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Review

Total parenteral nutrition for the very low birth weight infant

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SUMMARY

Preterm infants, especially very low birth weight (VLBW; <1500 g) and extremely low birth weight (ELBW; <1000 g) infants, are susceptible to growth failure in postnatal life if nutritional demands are not met. Poor postnatal growth in preterm infants is associated with adverse neurodevelopmental outcomes during childhood. Early parental nutrition is of paramount importance to provide appropriate protein and energy in VLBW infants when enteral nutrition is not feasible or is suboptimal. An "early and aggressive" approach of parenteral nutrition in preterm infants has been shown to prevent protein catabolism, induce positive nitrogen balance and improve postnatal growth.

1. Introduction

Infants born prematurely often fail to grow at rates similar to those estimated for the in-utero fetus. Embelton et al. showed that the significant accumulation of protein and energy deficits postnatally often are not recovered by hospital discharge. They suggested that the deficits were directly related to subsequent postnatal growth restriction [1]. A meta-analysis by Moyses et al. demonstrated that early parenteral nutrition provided benefit for short-term outcomes without evidence of increased morbidity and mortality [2]. Parenteral nutrition in preterm infants should be started immediately after birth either by a central or peripheral route. Balanced parenteral nutrition with an early and "aggressive" approach is important for preterm infants to minimize postnatal weight loss, promote an earlier return to birth weight and lessen extrauterine growth restriction. The energy intake of a premature infant on parenteral nutrition should be set at about 90–105 kcal/kg/d in order to achieve growth similar to those fed enterally. This energy intake is based on the minimum energy requirements that allow accretion of lean body mass. Above this energy intake, energy is stored as fat [3].

2. Energy requirements

Energy is needed for growth and metabolic functions. Very low birth weight (VLBW; <1500 g) infants have very high energy demands because of immaturity, growth needs, and high risk of hypo- and hyperthermia. In a thermo-neutral environment, the resting metabolic rate is ~40 kcal/kg/d when the infant is on total parenteral nutrition and 50 kcal/kg/d by 2–3 weeks of age when the infant is enterally fed. Estimated energy requirements for healthy growing preterm infants during the neonatal period are listed in Table 1.

3. Carbohydrates

Glucose is the main energy source and the most widely used carbohydrate in total parenteral nutrition (TPN) [5]. It has the advantage of being readily available to the brain. Although fructose, galactose, sorbitol, glycerol and ethanol have been used as sources of carbohydrates, none has been shown to be superior to dextrose. Dextrose provides 3.4 kcal/g and should provide 30–35% of daily caloric needs. Endogenous glucose production rates range from 5.5 mg/kg/min in full term healthy newborns to 8 mg/kg/min in VLBW infants [6]. Glucose infusion should match endogenous glucose production, so should be provided at 6–8 mg/kg/min soon after birth and adjusted to achieve blood glucose concentrations of 45–120 mg/dL [7]. As VLBW infants have limited carbohydrate stores, higher glucose infusion rates (GIRs) may be needed (~8 mg/kg/min) to match their higher endogenous production rate. VLBW infants are at risk to develop hyperglycemia in the first days of life. Slow increases in GIR are better tolerated and decrease hyperglycemia. Higher GIR can be achieved by increasing dextrose content and/or by increasing total fluid intake. Dextrose concentrations >12.5% should be provided via a central line. Excessive glucose infusion has many adverse effects including increased energy

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Table 1
Estimated energy requirement of the low birth weight infant.

Variable	Average estimation (kcal/kg per day)
Energy expended	40–60
Resting metabolic rate	40–50[a]
Activity	0–5[a]
Thermoregulation	0–5[a]
Synthesis	15[c]
Energy stored	20–30[b]
Energy excreted	15
Energy intake	90–120

Adapted from the Committee on Nutrition of the Preterm Infant, European Society of Pediatric Gastroenterology and Nutrition [4].
[a] Energy for maintenance.
[b] Energy cost of growth.
[c] Energy cost for synthesis.

expenditure, increased oxygen consumption, increased serum osmolality, osmotic diuresis, fatty infiltration of liver and excessive fat deposition [8]. Routine use of insulin may result in modest reductions of hyperglycemia but at the cost of an increased frequency and severity of hypoglycemia. Beardsall et al. studied 389 VLBW infants who were randomly assigned to receive either standard care for glycemic control or a parenteral infusion of 20% dextrose with early insulin therapy (0.05 U/kg/h) starting on the first day of life until seven days of age. The study found increased episodes of hypoglycemia and increased mortality at 28 days of life in the infants receiving insulin compared to infants who received standard neonatal care for hyperglycemia [9]. Thus, current evidence does not support the routine use of insulin in preterm infants and it should only be used if decreasing GIR to ≤4 mg/kg/min does not resolve hyperglycemia.

