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Enhancing Parenteral Nutrition Therapy for the Neonate

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ABSTRACT: The neonate receiving parenteral nutrition (PN) therapy requires a physiologically appropriate solution in quantity and quality given according to a timely, cost-effective strategy. Maintaining tissue integrity, metabolism, and growth in a neonate is challenging. To support infant growth and influence subsequent development requires critical timing for nutrition assessment and intervention. Providing amino acids to neonates has been shown to improve nitrogen balance, glucose metabolism, and amino acid profiles. In contrast, supplying the lipid emulsions (currently available in the United States) to provide essential fatty acids is not the optimal composition to help attenuate inflammation. Recent investigations with an ω-3 fish oil IV emulsion are promising, but there is need for further research and development. Complications from PN, however, remain problematic and include infection, hepatic dysfunction, and cholestasis. These complications in the neonate can affect morbidity and mortality, thus emphasizing the preference to provide early enteral feedings, as well as medication therapy to improve liver health and outcome. Potential strategies aimed at enhancing PN therapy in the neonate are highlighted in this review, and a summary of guidelines for practical management is included.

Growth and Development

High-risk neonates hospitalized for surgical or cardiac complications and premature infants (born before 37 weeks' gestation) pose a particular nutrition support challenge because nutrients need to be provided for maintenance, as well as growth. Determining the caloric, protein, lipid, vitamin, mineral, and trace element needs to support this rate of growth can be daunting. In addition, the preterm infant has missed the last trimester of nutrient accretion and body stores and will require immediate attention because of the vital need for brain glucose and limited fat stores. Most important, growth in the early weeks of hospitalization has been associated with improvement in developmental scores and cerebral palsy. In addition, it seems that poor early nutrition status of an infant may predispose the child to later health disparities, therefore requiring vigilant attention to nutrient quality, quantity, and constant updated practice based on current literature.

Parenteral Nutrition (PN)

Before the availability of PN, the high-risk or preterm infant unable to suck and swallow until 33 weeks' gestation was not able to survive. PN components (protein hydrolysates, fat emulsions, vitamins, and trace element sources) were finally enhanced for pediatric patients with the development of the pediatric-specific multivitamin infusion and a crystalline amino acid solution that mimicked a breast-fed infant's aminogram and decreased the incidence of hyperammonemia and hyperphenylalanemia caused by the early protein hydrolysates. Despite PN advancements, there remain difficulties with line infiltrations, infections, bone demineralization, and cholestasis, emphasizing the importance of early PN (within 24 hours after infant delivery), appropriate ratio of PN nutrients, early enteral nutrition medications to help with biliary health, and new emulsions for lipid sources that may be hepatoprotective. Specific nutrient dosages must also be considered.

Basis for Nutrient Requirements

Nutrient requirements for the neonate are based on fetal accretion estimates, energy expenditure studies, and balance studies, as well as hormonal and metabolic investigations. After delivery, the high-risk neonate has limited glycogen and fat reserves, making an immediate source of nutrition imperative. In the neonatal intensive care unit, significant nutrient deficiencies have been documented and infants have subsequently experienced growth failure from postnatal malnutrition, with many leaving the hospital at a weight less than...
Summary of nutrient needs can be seen in Table 1.

