

# Nutritional management of newborn infants: Practical guidelines

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## Abstract

The requirements of growth and organ development create a challenge in nutritional management of newborn infants, especially premature newborn and intestinal-failure infants. Since their feeding may increase the risk of necrotizing enterocolitis, some high-risk infants receive a small volume of feeding or parenteral nutrition (PN) without enteral feeding. This review summarizes the current research progress in the nutritional management of newborn infants. Searches of MEDLINE (1998-2007), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2007), abstracts and conference proceedings, references from relevant publications in the English language were performed, showing that breast milk is the preferred source of nutrients for enteral feeding of newborn infants. The number of nutrients found in human milk was recommended as a guideline in establishing the minimum and maximum levels in infant formulas. The fear of necrotizing enterocolitis and feeding intolerance are the major factors limiting the use of the enteral route as the primary means of nourishing premature infants. PN may help to meet many of the nutritional needs of these infants, but has significant detrimental side effects. Trophic feedings (small volume of feeding given at the same rate for at least 5 d) during PN are a strategy to enhance the feeding tolerance and decrease the side effects of PN and the time to achieve full feeding. Human milk is a key component of any strategy for enteral nutrition of all infants. However, the amounts of calcium, phosphorus, zinc and other nutrients are inadequate to meet the needs of the very low birth weight (VLBW) infants during growth. Therefore, safe and effective

means to fortify human milk are essential to the care of VLBW infants.

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**Key words:** Breast milk; Infant formula; Trophic feeding; Parenteral nutrition

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## INTRODUCTION

The requirements of growth and organ development create a challenge in nutritional management of newborn infants. The stress of critical illness further complicates the delivery of adequate nutrients. Enteral feeding has several advantages over parenteral nutrition (PN), such as preservation of the gastrointestinal mucosa and decreasing the occurrence of sepsis related to bacterial translocation. Although feeding through the gastrointestinal tract is the preferred route for nutritional management, there are specific instances when PN as an adjunctive or sole therapy is necessary to meet nutritional needs. When meticulous attention is paid to the requirements of fluid, calory, protein, and fat along with monitoring the metabolic status of patients, it is possible to provide full nutritional support for critically ill newborn infants.

## MACRO-NUTRIENTS OF BREAST MILK AND INFANT FORMULA

Breast milk is the preferred source of nutrients for newborn infants, and the number of nutrients found in human milk is recommended as a guideline in

establishing the minimum and maximum levels in infant formulas<sup>[1]</sup>. Following macronutrients (e.g. proteins, fatty acids and carbohydrates) for infant formulas based on scientific investigations of breast milk during the last decades were recommended by the American Academy of Pediatrics, Committee on Nutrition (AAP-CON) in 2003, and approved by Food Safety and Applied Nutrition, Food and Drug Administration (FDA)<sup>[2]</sup>.

### **Proteins and amino acids**

A minimum protein content of 1.7 g/100 kcal (i.e. total nitrogen  $\times$  6.25) and a maximum total protein content of 3.4 g/100 kcal in infant formulas have been recommended<sup>[2,3]</sup>. The current maximum protein content of 4.5 g/100 kcal is too high because there is no physiological reason to provide protein at this level. Milk contains two primary sources of protein: caseins and whey<sup>[2,3]</sup>. It has been reported that human breast milk contains whey/caseins at a ratio of 9/1 to 6/4 in different lactating periods. However, most of the marketing formulas for infants contain whey/caseins at a ratio of 6/4 to 4/6<sup>[2,3]</sup>.

Whey, a protein complex derived from milk, is touted as a functional food with a number of health benefits. The biological components of whey, including lactoferrin,  $\beta$ -lactoglobulin,  $\alpha$ -lactalbumin, glycomacropeptide, and immunoglobulins, demonstrate a variety of immune-enhancing properties<sup>[2,3]</sup>. In addition, whey, an antioxidant, can act as an antihypertensive, antitumor, hypolipidemic, antiviral, antibacterial, and chelating agent. The primary mechanism by which whey exerts its effects is by intracellular conversion of amino acid cysteine to glutathione, a potent intracellular antioxidant. A number of clinical trials have successfully been performed using whey in the treatment of cancer, human immunodeficiency virus (HIV) infection, hepatitis B, cardiovascular disease, osteoporosis, and as an antimicrobial agent<sup>[3]</sup>.