4. Protein

Preterm infants have limited energy stores at birth and must catabolize protein to meet their energy requirements if not supplemented by enteral or parenteral nutrition soon after birth. Protein provides 3.4 kcal/g and should provide 10–15% of total energy intake. The predicted daily protein accretion of a fetus at ~28 weeks of gestation is ~2 g/kg, so at least 3–3.5 g/kg (protein or amino acid) is needed to promote protein accretion, allow for obligatory losses [10] and prevent negative nitrogen balance. Studies have shown that amino acids started at ≥2 g/kg/d are safe shortly after birth [11–14]. Comparative studies do not show a difference in the pH or base deficit between groups administered different amino acid doses (initial amino acid dose ranged from 0 to 3 g/kg/d with a target range of 2.4–4 g/kg/d) [15,16]. Current recommendations suggest 2–3.5 g/kg/d of amino acids on the first day of life, increasing to 4 g/kg/d in the first week of life. The Cochrane review of early amino acids (in first 24 h) versus late amino acids (3 g/kg/d) in preterm infants included seven randomized controlled trials [17]. One trial reported no difference in crown–heel length and head circumference by day 10, and four trials found positive nitrogen balance and a significant difference in the level of blood urea nitrogen (BUN) in the first 48 h. Early administration of amino acid did not result in metabolic acidosis in the first 24 h [17]. They concluded that “there is no available evidence of the benefits of early administration of amino acids on mortality, early and late growth and neurodevelopment [17]. Other studies have found that positive protein balance is achieved in more aggressively fed preterm infants and is safe and effective and not associated with hyperammonemia, uremia or metabolic acidosis [18,19]. A recent study using a SCAMP (standardized, concentrated with added macronutrients parenteral) nutrition regimen – comprising high doses of AA, glucose, and lipid – demonstrated greater head growth with a mean difference corresponding to 6% and 5% difference in brain weight at 28 days of life and 36 weeks of corrected gestational age, respectively [20].

The most widely used amino acid solutions available for infusion are Trophamine® (Kendall–McGraw Laboratories, Irvine, CA, USA), Premasol® (Baxter Healthcare Corporation, Deerfield, IL, USA), and Aminosyn-PF® (Abbott Laboratories, North Chicago, IL, USA). These mixtures contain both essential and conditionally essential amino acids (cysteine, arginine, taurine and tyrosine) and non-essential amino acids. These solutions are available in 6% and 10% concentrations [21]. The commercial solutions do not contain cysteine, which must be added during compounding. A Cochrane review [22] evaluated the use of cysteine and N-acetyl cysteine in premature infants. The majority of patients in these trials were preterm. Five small trials evaluated short-term cysteine supplementation of cysteine-free parenteral nutrition. One large multicenter randomized controlled trial evaluated short-term N-acetylcysteine supplementation in parenteral nutrition in extremely low birth weight infants (≤1000 g). Growth was not significantly affected by cysteine supplementation (one trial) or by *N*-acetylcysteine supplementation (one trial). Nitrogen retention was significantly increased by cysteine supplementation (four trials). [Weighted mean difference is a statistical term that measures the absolute difference between the mean values in two groups in a clinical trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the control (WMD 31.8 mg/kg/d; 95% confidence interval: 8.2–55.4; $n = 95$, including 73 preterm infants).]

Plasma levels of cysteine were significantly increased by cysteine supplementation but not by N-acetylcysteine supplementation. N-Acetylcysteine supplementation did not significantly affect the risks of death by 36 postmenstrual weeks, bronchopulmonary dysplasia (BPD), death or BPD, retinopathy of prematurity (ROP), severe ROP, necrotizing enterocolitis requiring surgery, periventricular leukomalacia, intraventricular hemorrhage (IVH), or severe IVH [22].