Dextrose

The neonate requires a source of glucose after delivery. Because glucose supplied by facilitated diffusion in utero is ceased abruptly, there is an immediate need to provide a source of dextrose. Measurement of glucose production approximates 6 mg/kg/min; thus, a glucose supply of 6 mg/kg/min should be initiated, with daily increments to a maximal goal of 12 mg/kg/min. Current recommendations for blood glucose levels are that the neonate receiving PN should have a glucose level above 45 mg/dL. The basis for a minimum blood glucose level stems from early work from Lucas et al that described developmental differences in preterm infants who had several periods of low blood glucose levels. Infants with symptoms of hypoglycemia (and not receiving enteral feeding) should be treated regardless of blood glucose level with a glucose bolus of 2 mL/kg of 10% dextrose, followed by a constant infusion of dextrose to provide 4–8 mg/kg/minute; a repeat glucose level should be checked within the hour. Despite limited body stores, immature infants often paradoxically experience elevated glucose levels. Blood glucose levels >150 mg/dL have been associated with retinopathy of prematurity, increased risk of early death, grades 3 and 4 intraventricular hemorrhages (IVHs), and prolonged length of stay. The treatment for hyperglycemia is variable; some centers may lower glucose rate to normalize blood glucose levels. This practice inadvertently diminishes energy intake and may result in failure to thrive or inadequate nonprotein calories to allow for protein to be used for anabolism rather than energy. Studies have shown that a continuous source of insulin can safely be given to maintain an increased glucose supply. The insulin regimen goal (1 unit/mL) then should be diluted as 0.1–1 unit per mL in 0.9% or 0.45% normal saline and then loaded with 0.1 unit/kg/dose over 15–20 minutes to prime the tubing; the maintenance drip can then be infused at 0.01–0.1 unit/kg/h. Serum glucose monitoring should be done frequently and insulin and glucose titrated as needed to maintain a normoglycemic range. Insulin should be discontinued when blood glucose levels reach 100 mg/dL.

Peripheral vein tolerance for osmolarity typically ranges from 700 to 1000 mOsm/L. Osmolarity can be predicted using the equation osmolarity (mOsm/L) = [amino acids (g/L) × 8] + [glucose (g/L) × 7] + [Na (mEq/L) × 2] + [phosphorus (mg/L) × 0.2] – 50. With the availability of central venous access, carbohydrate load can be dramatically increased without the concern for osmolar irritability. However, excess calories could potentiate cholestasis or exacerbate lung mechanics from excessive CO2 production; therefore, keeping an appropriate ratio of carbohydrate to protein can be beneficial. Not only should the quantity of calories and protein be considered, but knowledge of potential enzymatic limitations in the preterm infant and quality and timing of amino acids should also be considered.

Amino Acids

The goal of amino acid delivery to the preterm infant is to provide an IV substrate that will allow protein deposition and subsequent gain of lean body mass that is comparable to that of the fetus in utero. This provides a challenge in that the fetus uses glucose at low insulin concentrations and lipid is minimally used until the third trimester; amino acids are used as the primary source for fetal energy production and growth. Because an artificial nutrient solution cannot mimic the nutrition efficacy of the placenta, PN does not match the ideal ratio of carbohydrate, fat, and protein. Once the umbilical cord is cut, an infant’s ideal nutrition delivery is discontinued. This transition period begins a time in which the infant receives insufficient calories to maintain a nitrogen balance; endogenous stores may be required to meet energy needs. Efforts should be made to prevent a state of catabolism by administering IV amino acids as soon as possible after birth. Perhaps the goal should be to minimize

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Table 1

Parenteral nutrient recommendations for the high-risk neonate (based on references 1, 5, 19, 21, 22)

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>Parenteral requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal/kg)</td>
<td>80–90</td>
</tr>
<tr>
<td>Carbohydrate (g/kg)</td>
<td>16</td>
</tr>
<tr>
<td>Protein (g/kg)</td>
<td>3–4*</td>
</tr>
<tr>
<td>Lipid (g/kg)</td>
<td>3–4</td>
</tr>
<tr>
<td>Sodium (mEq/kg)</td>
<td>3–4*</td>
</tr>
<tr>
<td>Potassium (mEq/kg)</td>
<td>2–4</td>
</tr>
<tr>
<td>Calcium (mg/kg)</td>
<td>80–120</td>
</tr>
<tr>
<td>Phosphorus (mg/kg)</td>
<td>60–90</td>
</tr>
<tr>
<td>Magnesium (mg/kg)</td>
<td>9–10</td>
</tr>
<tr>
<td>Copper (µg/kg)</td>
<td>65</td>
</tr>
<tr>
<td>Zinc (µg/kg)</td>
<td>350–450*</td>
</tr>
<tr>
<td>Vitamin A (IU/kg)</td>
<td>500</td>
</tr>
<tr>
<td>Vitamin D (IU/kg)</td>
<td>160</td>
</tr>
<tr>
<td>Vitamin E (IU/kg)</td>
<td>2.8</td>
</tr>
<tr>
<td>Vitamin K (IU/kg)</td>
<td>80</td>
</tr>
<tr>
<td>Vitamin B1 (mg/kg)</td>
<td>350</td>
</tr>
<tr>
<td>Vitamin B2 (mg/kg)</td>
<td>150</td>
</tr>
<tr>
<td>Niacin (NE/kg)</td>
<td>6.8</td>
</tr>
<tr>
<td>Vitamin B12 (µg/kg)</td>
<td>0.4</td>
</tr>
<tr>
<td>Vitamin C (mg/kg)</td>
<td>32</td>
</tr>
</tbody>
</table>