Lactoferrin is an important protein in human milk (range 0.02-0.2 g/dL) at different lactating stages<sup>[2,3]</sup>. Although it is technically feasible to add bovine lactoferrin or transgenic human transferrin to infant formulas, bovine lactoferrin does not bind consistently to human lactoferrin receptors and whether it increases iron absorption remains unknown. The efficacy and safety of adding human lactoferrin to infant formulas have not been adequately evaluated. Given the emerging knowledge about the biological importance of human lactoferrin in infant nutrition, lactoferrin supplementation is worthy of consideration. However, clinical studies will be essential to demonstrate the efficacy and safety of such addition.

A minimum carnitine content of 1.2 mg/100 kcal (a level similar to that in human milk) and a maximum content of 2.0 mg/100 kcal in infant formulas (a value similar to the upper limit in human milk), have been recommended<sup>[2,3]</sup>. Although evidence that dietary carnitine is essential for infants, biochemical changes are noted when infants are fed with a carnitine-free diet.

A few anecdotal reports are available on the abnormal clinical manifestations associated with diets low in carnitine<sup>[2]</sup>. Infants nourished with soy-protein-based formulas with a low carnitine content have lower plasma and urine carnitine levels and altered lipid metabolism, but no significant difference in rates of growth compared with those not nourished with soy-protein-based formulas with a low carnitine content.

Glutamine and taurine are free amino acids commonly detected in human breast milk<sup>[2-4]</sup>. The addition of glutamine to infant formulas is not recommended because no convincing evidence is available on glutamine requirement in diet. Also, no compelling evidence mandates the addition of taurine to formulas for infants. However, taurine has been used in some commercially available formulas. Currently, a minimum taurine content of zero and a maximum taurine content of 12 mg/100 kcal in infant formulas (a value similar to the limit in human milk) are recommended.

There are few compelling reasons for the addition of nucleotides to infant formulas<sup>[2,3,5]</sup>. The beneficial effects of nucleotide supplementation to infant formulas are intriguing, and further research in this area is strongly urged. When data from long-term, large-scale clinical trials are available, the question of adding nucleotides to infant formulas should be reconsidered. A maximum content with 16 mg/100 kcal of nucleotides and their precursors in infant formulas, a value similar to the upper limit in human milk, is recommended.

### **Fat and fatty acids**

A minimum fat content of 4.4 g/100 kcal (40% of total energy) and a maximum fat content of 6.4 g/100 kcal (57.2% of total energy) in infant formulas have been recommended<sup>[2,3,5,6]</sup>. With the proposed minimum protein of 1.7 g/100 kcal (6.8 kcal/100 kcal) and minimum carbohydrate of 9 g/100 kcal (36 kcal/100 kcal), a maximum value for fat may not, therefore, exceed 57.2 kcal/100 kcal, which is equivalent to 6.4 g/100 kcal.

Medium-chain triglyceride (MCT) is not recommended to be supplemented in infant formulas, with the exception of certain exempt formulas for infants with impaired fat digestion or absorption.

Linoleic acid (LA) is recommended with a minimum content of 8% of total fatty acids in infant formulas. With a minimum fat content of 4.4 g/100 kcal, the minimum LA content is, therefore, 350 mg/100 kcal. Concentrations of LA in human milk vary widely as a reflection of maternal dietary intake, but values less than 8% of fatty acids are rarely reported. Currently, marketed infant formulas provide more than 8% of fatty acids as LA. A maximum LA content of 35% of total fatty acids in infant formulas is recommended. With a maximum fat content of 6.4 g/100 kcal, the maximum LA content is, therefore, 2 240 mg/100 kcal. The polyunsaturated vegetable oils (corn, safflower, and soybean oils) used in manufacture of infant formulas contain an abundant amount of LA (usually 45%-70% of total fatty acids). Historically, infant formulas, particularly corn-oil-based

formulas, contained LA exceeding 35% of fatty acids, with no adverse effects. Moreover, this value (35% of fatty acids) is within the limit reported for individual human milk samples<sup>[2,3]</sup>.