There is currently general agreement among neonatologists and nutritionists that, in VLBW infants, early appropriate protein and energy intake is crucial to prevent extrauterine growth restriction [23].

5. Lipids

Lipids are a major source of energy. One gram of fat provides 9 kcal. Lipids should provide 25–40% of non-protein parenteral nutrition calories. Commercial lipid emulsions are based on soybean oil, or mixtures of olive and soybean oils, olive and fish oils. The primary soybean-based intravenous lipid emulsions currently approved in the USA are Intralipid® [Sigma Aldrich, St Louis, MO, USA] and Liposyn® [Hospira, Lake Forest, IL, USA] in a 20% (2 kcal/mL) emulsion which is rich in n-6 polyunsaturated fatty acid (PUFA) (53% linoleic acid) and low in n-3 PUFA. Lipid tolerance is optimal with a 20% preparation because of a lower phospholipid to triglyceride ratio; it is better tolerated and preferred in neonates [24]. Osmolality of the emulsion is the same as the plasma, so it can safely be administered through a peripheral or central vein. In VLBW infants, the initial dose of lipid emulsion could be ≥2 g/kg/d [25] and step-wise increments of lipid emulsion by 0.5–1 g/kg/d to a maximum of 3 g/kg/d should be followed. However, a lower initial dose and a maximum of 3 g/kg/d is also practised widely. A source of essential n-6 and n-3 fatty acids and long-chain polyunsaturated fatty acid (LC-PUFA) derivatives is necessary for central nervous system development and retinal growth. Lipid emulsions prevent essential fatty acid deficiency which is biochemically

evident in premature infants within 72 h [26]. Soybean-based lipid emulsions are not well suited for prolonged (>2 weeks) parenteral nutrition, as it may hasten the development of cholestasis and liver dysfunction [27,28]. Fish oil-containing lipid emulsion is the most recent development in lipid emulsions. Fish oil is currently found in either pure fish oil emulsion (Omegaven®, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) or as a mixture (SMOFlipid®, Fresenius Kabi AB, Uppsala, Sweden) of 30% medium chain triglycerides, 30% soybean oil, 25% olive oil, and 15% fish oil. Fish oil is rich in n-3 PUFA, especially EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Picher et al. reported that the use of SMOF mixtures in infants with parenteral nutrition-associated liver disease (PNALD) increased resolution of abnormal liver function tests compared to soybean based emulsion [29]. Gura et al. [30] studied 18 infants with short bowel syndrome who developed cholestasis while on soybean-based emulsion, and found that the use of fish oil-based emulsion caused faster reversal of cholestasis. They also found that fish oil emulsion was not associated with essential fatty acid deficiency, hypertriglyceridemia, coagulopathy, infections, or growth delay [30]. Use of fish oil-based lipid emulsion seems to be especially advantageous as it may reverse parenteral nutrition-associated cholestasis [30,31], but so far it has not played a role in prevention of cholestasis. Fat tolerance can be assessed indirectly by measuring serum triglyceride concentrations, which should be kept at <200 mg/dL [32]. A dosage reduction of lipid should be considered at triglyceride level >250 mg/dL, but there should always be a minimum linoleic acid intake to prevent essential fatty acid deficiency. Early introduction of lipids during the first week is safe and well tolerated in VLBW infants and is associated with weight gain and could improve early nutritional support for these infants [33,34]. There are concerns that lipid emulsion may increase risk of infection, especially coagulase-negative staphylococcal bacteremia, although nutritional benefits of lipid supplementation outweigh these potential risks [25].

6. Vitamins and macro/micronutrients

Vitamins and minerals should be provided with all parenteral nutrition regimens. Two parenteral vitamin solutions are available for use in infants in the USA, MVI® Pediatrics (AstraZeneca Pharmaceuticals, Westborough, MA, USA) and Infuvite® Pediatrics (Boucherville, Quebec, Canada). Both contain water- and fat-soluble vitamins. The recommended daily dose of parenteral vitamins for preterm infants is 40% of the currently available reconstituted single dose (5 mL) of the multivitamin solution [35,36]. Table 2 lists the amounts of different vitamins in MVI solution for TPN.