*Illeostomy, surgical drains, chest tubes can increase losses, so intake may need to increase concomitantly.
the number of hours, not days, that the infant receives suboptimal nutrition substrates, resulting in loss of lean body mass. In addition, one should strive to provide an environment that reduces energy expenditure in order to preserve the body stores. These strategies may decrease the number of days required by an infant to regain birth weight and minimize the need to address “catch-up” growth, assuming enteral feedings are initiated early.39,40

The amounts of nutrients to support fetal growth rates are ~3 g/kg/d of protein and ~90 kcal/kg/d.19,38 Historically, it has not been standard practice to provide this level of nutrition to a premature infant during the first few days of life. However, it recently has become evident that a protein delivery of 3 g/kg/d beginning on day 1 of life can be safe and, at this level, provides plasma amino acid concentrations similar to that in second- and third-trimester fetuses.41 Protein deliveries as minimal as 1.5 g/kg/d have resulted in a neutral/positive nitrogen balance in most infants,37 but maximizing protein to provide 3 g/kg/d as soon after delivery as possible may further enhance protein deposition, which is vital to early growth.42 Further analysis is needed to describe the optimal protein intake for infants who are born with sepsis or significant hepatic or renal dysfunction. Very premature infants may require up to 4 g/kg/d of IV protein to maintain stores and facilitate growth.43

The quality of the protein must also be taken into consideration because the premature infant has immature enzymatic capacities for cystathionase activity,44 and thus cysteine and taurine are often considered semiessential amino acids. Cysteine may also be important for redox/antioxidant mechanisms and in the composition of glutathione (γ-glutamylcysteinylglycine, or GSH). Children with severe malnutrition supplemented with cysteine showed restored levels of GSH45; preterm infants have been documented to have low levels of cysteine production46 and glutathione levels.47 It would be ideal to provide an amino acid solution that mimics a preterm infant’s need for increased doses of semiessential amino acids. However, adding cysteine to the solution is technically difficult and so is often added before delivery at a dose of 30–40 mg/g amino acid. This practice decreases the pH of the solution and reduces the risk of calcium and phosphorous precipitation.48

