenever CVC is not in use, CVC should be flushed with heparin at least weekly.

- Terminal in-line filters should be used for all PN solutions and if occlusion occurs, a prompt investigation should be done.

- Blood sampling via CVC should be avoided if possible.

- Syringes less than 10mL should not be routinely used on CVC and unblocking the CVC with a guide wire is not recommended.

7.3.2 Thrombosis and Pulmonary Embolism

- Central venous thrombosis (CVT) and pulmonary embolism (PE) could be fatal especially for those children receiving prolonged PN.

- CVT and PE mostly are associated with recurrent CVC infection, repeated CVC changes, position of the CVC tip, frequent blood sampling, concentrated glucose solution, chemotherapeutic agents and it could be due to idiopathic cause.

- Symptoms of CVT and PE include distress of the child, breathlessness, redness or swelling in the neck or limbs, leakage from the exit or stiffness of the CVC during flushing.

- Thrombolytic agents or anticoagulation is recommended for the treatment of acute symptomatic thrombosis.

- Children that are on long term PN, vitamin K antagonists or low molecular weight heparins can be given prophylactically.
7.3.3 Accidental Removal or Damage

- Accidental removal or damage can occur accidentally or deliberately by traction to the CVC. Therefore, it is recommended that CVC should be securely taped to the body.
- Secure postoperative dressings should be in place in which the exit site can be observed easily and easier for dressing removal.
- Accidental leakage and haemorrhage events can be minimised by using Luer-lock connectors.

7.4 Metabolic or Nutritional Complications

7.4.1 Refeeding Syndrome

- Feeding to a malnourished child may cause refeeding syndrome which is principally associated with hypophosphataemia, hypomagnesaemia, hypokalaemia, vitamin deficiency and fluid retention.
- Refeeding syndrome could be life threatening, thus PN regimen must be formulated wisely and monitored closely.
- In the initial phase of re-nutrition of severely malnourished infants and children, several condition must be taken into consideration as follow:
  
  i. Prevention of water and sodium overload:
    - Water and sodium intake should be reduced. However, this is depending on the hydration status of the malnourished infants and children.
    - Fluid monitoring is essential to detect early fluid retention which could be observed by patients excessive weight gain. Maintaining stable weight is highly recommended or may try to achieve weight loss during the first 2-3 days of parenteral re-nutrition.
    - Slow infusion of albumin at 1g/kg, twice a day can be given if necessary for preserving the oncotic pressure.
    - Insensible losses or losses from the gastrointestinal tract, intraperitoneal
or intestinal fluid retention should be monitored.

ii. Carbohydrate intake:
- Continuous glucose infusion provided should be tailored to the age of the patient and the rate may be at least equal to the glucose production rate.

iii. Potassium repletion:
- Potassium correction should be done progressively with monitoring of renal and cardiac function as it can be fatal if the deficiency is corrected too rapidly. Excessive potassium intake may cause hyperkalaemia and cardiac arrhythmia.

iv. Phosphorus repletion:
- Phosphorus depletion should be corrected progressively with monitoring of neurological status and renal function.
- Minimum intake of 0.5mmol/kg/day is recommended and proportionally increased according to the total protein energy intake up to 1.0mmol/kg/day.
- It is mandatory for daily monitoring of phosphoraemia and phosphaturia by aiming at a limited phosphaturia.

v. Protein and energy intake:
- An intake of 0.5-1g/kg of parenteral amino acids or oral peptide is recommended in the initial phase of re-nutrition as excessive nitrogen intake may cause hyperammonaemia/metabolic acidosis.
- The protein energy deficiency should be made gradually and must be corrected during the days following the initial period of stress.
- It is important to provide both nitrogen and calories simultaneously and in the correct ratio.
7.4.2 Metabolic Bone Disease

- Little data of PN related metabolic bone disease (MBD) exists in children, although its occurrence has been reported in children with long term PN.