Table 2
Vitamins provided with parenteral nutrition solutions.[a]

Vitamin	Amount provided per 5 mL
Ascorbic acid (Vitamin C)	80 mg
Vitamin A (retinol)[b]	2300 USP units
Vitamin D[b]	400 USP units
Thiamine (vitamin B1)	1.20 mg
Riboflavin (vitamin B2)	1.4 mg
Pyridoxine (vitamin B6)	1.0 mg
Niacinamide	17.0 mg
Dexpanthenol	5 mg
Vitamin E[b]	7.0 USP units
Biotin	20 μg
Folic acid	140 μg
Vitamin B12	1.0 μg
Vitamin K1[b]	200 μg

Adapted from the American Academy of Pediatrics [32].
[a] MVI Pediatric is a lyophilized, sterile powder intended for reconstitution and dilution in intravenous infusions. Infuvite Pediatric is supplied as a 4 mL and 1 mL vial that may be combined for administration. For each vitamin mixture, 5 mL of reconstituted product supplies the indicated amounts of the vitamins. The recommended dose is 40% (2 mL) of the currently available reconstituted single dose (5 mL) of the MVI mixture.
[b] Fat-soluble vitamins solubilized with polysorbate 80.

Fluid management should be prudent in the first few days after birth in VLBW infants, as fluid overload during early postnatal life has been associated with increased respiratory morbidity, symptomatic patent ductus arteriosus and later bronchopulmonary dysplasia [37]. Total fluid supplementation in VLBW infants should be based on maintenance needs and ongoing losses (sensible and insensible water losses). The total body water (TBW) and extracellular fluid content increases with decreasing gestational age. Postnatally, intracellular fluid increases and contraction of extracellular fluid occurs, marked by a period of diuresis. During this period of physiologic adaptation, the VLBW infant does not necessarily need electrolytes such as sodium, potassium and/or chloride. Frequent monitoring of these electrolytes is essential in these infants during this period. Table 3 lists requirements of these electrolytes in preterm and term infants.

Calcium and phosphorus are important minerals, as inadequate supplementation in postnatal life is associated with poor bone mineralization. The majority of calcium and phosphorus accretion in utero occurs in the third trimester. Estimated accretion rates approach 120 mg/kg/d of calcium and ~60 mg/kg/d of phosphorus between 24 weeks and term gestation [38,39]. Therefore the preterm infant is at high risk for these mineral deficiencies and subsequently at risk for worsening osteopenia of prematurity (also known as metabolic bone disease) which has long-term consequences, including short stature and osteopenia, in adulthood. Besides prematurity, multiple other risk factors such as lack of physical activity, lack of in-utero mineral accretion, bronchopulmonary dysplasia, use of osteolytic medications (caffeine, diuretics, and glucocorticoids) and the inability to provide optimal calcium and phosphorus concentrations in TPN puts them at highest risk of developing metabolic bone disease. The current rate of metabolic bone disease in VLBW infants may be as high as 40% [41]. The most widely used biomarkers to assess bone mineralization are serum phosphorus and alkaline phosphatase [42]. Backstrom et al. [43] studied levels in preterm infants and correlated values with dual energy X-ray absorptiometry (DEXA) at a corrected age of 3 months, finding that low phosphorus levels (<4.6 mg/dL) and high alkaline phosphatase levels (>900 IU) had 100% sensitivity and 70% specificity for low bone mineral density. Calcium and phosphorus should be supplemented soon after birth in premature infants. Parenteral nutrition does not provide optimal concentrations of calcium and phosphorus because of solubility issues. The ideal ratio of calcium:phosphorus (mg:mg) for parenteral nutrition should be 1.3–1.7:1 [44]; this ratio appears to promote the highest retention of these minerals. The current recommendation to prevent metabolic bone disease is to provide early and appropriate supplementation of calcium/phosphorus, vitamin D, and fortification of human milk.

Table 3
Daily electrolyte and mineral requirement.