The timing for providing amino acids also seems to be crucial. According to current evidence, a minimum intake of 3 g/kg/d soon after delivery would be beneficial. Table 2 reviews selected studies and outcomes. There have been 3 pediatric amino acid products available for infant use in the United States. TrophAmine (B. Braun, Inc, Bethlehem, PA) has been most extensively studied and was developed to produce plasma amino acid concentrations similar to that of breast-fed infants of similar gestational age.7 TrophAmine contains an enhanced ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Amino acid solution</th>
<th>Birthweight (mean in grams)</th>
<th>Gestational age (mean in weeks)</th>
<th>Protein delivery (g/kg/d)</th>
<th>Timing after delivery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Lingen et al52</td>
<td>Supplemented group (n = 9) vs unsupplemented (n = 9)</td>
<td>Aminovenos 1500 vs 1400</td>
<td>30 vs 31</td>
<td>2.3</td>
<td>DOI 2</td>
<td>N15 enrichment reflected increased protein synthesis</td>
<td></td>
</tr>
<tr>
<td>Rivera et al37</td>
<td>Supplemented group (n = 12) vs unsupplemented (n = 11)</td>
<td>Aminosyn PF</td>
<td>1000 vs 1000</td>
<td>28.5</td>
<td>1.5</td>
<td>DOI 1</td>
<td>Improved protein balance based on labeled leucine</td>
</tr>
<tr>
<td>Van Goudoever et al53</td>
<td>Treatment group (n = 9) vs control group (n = 9)</td>
<td>Pimere 10% 1300 vs 1400</td>
<td>29</td>
<td>1.15</td>
<td>DOI 1</td>
<td>Using labeled leucine, treatment group had improved nitrogen retention with TrophAmine and plasma insulin with TrophAmine</td>
<td></td>
</tr>
<tr>
<td>Thureen et al41</td>
<td>Treatment group (n = 15) vs control group (n = 13)</td>
<td>TrophAmine 947 vs 946</td>
<td>22 h</td>
<td>3 vs 1</td>
<td>Within 5 DOL</td>
<td>Positive growth failure with TrophAmine</td>
<td></td>
</tr>
<tr>
<td>Ibrahim et al54</td>
<td>Treatment group (n = 16) vs control group (n = 16)</td>
<td>TrophAmine 846 vs 968</td>
<td>3 h</td>
<td>22 h</td>
<td>Within 5 DOL</td>
<td>Positive growth failure with TrophAmine</td>
<td></td>
</tr>
<tr>
<td>Poindexter et al55</td>
<td>Treatment group (n = 182) vs control group (n = 836)</td>
<td>TrophAmine 805 vs 791</td>
<td>26</td>
<td>26</td>
<td>Less growth failure with TrophAmine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Amenovenos, Fresenius Germania, France; Pimere, Clintec, Baxter, Benelux NV, Brussels, Belgium; TrophAmine, B Braun, Bethlehem, PA; Aminosyn PF, Abbott Park, IL. DOL, day of life.
of essential to nonessential amino acids and has been demonstrated to result in higher plasma concentrations of branched-chain amino acids (leucine, isoleucine, and valine) compared with standard amino acid formulas; this ratio has been shown to improve protein synthesis and nitrogen balance.\textsuperscript{7,49} TrophAmine has also been associated with a decreased incidence and degree (level of serum direct bilirubin concentration) of PN-associated cholestasis.\textsuperscript{50} The United States patent for TrophAmine expired in 2003, at which time Premasol (Baxter Healthcare Corp, Deerfield, IL) became available. It is therapeutically equivalent to TrophAmine but is sulfite free. Sulfites are antioxidants and help protect against peroxide formation. In a recent \textit{in vitro} comparison of Premasol and TrophAmine infused through clear and UV-resistant tubing exposed to phototherapy light, there was a significant difference in the formation of peroxides in the tubing. There was no peroxide formation in the tubing infused with TrophAmine; however, there was peroxide formation in both types of tubing infused with Premasol.\textsuperscript{51} Sulfites may help protect against peroxide formation. Future studies are needed to evaluate the clinical relevance of these oxidized products.

**Lipid Emulsions**

IV fat emulsions provide the sole source of essential fatty acids—linoleic acid, (18:2, ω-6) and linolenic acid, (18:3, ω-3)—in the nonenterally fed infant. Essential fatty acids are those that cannot be synthesized endogenously (placement of the double bonds in that position) by the body and so must come from dietary sources. Without a source of dietary fat, essential fatty acid deficiency can occur as soon as 3 days and definitively within 7 days in the preterm infant.\textsuperscript{56–59} The more premature the infant, the earlier this deficiency may occur because the adipose tissue and the liver are likely the only source of endogenous essential fatty acids in the absence of IV fat emulsion.\textsuperscript{60} The minimal amount of IV fat emulsion required to prevent essential fatty acid deficiency is 0.5 g/kg/d and may be as high as 1 g/kg/d; however, others suggest the minimal requirement is 0.25 g/kg/d for preterm and 0.1 g/kg/d for term infants.\textsuperscript{62} The minimal requirement will depend on overall total energy intake, as well as individual nutrition status, which, in turn, is influenced by gestational age, postnatal age, and degree of illness. The risk of essential fatty acid deficiency may be higher when the total energy intake is low and fatty acids are more likely to be used for energy rather than fat deposition.\textsuperscript{63,64}