- Therefore, regular measurements is recommended to be performed on urinary calcium, plasma calcium, phosphorus, parathyroid hormone, vitamin D concentrations and serum alkaline phosphatase particularly for children on long term PN.

- Risk of contamination with aluminium in PN solutions should also be avoided and minimised.

- In order to prevent MBD, regular assessment of bone mineralisation should be performed.

7.4.3 Hepatobiliary complications of PN:

- Risk of developing liver disease can be due to patient related condition such as patient on prolonged PN, absence of oral feeding, short bowel syndrome as well as recurrent septic episodes.

- However, PN may also aggravate liver injury due to excess of total energy delivered that induces liver lesions, excessive or inadequate amino acid supply, continuous PN infusion or excessive glucose intake which may lead to hyperinsulinism and subsequent steatosis, inadequate lipid supply with excessive delivery of fat and subsequent lipoperoxidation as well as the phytosterols contain in the lipid emulsion.

- Liver disease can be prevented by reducing both patient related and PN related risk factors as mentioned above by:
  
  i. Providing maximal tolerated enteral nutrition despite of minimal residual gut function.
  
  ii. Introducing cyclical PN immediately.
  
  iii. Treat intraluminal bacterial overgrowth by giving metronidazole or by performing venting enterostomy or tapering enteroplasty.
  
  iv. May reduce or stop IV lipids temporarily if conjugated bilirubin progressively increases with no other explanation.
v. Commencing ursodeoxycholic acid at 10 to 30mg/kg/day if the transaminases, alkaline phosphatase or conjugated bilirubin are increasing.\textsuperscript{32}

vi. Early referral and assessment from an experienced paediatric liver and intestinal transplant centre is highly recommended if the infants/children have poor prognosis or if on PN for 3 months and serum bilirubin 50µmol/L, platelet count less than 100, PT more than 15 seconds, PTT more than 40 seconds or hepatic fibrosis.\textsuperscript{4}

### 7.4.4 Growth Retardation

- Infant or children on prolonged PN must receive adequate nutrition not only to meet its basic metabolic requirements but also to allow for normal growth.

- Therefore, paediatric patients on long term PN require regular monitoring of growth and body composition to prevent abnormalities in growth and nutritional status in later childhood.\textsuperscript{4,33}

### 8.0 Discontinuing PN

While transitioning from PN to EN, calorie intake and glycaemic control should be optimised. Total fluids intake should be maintained while weaning off PN and increasing EN.

PN solution should be decreased at equal amount or slightly more than EN being instituted.\textsuperscript{4,10} If EN achieving 75% of the total fluids, PN can be discontinued.\textsuperscript{10}
Appendix 1

Calculation of PN Osmolarity

1. Osmolarity (mOsm/L) = \([\text{CHO}(g) \times 5] + [\text{AA}(g) \times 10] + [\text{Fat}(g) \times 0.71] + [\text{Elec}(m\text{Eq}) \times 1]\) 
   Volume (L)

   - CHO: Carbohydrate
   - AA: Amino Acids
   - Elec: Electrolytes


2. Osmolarity (mOsm/L) = Carbo(g)\times 5 + AA(g)\times 10 + Cations^*\times (m\text{Eq}) \times 2@4 \text{Volume(L)}

   *Cations with mono-valens (x2)
   *Cations with di-valens (x4)

References


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11. Muhlebah S, University Hospital Berne, Approach to Parenteral Nutrition, 2007
12. Hughes B, Newborn Services Drug Protocol, Department of Pharmacy, Auckland Healthcare


17. Product Leaflet. Intralipid 20%

18. Product Leaflet. Smoflipid 20%

19. Product Leaflet. Lipofundin 20%

20. Product Leaflet. Lipidem 20%


22. Product Leaflet. Vitalipid N TM


24. Product Leaflet. Peditrace TM


26. e-SPEN, the European e-Journal of Clinical Nutrition & Metabolism, 2010


