Invited Review

Pediatric Parenteral Nutrition: Putting the Microscope on Macronutrients and Micronutrients

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Parenteral nutrition can be a life-saving therapy, but its benefits need to be balanced with a unique set of risks and complications. Methods of practice vary because there is a dearth of research in the area of pediatric parenteral nutrition. This article reviews the available literature on parenteral nutrition in children and provides suggestions on prevention and management of parenteral nutrition–associated liver disease. Some of the issues discussed in this article include glucose infusion rates, cycling of parenteral nutrition, copper and manganese toxicity, and the provision of glutamine, selenium, and carnitine. (*Nutr Clin Pract.* 2009;24:481-486)

Keywords: cholestasis; trace elements; micronutrients; manganese; copper; selenium; glutamine; liver diseases; parenteral nutrition; parenteral nutrition, total; pediatrics; child; infant

Parenteral nutrition (PN) is designed to provide nutrition support to the patient whose gastrointestinal (GI) tract is not functioning or who is unable to tolerate sufficient enteral nutrition. The benefits of PN must be balanced with the risks and complications that are exacerbated when this life-saving therapy is administered for a long period.

A lack of evidence-based guidelines for pediatric PN leads to variations in practice. This article reviews the available literature on pediatric PN and provides suggestions for managing some of the more controversial aspects.

Parenteral nutrition–associated liver disease (PNALD) remains a dreaded complication of PN in children. PNALD usually occurs with prolonged PN use and includes hepatic steatosis, cholestasis, and cholelithiasis diagnoses. Hepatic steatosis occurs more frequently in adults, whereas cholestasis is more common in children.[1]

The major controversies associated with PN in children are directly or indirectly related to PNALD. This article also reviews the role of macronutrients and micronutrients in PNALD, including the provision of glutamine, selenium, and carnitine in pediatric PN. This review excludes premature infants.

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Parenteral Nutrition–Associated Liver Disease

PNALD is associated with a prolonged duration of PN administration (usually >2 weeks) and is characterized by cholestasis (a conjugated bilirubin >2 mg/dL). This can progress to liver failure and death.[1] The etiology of PNALD is poorly understood, as are its prevention and treatment.[2]

Current practices in the prevention and management of PNALD involve avoiding overfeeding, providing a balanced macronutrient distribution, cycling parenteral infusions, and initiating and maintaining as much enteral nutrition as tolerated[1,3,4] (Table 1).

Overfeeding

Provision of excess calories can induce hepatic steatosis, but this is reversible once calories are reduced.[1,3] Literature reviews have suggested that glucose infusion rates (GIR) >12 mg/kg/min may be associated with steatosis, attributable to the conversion of the purported excess of glucose to glycogen or lipid.[3] It is critically important to avoid overfeeding infants and children receiving PN.

Macronutrient Distribution

Providing appropriate proportions of carbohydrate, protein, and lipid in PN solution may be vital to treatment

Table 1. Prevention and Management of Parenteral Nutrition–Associated Liver Disease (PNALD)

Prevention: These measures should be considered in all pediatric patients receiving parenteral nutrition (PN) for >2 weeks to minimize the risk of PNALD:
Avoid overfeeding.
Initiate parenteral nutrition with a balanced macronutrient mixture:
50%-60% carbohydrate
10%-20% protein
20%-30% lipid
Cycle PN whenever possible.
Start and provide the maximum amount of enteral nutrition that will be tolerated.
Management
Continue or initiate all of the measures mentioned under prevention.
Consider stopping or decreasing soy-based lipid emulsion to 1 g/kg/d (if possible).

and avoidance of PNALD.[4] Each of these 3 macronutrients has been associated with PNALD.

Dextrose infusion that exceeds the maximum glucose oxidation rate (GIR >14 mg/kg/min) in infants has been linked with steatosis but not cholestasis.[5,6] Zagara and Locati[7] showed that 53% of patients receiving PN without lipids developed liver dysfunction. When lipids were administered in conjunction with PN, only 17% of patients developed steatosis.[7] These data, though not obtained from children, suggest that balanced administration of the macronutrients contained in PN solution may prevent steatosis.