Maximum lipid dose will be dependent not only on glucose intake but also on the infant’s ability to metabolize the fat emulsion particles as measured via serum triglyceride and cholesterol levels. The triglyceride portion of the fat emulsion is hydrolyzed by lipoprotein lipase, which is released from capillary endothelium. Endothelium tissue is available in reduced amounts in the preterm and malnourished patient, who, as a result, tends to have lower levels of lipoprotein lipase than term infants.\textsuperscript{65} The amount of lipoprotein lipase available determines the rate of triglyceride clearance.\textsuperscript{66} When fat emulsion is infused at a rate that is equal to or less than the rate of hydrolysis, elevated triglyceride levels are unlikely. When the rate of lipid infusion exceeds the rate of hydrolysis by lipoprotein lipase (enzyme saturation), serum triglyceride levels will increase;\textsuperscript{66} therefore, infusions of IV fat emulsion over 24 hours are more likely to be tolerated than those infused over shorter periods of time with lipid-free intervals.\textsuperscript{67–69} Preterm infants may be at higher risk than term infants for hypertriglyceridemia due to their limited muscle and fat mass. Decreased clearance of free fatty acids by these tissues would result in uptake by the liver and subsequent secretion of very low density lipoprotein (VLDL) triglyceride.\textsuperscript{62}

Other conditions and some drugs can contribute to the development of elevated serum triglyceride levels. Liposomal amphotericin B and propofol (10% emulsion) contain fat emulsion and may need to be calculated into the daily lipid requirement. The administration of exogenous corticosteroids used in the infant population (such as dexamethasone, hydrocortisone, or methylprednisolone) can result in transient elevated triglyceride levels.\textsuperscript{70} Medical conditions (eg, sepsis, surgery, and trauma) that are associated with “stress,” and the stimulation of the “flight or fight” response will result in the release of cortisol and catecholamines that promote lipolysis of fat stores and peripheral insulin resistance, subsequently resulting in transient elevated serum triglyceride levels.\textsuperscript{71–73} It is not clear what level of serum triglyceride can be considered harmful. In older pediatric patient populations, triglyceride levels of 300–400 mg/dL are considered acceptable. These levels are considered acceptable because lipoprotein lipase becomes saturated at 400 mg/dL in these older patient populations.\textsuperscript{74} Infants who are enterally fed commonly have serum triglyceride levels of 100–200 mg/dL. As described previously, preterm infants have lower amounts of lipoprotein lipase compared with older pediatric patient populations. The age at which levels of lipoprotein lipase mature quantitatively is not known; therefore, it would seem reasonable to accept a lower triglyceride serum level limit of 200 mg/dL to perhaps 250 mg/dL in the preterm and infant patient population.\textsuperscript{22,62} The absolute number assigned to a triglyceride serum level may be less important than the degree of change in serum level after an increase in dose of IV fat emulsion. Large increases in serum triglyceride levels will occur when the enzyme lipoprotein lipase becomes saturated (zero-order enzyme saturation kinetics). Small increases in serum triglyceride levels do not indicate enzyme saturation.
Lipid emulsions also contain varying amounts of phospholipids, which can interfere with the rate of lipid hydrolysis. The 10% emulsion contains greater amounts of phospholipids than the 20% or 30% emulsion and will contribute to the development of hyperphospholipidemia and subsequent hypercholesterolemia. The use of 10% IV fat emulsion should be avoided in the preterm patient population.

Commercially available IV fat emulsions in North America consist of vegetable oil (soybean and safflower oil) triglycerides emulsified with egg yolk phospholipids. Other commercially available IV fat emulsions consist of soybean oil combined with olive oil, or mixtures of medium-chain triglycerides (MCTs). European countries use a fish-oil-based IV fat emulsion that is not yet approved in the United States as a supplement to the vegetable-based fat emulsion. Fish oil contains the fatty acid linolenic acid (18:3, ω-3) and no linoleic acid (18:2, ω-6). Soybean oil contains 45%–55% linoleic acid and 6%–9% linolenic acid and very little saturated and monounsaturated fat, which is a significantly different composition from that of human milk. Alternative formulations of fat emulsion have been developed in an effort to decrease the amount or percentage of fatty acids delivered as linoleic acid to achieve less lipid peroxidation. In addition, the preterm infant misses the intrauterine accretion of docosahexaenoic acid (DHA) and has limited endogenous capacity to elongate and desaturate the essential fatty acid linolenic acid to DHA, thus making it a potentially semiessential nutrient. Recent case reports suggest that PN-induced cholestasis may be reversed with the administration of fish-oil-based emulsions without causing essential fatty acid deficiency. These case reports raise interesting questions regarding the fatty acid content of commercially available IV fat emulsions and the need for a specific DHA-containing solution.