Electrolytes	Preterm neonates (mEq/kg)
Sodium	2–5
Potassium	2–4
Calcium	2–4
Phosphorus	1–2
Magnesium	0.3–0.5
Acetate and chloride	As needed to maintain acid–base balance

Individual infant's requirement may vary based on the clinical status and associated morbidities.
Adapted from Mirtallo et al. [40].

Table 4
Parenteral intakes of trace minerals in stable clinical condition.

Element	Weight <1000 g (μg/kg/day)	Weight 1000–1500 g (μg/kg/day)
Zinc	400	400
Copper[a]	20	20
Selenium	1.5–4.5	1.5–4.5
Chromium[b]	0.05–0.3	0.05–0.3
Manganese[a]	1	1
Molybdenum	0.25	0.25
Iodide	1	1
Iron	100–200	100–200

Adapted from the American Academy of Pediatrics [32].
[a] Omit in patients with obstructive jaundice (manganese and copper are excreted primarily in bile).
[b] Omit in patients with renal dysfunction.

One issue that has not received much attention is the influence of early and high amino acid intake on calcium and phosphorus homeostasis. Bonsante et al. [45] studied 154 infants below 33 weeks of gestational age at birth. Amino acid intake was started on day 1 and increased daily to 3.5 g/kg/d at the end of the first week (n = 154). Low (<1.5 g/kg/d), medium (1.5–2 g/kg/d), and high (>2 g/kg/d) amino acid intake were evaluated for their effect on calcium and phosphorus. Hypercalcemia (>11 mg/dL) and hypophosphatemia (<4 mg/dL) were observed in the high amino acid group. This study highlights the potential risk of early calcium and phosphorus imbalance while providing "early aggressive" nutrition, and one should be vigilant concerning these electrolytes' imbalance. These calcium and phosphorus imbalance effects from high amino acid supplementation have also been observed by others [46–50].

Trace minerals are important in various cell functions such as enzyme activity, protein and lipid metabolism, endocrine functioning including thyroid, and immune/inflammatory modulations. Table 4 suggests trace mineral requirements. The trace minerals zinc and selenium need to be supplied from the first day of life in TPN [51,52]. Iron is probably not required in VLBW infants immediately after birth, potentially contributing to oxidative stress with parenteral supplementation, and may be best supplemented when the infant is on full enteral feeds [53].

7. Indications and complications

Because of associated morbidities of prematurity such as respiratory distress syndrome, hypotension, temperature instability, gut immaturity and surgical lesions that preclude enteral nutrition, it is usually not feasible to initiate enteral feeds immediately after birth. Therefore, parenteral nutrition should be initiated as soon as possible after birth of the VLBW infant, either through an umbilical venous line or peripheral venous line. The early use of parenteral nutrition promotes positive nitrogen balance, decreases postnatal weight loss, improves growth and possibly neurodevelopmental outcome, and may reduce mortality and adverse outcomes such as bronchopulmonary dysplasia and necrotizing enterocolitis [54]. However, parenteral nutrition may cause short- and long-term adverse effects in VLBW infants. Complications of parenteral nutrition may be broadly divided into three major categories (Table 5).

One of the complications associated with TPN is cholestatic liver disease and is strongly related to the duration of PNALD [55]. The incidence may be up to 50% in infants who receive parenteral nutrition for up to two months [27]. Histological changes of cholestasis in the liver may be observed within two weeks on total parenteral nutrition, and fibrosis is detected within six weeks after commencing parenteral nutrition. Widely used criteria to diagnose TPN-induced cholestasis include two consecutive measurements of direct bilirubin >2 mg/dL without other causes of hepatic dysfunction over 14 days of TPN [56]. The exact etiology of cholestasis in not clear but multiple risk factors have been identified: prematurity, low birth weight, prolonged parenteral nutrition, lack of enteral feedings, sepsis, and photo-oxidation of parenteral nutrients [57,58]. Recently, lipids have emerged as the major risk factor for development of PNALD. Studies have demonstrated that n-6 PUFA (which represents >60% of fatty acids in soy-based lipid emulsions) may promote cholestasis [59–61]. In addition, soybean oil emulsion contains high levels of plant-based phytosterols, which correlates with severity of cholestasis [62]. The most important step in treatment of PNALD is to continue to promote enteral feedings when feasible, as it enhances intestinal adaptation, intestinal hormonal secretion and bile acid secretion. In some infants PNALD resolves after provision of full enteral feeds. Decreasing lipid emulsion to treat PNALD has not been beneficial. A retrospective study [63] in surgical infants requiring TPN for a mean of nearly 60 days demonstrated a reduction in PNALD with lipid restriction to 1 g/kg/d compared to 2–3 g/kg/d. Urosdiol was also used in all patients who met the definition of cholestasis. The lipid reduction was accompanied by an increase in glucose intake to compensate for the decrease in energy intake. A significant reduction in maximum conjugated bilirubin was demonstrated in the lipid-reduced group. However, length of stay, duration of TPN, and incidence of late onset sepsis were not different between the groups. The average weight gain was