There is increasing evidence that the lipid formulations available in the United States may play a significant role in PNALD. Standard soybean oil emulsions, which predominantly contain ω-6 fatty acids, have been shown to impair biliary secretion,[8] generate a proinflammatory response,[9] and impair immune function.[9] In a study involving 10 children receiving long-term PN, 17 of 23 episodes of cholestasis reversed when lipid emulsions were temporarily discontinued.[10] Another study in adults showed that cholestasis was related to the use of >1 g/kg/d of lipid.[11] Replacing the soybean oil content of intravenous lipids with medium-chain triglyceride or monounsaturated fatty acids has also been shown to decrease the incidence of cholestasis.[4]

The most striking evidence implicating soybean oil emulsions in the pathogenesis of PNALD comes from a study in which infants with PNALD received fish oil–based lipid emulsions, which contain ω-3 fatty acids. These infants, who received fish oil–based lipid emulsion at 1 g/kg/d, had a reversal in their cholestasis 4.8 times faster than historical controls who received soybean oil–based emulsions. Their cholestasis was reversed, regardless of fish oil dosage.[2] Other important findings of the study were that fish oil emulsions were not associated with essential fatty acid deficiency (EFAD), elevated triglyceride levels, coagulopathy, infection, or growth delay.[2] One study compared patients receiving fish oil–based emulsion at 0.5-1 g/kg/d with a historical cohort of patients who received soybean oil–based emulsion at 1-4 g/kg/d. This study concluded that the median time to reversal of cholestasis was 9.4 weeks and 44.1 weeks, respectively. The subgroup that received 1 g/kg/d soybean oil–based emulsion demonstrated delayed improvement of cholestasis compared with the fish oil–based emulsion group.[2]

There is a concern that fish oil–based emulsions may be associated with EFAD. This notion is based on the currently accepted standard that 1% of total energy intake from linoleic acid is required to prevent EFAD.[12] However, Strijbosch et al[12] demonstrated that providing fish oil emulsions alone did not induce EFAD. In their study, only 0.3%-0.56% of total energy intake was needed from linoleic acid to prevent EFAD.[12]

Amino acids can also affect liver function. Protein formulations of PN in the past had large amounts of dipeptides, tripeptides, and ammonia, and variable amounts of nonessential amino acids that sometimes led to hepatic dysfunction.[13,14] These problems no longer exist with present-day amino acid formulations. Cholestasis in infants has been associated with a higher intake of amino acids.[15-17] Because most of these studies correlated cholestasis with administration of >3 g/kg/d protein, it may be prudent to limit protein provision to 3 g/kg/d in most infants.

Cycling PN

Cycling PN to avoid continuous dextrose and amino acid infusion may prevent or delay onset of liver dysfunction.[1,4] Providing high amounts of glucose in PN increases the release of insulin, which can induce excess lipogenesis in the liver resulting in steatosis.[4] Adverse effects of hyperinsulinemia may explain why cycling PN is beneficial in long-term PN patients.[4] Studies have found that cycling PN over the course of 16 hours improves serum liver function tests, insulin levels, and hepatomegaly.[1]

In adults, stopping continuous dextrose infusions abruptly may induce hypoglycemia; therefore, it is commonly recommended that PN infusion rates be weaned over a period of 30-60 minutes prior to being discontinued.[18] However, based on a study of 15 children, abrupt discontinuation of PN is not a concern in most children >2 years of age. Serum glucose and insulin levels returned to normal quickly and without consequence in these children when PN was stopped abruptly.[19]

These findings indicate it may be a good practice to cycle PN after the first 2 weeks of infusion in patients who

are hemodynamically stable with normal serum electrolyte levels.[20] A common hesitation with cycling involves the concomitant increase in GIR with compression of PN infusion over shorter periods of time. However, because GIR does not appear to be the most important concern with regard to PNALD,[2] and given conclusive evidence to recommend cycling of PN, we cycle PN in all long-term patients who are stable enough to tolerate it. To ensure safety, blood glucose levels should be monitored during and after infusion to prevent hyperglycemia and hypoglycemia.[1]

In summary, PN calories should be maintained to facilitate optimum growth, but overfeeding must be avoided. Current research suggests that it may be important to maintain GIRs <12-14 mg/kg/min in children without cholestasis, while avoiding large amounts of fat or protein in the PN.

Available data indicate that once cholestasis has developed, it may be more important to reduce the amount of soybean oil–based fat emulsion while ignoring high GIRs, because it is usually not possible to provide adequate calories to PN-dependent children without exceeding acceptable GIRs. When possible, fish oil–based lipid emulsion should be considered for use in children with cholestasis. To date, these emulsions are not approved by the U.S. Food and Drug Administration (FDA), but the FDA has started to allow their importation from Europe for compassionate use while billing the child's insurance company for the cost.