$\alpha$ -Linolenic acid (ALA) is recommended with a minimum content of 1.75% of fatty acids in infant formulas, with the further stipulation that the ratio of LA:ALA should not exceed 16 to 1. With the minimum total fat content of 4.4 g/100 kcal, the minimum content of ALA is 77 mg/100 kcal, approximately 0.7% of energy. This recommendation is based on the essentiality of ALA as a precursor of the n-3 series of long-chain polyunsaturated fatty acids (LCPUFAs). Studies showed that formulas providing ALA at levels below this may be associated with delayed development of visual function and lower levels of docosahexaenoic acid (DHA) in the brain<sup>[6]</sup>. The recommended upper limit for the ratio of LA:ALA (16:1) is intended to prevent an inappropriate combination of high LA content with low ALA content, which might interfere with the formation of longer-chain fatty acids of the n-3 series. A maximum ALA content of 4% total fatty acids in formulas can be additionally stipulated that the ratio of LA:ALA is not less than 6 to 1. With a maximum fat content of 6.4 g/100 kcal, 4% of fatty acids from ALA amounts to 256 mg/100 kcal. The maximum is based on the long history of use of formulas containing soy oil (soybean oils typically contain 6%-9% ALA) as the source of unsaturated fatty acids. The recommended minimum ratio of 6 to 1 is intended to ensure that combination of the minimum LA content with the maximum ALA level does not interfere with the production of longer-chain fatty acids of the n-6 series<sup>[2,3]</sup>.

LCPUFAs, including arachidonic acid (AA) and DHA, are not recommended in infant formulas. Breast milk contains adequate AA and DHA (range 5-20 mg/dL). However, whether AA + DHA should be added to infant-formula milk is uncertain. The results of studies on the growth and neurodevelopment in infants fed with milk formula supplemented with AA + DHA are inconsistent<sup>[6,7]</sup>, suggesting that LCPUFAs are not essential in the diet of infants. Because of the uncertain efficacy and safety, LCPUFAs should not be added to infant formulas. The FDA expert panel plans to revisit this field in 5 years when more data from larger studies are available<sup>[2,3,6,7]</sup>.

### **Carbohydrate and oligosaccharides**

An energy density of 63-71 kcal/dL in infant formulas is recommended. Carbohydrate is the most important nutrient for energy. A minimum total carbohydrate content of 9 g/100 kcal in infant formula is recommended. This minimum is based on a theoretical calculation taking into account the amount of glucose needed for obligatory central nervous system oxidation. A maximum of 13 g/100 kcal is recommended for total carbohydrate in infant formulas. This value is obtained by subtracting from 100% of the total energy (63 to 71 kcal/dL), the minimum energy provided by protein (1.7 g protein/100 kcal = 6.8 kcal) and the minimum

energy from fat (4.4 g fat/100 kcal = 39.6 kcal), resulting in a maximum of 53.6 kcal from carbohydrate, which is equivalent to 13.4 g/100 kcal<sup>[2,3]</sup>.

The addition of glucose to infant formulas is not recommended, because inclusion of glucose in infant formulas offers no biological advantage over other carbohydrate sources and would unnecessarily increase the osmolality of formulas. Lactose is safe and appropriate for use in formulas by most healthy infants, and may be used as a sole carbohydrate source. However, it should not be used at a level higher than the recommended maximum value for total carbohydrate (i.e. 13 g/100 kcal). Also, addition of sucrose to infant formulas is safe and may be used for the palatability of some formulas (e.g. protein-hydrolysate-based formulas).

The concentration and composition of oligosaccharides in breast milk are increased in a dynamic process. The highest amount of oligosaccharides, 2 g/dL milk, is reached on the fourth day of life. On days 30 and 120 of lactation, it decreases to 20% and 40%, respectively, in comparison to that on day 4. Most studies have reported that oligosaccharide in human milk consists of approximately 70%-90% galacto-oligosaccharides (GOSs) and 10%-30% fructo-oligosaccharides (FOSs) in the first few months. The available data are insufficient at present to establish a minimum or a maximum level of these substances in infant formulas. However, some infant formulas supplemented with GOS 0.2-0.4 g/dL and FOS 0.05-0.1 g/dL are available on the market. Although glucose polymers are safe and appropriate for use in formulas by most healthy infants, either a minimum or a maximum level of such substances is not recommended. The amount of carbohydrate from glucose polymers in a formula should be within the lower and upper limits of total carbohydrate. Inclusion of modified food starches in infant formulas involves toxicologic concerns rather than nutritional concerns. Therefore, such food starches in infant formulas are not recommended<sup>[2,3,8]</sup>.