**Carnitine**

Carnitine is essential to oxidize long-chain fatty acids; preterm infants have reduced production of carnitine from lysine and thus require an exogenous source. Mother's human milk and formulas contain carnitine; but if the infant is receiving PN without enteral feeding, we recommended L-carnitine supplementation to the PN at 2–5 mg/kg/d, which would be similar to the intake of the breastfed infant.

**Sodium**

Sodium can play an important role in the successful adaptation of fluid and electrolyte homeostasis during the first week of life. This “postnatal adaptation” can be divided into 3 stages: stage I, transition; stage II, intermediate period; and stage III, growth. Stage I is characterized by a redistribution of water from the intracellular space to extracellular space, resulting in an expansion of extracellular fluid (ECF) volume. A serum sodium level measured at this time, before the establishment of postnatal diuresis, may be low (130–134 mEq/L), reflecting an expanded ECF volume. Adding sodium at this stage can prevent the postnatal diuresis and further expand the ECF, contributing to edema formation in the periphery, as well as the lungs. Furthermore, sodium administration beyond physiologic needs can contribute to the development of hypernatremia, necessitating the administration of unplanned excess fluids. Excess fluid administration during this time can lead to delayed recovery from respiratory distress syndrome (RDS) and other potential subsequent morbidities such as patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), and IVH. Fluid and electrolyte derangements are best avoided when environmental and evaporative barriers are in place to minimize transepidermal water loss. Exogenous sodium administration should be delayed until stage I is complete or nearing completion and there is a documented weight loss below birth weight of at least 6%. The end of stage I is characterized by a drop in urine output, urine osmolarity > serum osmolarity, fractional excretion of sodium (FENa) decreasing from >3% to ≤1%, and a urine specific gravity >1.012. Successful transition depends on prospective individualized fluid management that allows contraction of the ECF and also maintains maintenance of intravascular volume and subsequent hemodynamic stability.

The goal for stage II is to advance PN to full maintenance requirements (macro- and micronutrients) and to initiate enteral feedings if medically stable. It seems possible for the premature infant to accrete body mass starting from birth, when adequate electrolytes and minerals are available for production of new tissue, although further research is needed. Deficits of sodium and phosphorous likely interfere with the low-birth-weight infant’s protein or amino acid use, as well as bone mineralization. Infants who receive higher intakes of sodium and phosphorous demonstrate greater growth and nitrogen retention.

Storage of sodium in the amount of 1–1.5 mmol/kg/d occurs when a growth rate of 15 g/kg/d is achieved. Additional sodium losses may occur due to the presence of an ileostomy, pleural effusion, peritoneal drainage, bowel obstruction, or cerebrospinal fluid drainage, as well as chronic diuretic use. Assessment of estimated losses of sodium, in addition to requirements for growth, will allow reasonable delivery of sodium to support growth. Begin supplementation at 2–3 mEq/kg/d and advance to 4 mEq/kg/d. Infants who are small for gestational age (SGA) or who have sources of ongoing losses will require increased amounts of delivered sodium to support adequate growth. It is pos-
Calcium and Phosphorus

The preterm infant misses the majority of calcium accretion and phosphorus that occurs in utero, in which approximately 80% of fetal bone is produced. The ability to achieve the rates of estimated 150 mg/kg/d of calcium and 75 mg/kg/d of phosphorus is technically difficult in PN solutions; therefore, 10% of preterm infants may experience fractures. To try to maximize delivery of these nutrients, calcium and phosphorus are best absorbed when given together. Providing 1.7 mmol/dL calcium and 2 mmol/dL phosphorus in PN solution has been shown to improve mineral retention and bone mineral content when using cysteine and TroPhAmine solutions. Providing calcium:phosphorus ratios of 1.3:1 by weight or 1:1 molar with 25 IU vitamin D added seems to produce normal serum vitamin D levels and calcium and phosphorus homeostasis.