Enteral Nutrition

Enteral feeding can be effective in preserving gut integrity, preventing bacterial translocation, and protecting against PNALD.[1] Feeding the gut as early as medically possible is the best practice to avoid liver dysfunction associated with PN.[1] Early introduction of even low rates of enteral nutrition can prove beneficial for the prevention of sepsis and translocation of gut bacteria. Enteral nutrition can improve biliary flow and intestinal stasis and decrease the risk of bacterial overgrowth.[3]

Micronutrient Issues in PNALD

Copper and Manganese

Copper (Cu) and manganese (Mn), which are considered essential trace elements, are routinely added to trace element solutions in PN. Because biliary excretion maintains homeostasis of Cu and Mn, these minerals are commonly removed from PN solutions to prevent toxicity in the presence of cholestasis. However, hypercupremia has also been seen in patients without cholestasis. In one study of 54 pediatric patients, 8 patients presented with high Cu levels despite a serum direct bilirubin <2 mg/dL.[21] In contrast, cholestatic patients receiving long-term PN without Cu supplementation have demonstrated Cu deficiency, which manifests as neutropenia, hypochromic microcytic anemia, and poor bone growth.[22,23] These results suggest that serum bilirubin should not be the sole factor for determining the provision of Cu in PN.

Regardless of bilirubin levels, serum Cu levels should be monitored in all long-term PN patients. General guidelines for Cu administration in PN include checking serum Cu levels 2 weeks after initiating PN, and then monthly to monitor for toxicity and deficiency.[21] There are 2 options for Cu management in cholestatic children. The first is to obtain a serum Cu level at baseline and supplement based on that level. The second option is to initially remove Cu from the PN, follow serum Cu levels at regular intervals, and supplement when hypocupremia occurs.

Currently there is no Recommended Dietary Allowance (RDA) for Mn; however, Mn deficiency is rare and has not been reported in patients receiving PN. Mn homeostasis in humans is achieved through intestinal regulation of Mn absorption and through biliary excretion.[24] Because PN bypasses the intestine and PN patients frequently have hepatobiliary impairment, there is an increased incidence of Mn toxicity in long-term PN patients.

Various groups have published recommendations for Mn dosing in PN, ranging from 1 mcg/kg/d to a maximum of 40-100 mcg/kg/d for pediatric patients >40 kg.[25] There is current speculation that these recommendations may be too high for long-term PN use.[24] Because Mn is often a contaminant in the PN solution, patients will likely receive small doses of Mn even if the trace element solution does not specifically provide Mn.[24]

Removal of Mn from PN is common practice if the serum conjugated bilirubin is ≥2 mg/dL. Mn toxicity can still occur but is not directly correlated with serum bilirubin levels.[21,26] Data in one study demonstrated that serum bilirubin levels alone were not a strong predictor of elevated Mn levels.[21] However, removing Mn from PN has been shown to reduce accretion of manganese in the basal ganglia and may help prevent future development of PNALD.[27]

Although it may be wise to remove Mn from PN,[21] it is ideal to monitor whole-blood Mn levels in all long-term pediatric patients receiving PN and adjust the Mn dose on an individual basis.[21]

Other Micronutrient Issues

Carnitine

Carnitine aids the transport of long-chain fatty acids into mitochondria for oxidation and is synthesized in human

kidneys from lysine and methionine.[28] Carnitine is found in human milk and is ubiquitous in a general diet. It is added to infant formulas but is not commonly supplemented in pediatric PN solutions. Although carnitine is generally considered nonessential, in adults receiving hemodialysis, adults with liver disease, preterm infants, and children with carnitine deficiency metabolic disorders,[29] evidence shows that carnitine is conditionally essential.[30] Whether pediatric patients with acute illness and PN dependence have a conditionally essential need for carnitine supplementation remains unclear.

Serum and tissue carnitine levels can be depleted in infants and children who depend exclusively on PN for extended periods of time.[31] Inadequate carnitine may impair fatty acid transport into mitochondria, inhibiting oxidation and decreasing energy production.[31] Symptoms of deficiency include increased serum triglyceride levels, muscle weakness, and hypoglycemia.[30] Carnitine deficiency can also result from use of valproic acid, trauma, sepsis, organ failure, and other metabolic stressors.[32]

Carnitine status is assessed through clinical assessment (muscle weakness, hepatic insufficiency, hyperbilirubinemia, nonketotic hypoglycemia, metabolic acidosis, cardiomyopathy), decreased fatty acid oxidation (increased serum triglyceride levels and poor weight gain), and plasma free carnitine concentration, although the validity of this laboratory marker for assessing total body carnitine is not optimal.[33]