Table 5
Complications of total parenteral nutrition.

Acute	Chronic
Metabolic complications	**Systemic complications**
Hypoglycemia Hyperglycemia Metabolic acidosis Hypophosphatemia and other electrolytes imbalance Hyperlipidemia	Parenteral nutrition associated liver disease Metabolic bone disease
Mechanical complications	**Infectious complications**
Extravasation and tissue necrosis Infiltration Thrombosis Pleural or pericardial effusion Cardiac arrhythmia from malposition of catheter	Bacterial infections especially staphylococcal species Fungal infections: candida species, malassezia furfur

Adapted from Mundy C and Bhatia J. Feeding the premature infant. In: Berdanier CD, Dwyer JT, Heber D [eds]. Handbook of Nutrition and Food. Boca Raton, FL: CRC press; 2014:279–290 [21].

about 2 g/kg/d in both groups, with both groups demonstrating extrauterine growth restriction at discharge (weight <5th percentile, 75% non-lipid-restricted, 80% lipid restricted) [63]. Further, this strategy raises the concern that the loss of energy by reduction of lipids may be compensated for by an increase in carbohydrates and that, in turn, may alter the protein:energy ratio and allow increased deposition of fat. Fish oil-based emulsions have successfully been used in infants with PNALD [30,64], and are superior to mixed lipid emulsions and soybean oil lipid emulsions [29,65].

Infection, especially central line-associated bloodstream infection (CLABSI), is a major cause of mortality and morbidity associated with the use of prolonged intravenous devices and leads to prolonged hospitalization and increased hospital costs [66]. CLABSI is estimated to cause up to 70% of all hospital-acquired bloodstream infections in preterm infants [67]. Studies have shown that implementing strategies that involve line site care, training for staff and parents, multidisciplinary discharge planning, and monitoring compliance, reduce the rates of CLABSI [68]. The US Centers for Disease Control and Prevention recommends development and implementation of "bundles" to improve compliance and outcomes, and have been shown to reduce the rate of CLABSI [69]. Mechanical complications can be prevented by careful positioning of central catheters and frequent monitoring of catheter position by imaging studies.

8. Conclusion

Birth of a VLBW infant should be considered a nutritional emergency. TPN is of paramount importance to provide energy, protein, and fat when optimal enteral nutrition is not attainable. After introduction of parenteral nutrition, survival of VLBW infants has changed rapidly. The early and "aggressive" balanced nutrition approach has been shown to reduce postnatal growth failure, prevent negative nitrogen balance, essential fatty acid deficiency, trace mineral deficiency, and to promote growth [70]. PNALD is a well-known entity associated with prolonged parenteral nutrition. Fish oil-based lipid emulsions have shown promising results in reversing PNALD. Enteral nutrition should be initiated as soon as possible when the infant's medical condition allows, while simultaneously weaning TPN, at the same time ensuring provision of adequate nutrients for the best growth possible.

Practice points

- TPN is an important part of neonatal nutrition.
- Provision of early and balanced nutrients has been shown to mitigate the extrauterine growth restriction.
- Emerging fish-oil based lipid emulsion has shown encouraging results in reversing hepatic dysfunction associated with prolonged parenteral nutrition.
- TPN provides numerous short-term benefits in VLBW infants; further randomized trials are needed to evaluate long-term neurodevelopmental benefits.

Conflict of interest statement

None declared.

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