Vitamins and Trace Elements

As with other nutrients, the preterm infant misses many last-trimester nutrient accretions. Two problematic nutrients for preterm infants include vitamin A and zinc. Fat-soluble vitamin A adsorption to tubing and delivery can be problematic, resulting in one-third lost in the infusion set. In some preterm infants receiving PN containing a pediatric multivitamin infusion, serum retinol levels fail to respond to multivitamin infusion. These patients may, at some point, need to have vitamin A delivered with fat emulsion. The concern is that limited vitamin A intake has been associated with BPD. Zinc deficiencies also are of concern in preterm infants because serum zinc concentration is negatively correlated to birth weight; however, birth weight responds to a heightened parenteral intake appropriately. Once feeding is started, a transition guideline, as shown in Table 5, can be helpful.

Table 3
Example of a pediatric hospital standardized parenteral nutrition (PN) solution

<table>
<thead>
<tr>
<th>Component</th>
<th>Dose/100 mL</th>
<th>Dose at 130 mL/kg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose (g)*</td>
<td>12.5</td>
<td>16.25</td>
</tr>
<tr>
<td>Amino acids (g)*</td>
<td>2.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Calcium (mmol)*</td>
<td>1.2</td>
<td>1.56</td>
</tr>
<tr>
<td>Phosphorus (mmol)</td>
<td>1.2</td>
<td>1.56</td>
</tr>
<tr>
<td>Magnesium sulfate (mg)</td>
<td>6</td>
<td>7.8</td>
</tr>
<tr>
<td>Potassium sulfate (mEq)</td>
<td>0.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Sodium chloride (mEq)</td>
<td>2.6</td>
<td>3.4</td>
</tr>
</tbody>
</table>

*Dextrose, amino acids, calcium, and heparin are the sole components of starter PN for the first 24–48 hours; add other components later.

Other PN additives:
- Cysteine: 40 mg/g amino acids
- Calcium:Phosphorus ratio = 1:1 molar
- Standard Vitamins
- Standard Trace Elements
- Heparin 1/2 unit per mL of PN solution
- Carnitine 2–5 mg/kg if PN required more than 2 weeks and there is no enteral intake
- Acetate may be necessary if serum CO2 levels are <18 mEq/L; add acetate by replacing some of the sodium chloride with sodium acetate (the dose cannot exceed 4 mEq/kg in order to maintain calcium and phosphorus solubility in the PN solution)

When a standardized formula is utilized, a strategy for advancement can be seen in Table 4.
Table 5
Example of a critical pathway for neonates receiving parenteral nutrition (PN)

<table>
<thead>
<tr>
<th>0–24 h</th>
<th>Day 2</th>
<th>Days 3–7</th>
<th>Day 7</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggested PN components by time after birth</strong></td>
<td><strong>Suggested monitoring parameters by time after birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose 6–8 mg/kg/min</td>
<td>Weight; head circumference; length; kneemometry</td>
<td>Weight; head circumference; length; kneemometry</td>
<td>Weight; head circumference; length; kneemometry</td>
<td>Weight; head circumference; length; kneemometry</td>
</tr>
<tr>
<td>Glucose 6–8 mg/kg/min</td>
<td>Calcium; electrolytes</td>
<td>Calcium; electrolytes; triglyceride level</td>
<td>Calcium; electrolytes; phosphorus; alkaline phosphatase; magnesium; albumin; prealbumin</td>
<td>Calcium; electrolytes; phosphorus; alkaline phosphatase; magnesium; albumin; prealbumin</td>
</tr>
<tr>
<td>Amino acids 3 g/kg</td>
<td>Amino acids 3–3.5 g/kg</td>
<td>Amino acids 3–4 g/kg</td>
<td>Amino acids 3–4 g/kg</td>
<td>Amino acids 3–4 g/kg</td>
</tr>
<tr>
<td>Calcium</td>
<td>Calcium; electrolytes</td>
<td>Calcium; electrolytes; phosphorus; vitamins; trace elements</td>
<td>Calcium; electrolytes; phosphorus; vitamins; trace elements</td>
<td>Calcium; electrolytes; phosphorus; vitamins; trace elements</td>
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<tr>
<td>Fat 0.5–1 g/kg/d</td>
<td>Fat 0.5–1 g/kg/d</td>
<td>Fat: increase from 0.5 to 1 g/kg/d to a goal of 3–4 g/kg/d</td>
<td>Fat goal 3–4 g/kg/d</td>
<td>Fat 3–4 g/kg/d</td>
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<td>Carnitine 5 mg/kg</td>
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Suggested Strategy for PN Support of the Neonate