Supplementing carnitine raises serum carnitine levels[34]; however, several studies have found no negative effects from low carnitine values and no significant changes in serum triglyceride levels, weight gain, lipid utilization, or ketogenesis with supplementation.[1,27,35-38] No study was identified that supported routine carnitine supplementation in PN pediatric patients. Although in one study in which carnitine was provided to infants receiving long-term PN who had low serum carnitine levels, biochemical markers of liver disease did not improve, whereas the carnitine levels returned to normal range.[39] This review excludes premature infants, and there are alternative recommendations regarding supplementation of carnitine in PN for this population.[33]

The current standard practice is to consider supplementing carnitine if PN has been the sole nutrition source for >2 weeks or if hypertriglyceridemia, hypoglycemia, and low serum carnitine levels are present.[40] At our institution, we consider supplementation of 10-20 mg/kg/d when a patient has received only PN for >2 weeks or has hypertriglyceridemia. There are no noted negative effects of carnitine supplementation.[32]

Glutamine

Glutamine is considered a nonessential amino acid. Plasma concentrations of glutamine decrease postoperatively, during sepsis, after multiple trauma, and following major burns. In Canada and Europe, the current standard of practice is to provide glutamine in PN during critical illness, particularly in trauma and burns.[41-45] Intravenous forms of glutamine are not readily available in the United States. Safety issues of supplementing PN have been mainly ruled out, with most studies showing no concerns.[46]

In children, glutamine has only been investigated in preterm neonates and in oncology. Because it is a primary fuel for enterocytes and for gut-associated lymphoid tissue, administration of glutamine in cancer patients was hoped to prevent or lessen hematopoietic cell transplantation (HCT)–induced GI toxicity. Several adult clinical trials have failed to show a clear preventive or curative effect of parenterally administered glutamine on mucositis.[47-49] Nonetheless, glutamine improved nitrogen balance,[47,48] decreased infectious complications,[47] lessened duration of hospital stay,[47] and prevented and ameliorated veno-occlusive disease[50,51] in these patients.

In a small pediatric study, intravenous glutamine supplementation was shown to reduce the duration of fever and decrease the incidence of veno-occlusive disease during the HCT course.[52] In addition, a decrease in drug-related toxicity and, in contrast with the previously mentioned study with adults, a trend toward reduced incidence of severe mucositis were observed.[52] A Cochrane review of adult patients found that glutamine in PN reduced the incidence of positive blood cultures and recommended that in the event of a patient suffering severe GI failure even with a trial of enteral feeding, PN with the addition of glutamine could be considered.[53]

Further studies are required in children undergoing HCT to investigate this potential therapeutic role of glutamine.

Selenium

Selenium is an essential trace element present in the human as a component of proteins called selenoproteins.[54] Much of the biochemical function of selenoproteins remains unknown; however, multiple glutathione peroxidases that contain selenium have been shown to be present in all cells.

The current standard of practice in pediatric PN is to supplement selenium when exclusive PN is required for >4 weeks. Selenium is not typically given when PN is used for shorter time periods. Supplementation guidelines suggest giving 2 mcg/d to term infants and children through 6 years of age and 1-2 mcg/d to children 7-10 years of age.[55] The pediatric RDA for selenium is 15-30 mcg/d for ages 0-8 years.[56] Selenium toxicity is rare; symptoms include nausea, diarrhea, irritability, fatigue, peripheral neuropathy, hair loss, and nail changes. Observed deficiency symptoms include cardiomyopathy,[54] growth retardation,[54] pseudoalbinism,[57] and skin disorders.[58]

Selenium deficiency from selenium-free PN is well documented.[54,57,59-61] Studies have shown that deficiency can develop within 6 weeks of providing selenium-free nutrition support.[54] Current guidelines to begin supplementation after 4 weeks appear appropriate, and there are no contraindications to beginning sooner.

At our institution, selenium is part of the trace element mixture at 2.25 mcg/0.15 mL, and trace elements are dosed at 0.15 mL/kg with a maximum of 4 mL/d. When additional selenium is warranted, it is available as a separate PN additive.

It may be appropriate to begin supplementing selenium when PN is the sole source of nutrition for >2 weeks. Two case reports demonstrated that patients had selenium deficiency from lymphangiomatosis and protein-losing enteropathy despite receiving the recommended dose of selenium in the PN.[58,62] Long-term PN patients with extended periods of chyle loss may need more than standard selenium supplementation.

Conclusions

PN serves as nutrition life support for patients with intestinal failure. Managing the individual constituents of PN solutions in a manner that is most effective for each patient is imperative. Dosing of macronutrients and micronutrients must be individualized and carefully monitored. Although data are available to guide practice in several of the controversial areas of pediatric PN practice, some areas have suffered from a lack of research. Standardization of practice based on currently available evidence will benefit the individual patient, but only further research will provide advancements and benefit all children who require this life-saving therapy.

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