In summary, the authors suggest these steps to provide safe, effective PN for the neonate:
1. Use a pediatric-specific amino acid solution such as TrophAmine. Basis: TrophAmine has an increased essential to nonessential amino acid profile and results in an aminogram similar to that of a breast-milk-fed infant\(^\text{39}\) \textit{vs} that achieved when using adult amino acid formulations. In addition, clinical studies with TrophAmine have shown improved nitrogen balance\(^{37,41}\) reduced liver cholestasis\(^{50}\) and enhanced calcium and phosphorus solubility.\(^{48}\)

2. Standardize PN components and quantity. Basis: Standardized PN results in less cost\(^\text{102}\) and possibly improved patient care. Our own standardized solution can be seen in Table 3.

3. Add cysteine to amino acid solutions at a dose of 40 mg/g amino acids. Basis: Cysteine may be a semiessential amino acid in the preterm infant because of limited cystathionase activity.\(^{44}\) The addition of cysteine lowers the pH of the PN solution, allowing increased calcium and phosphorus solubility.\(^{38}\) In addition, this may offer an enhanced source of cysteine for GSH production.\(^{47}\)

4. Start infusion of amino acids and dextrose within the first 24 hours of life. Basis: Clinical studies show that this strategy improves nitrogen balance and glucose tolerance.\(^{37,41}\) In addition, earlier initiation of PN may results in cost savings\(^\text{103}\) by reducing the needed duration of PN.

5. Follow vitamin and trace element recommendations given by an expert panel,\(^\text{5}\) to include 40% of a 5-mL vial of MVI-Pediatric (Mayne Pharma, Paramus, NJ) for neonates <2.5 kg and a full 5-mL vial for infants >2.5 kg. Trace elements should be provided individually for infants <2.5 kg: 400 \(\mu\)g/kg/d zinc, 20 \(\mu\)g/kg/d copper, 0.2 \(\mu\)g/kg/d chromium, 1 \(\mu\)g/kg/d manganese, and 2 \(\mu\)g/kg/d selenium, whereas infants >2.5 kg should receive 250 \(\mu\)g/kg/d zinc, 20 \(\mu\)g/kg/d copper, 0.2 \(\mu\)g/kg/d chromium, 2.5 \(\mu\)g/kg/d manganese, and 1.5 \(\mu\)g/kg/d selenium.

6. Add heparin to the PN solution at a dose of 0.5 unit/mL solution.\(^{104,105}\)

7. Add 20% fat emulsion within the first 24 hours of birth. IV fat emulsion should infuse over 24 hours\(^\text{68}\) and progress to desired lipid intake (maximum goal of 20 mL/kg/d of a 20% solution) over the next few days, advancing the rate slowly while monitoring serum triglyceride levels.\(^{106}\)

Conclusion

In conclusion, the preterm/high-risk infant requires immediate and qualitative delivery of PN to promote nitrogen balance, growth, and positive outcomes. Other interventions such as bonding (through skin-to-skin holding) and nonnutritive occupational and physical therapy interventions can be helpful. Using a critical pathway, as seen in Table 5, ensures evaluation of nutrient, chemistry, bone mineral, and liver status, and helps with infant development. Early minimal feeding or ursodiol therapy should be initiated to prevent or minimize cholestasis. Providing PN to the preterm infant involves many unique challenges; additional research is needed to further our knowledge and practice in this population.

References