## **TROPIC AND ENTERAL FEEDING**

The provision of adequate enteral nutrition for preterm infants is one of the major clinical challenges facing neonatologists throughout the world. Many preterm infants are too ill to receive substantial enteral feeds and require prolonged PN. It was reported that normal gastrointestinal structure and function are lost, villi become shorter, mucosal DNA is lost, protein content and enzymatic activity are reduced both in animal models and in children, although an anabolic state is maintained by PN<sup>[9]</sup>. In a rat model, atrophy occurred after only 3 d of no enteric intake, while gastrointestinal atrophy and dysfunction were reversed following enteral feeding<sup>[9]</sup>.

Trophic feeding (synonyms include minimal enteral feeding or nutrition, gastrointestinal priming, gut priming, and early hypocaloric feeding) is a relatively recent concept that has been introduced into clinical practice in an attempt to counter the effects of enteral starvation<sup>[9,10]</sup>. It may be defined as the practice of feeding nutritionally insignificant volumes of enteral

Table 1 Evidence-based enteral nutrition in preterm newborns

Evidence-based enteral nutrition	
Human milk	Human milk from the preterm infant's own mother is the first choice. Human milk can be stored at room temperature for up to 24 h after expression in colostrum and up to 6 h for mature milk. Beyond that, it should be stored at 3-4°C before use. If not used for more than 5 d, it should be frozen
Human milk fortifier	Human milk fortifier is indicated in preterm infants < 31 wk and/or < 1500 g. Human milk (100 mL/kg) is given per day and discontinued when the infant has established full breast-feeding
Formula milk	If human milk from the preterm infant's own mother is not available, the only acceptable alternative is a preterm formula. A concentration of about 60 kcal/100 mL or 20 kcal/oz is recommended, but should be increased to 80 kcal/100 mL or 24 kcal/oz when the infant has achieved full enteral feeds
Feeding methods	Gavage feeding is given via an indwelling nasogastric tube during mechanical ventilation. An indwelling orogastric tube is used after endotracheal extubation. Intermittent intragastric feeding is the first choice method, but continuous transpyloric feeding can be tried in selected preterm infants with extremely poor gastric emptying and symptomatic gastro-esophageal reflux
Commencement of feeds	Hourly feeds of 1 mL are generally used in infants weighing less than 1000 g, 2-h 2 mL for infants weighing 1000-1500 g, 3-h 3 mL for infants weighing 1500-2000 g, and 4-h 4 mL for infants weighing more than 2000 g, unless there is significant respiratory distress, when the infant remains on 1-2-h feeds. If this might not be tolerated, milk may be commenced at 1 mL every 2 h, even less than 1 mL every 4-6 h. Such trophic feeding should begin as soon as possible after birth, and definitely within the first 3-4 d
Progression of feeds	Daily increment in the range of 10-30 mL/kg of milk feeds is safe. Demand feeding is started after infants have established full milk feeds on a 4 h regimen. Non-nutritive sucking is beneficial without side effects
Supplements	Multivitamin supplement is started when the infant has established full enteral feeds, and iron is started when the infant has doubled their birth weight (usually at 2 mo). Medium-chain triglycerides can be used as an energy supplement for preterm infants who fail to thrive

substrate to sick neonates, to supply nutrients to, and directly stimulate, the developing gastrointestinal system without increasing disease severity. Typically, a milk volume of 10-20 mL/kg per day is given at the same rate for at least 5 d. Several studies have examined the clinical outcome after trophic feeding<sup>[9-11]</sup>, showing that milk tolerance, liver function, metabolic bone disease, days to hospital discharge, and weight gain are improved after trophic feeding. Nosocomial infections due to PN (because of its interference with the immune system and translocation of enteric pathogenic microorganisms into the circulation) may be reduced either because of improved gastrointestinal mucosal barrier function or because of beneficial alteration of the enteric flora.

Since premature infants are unable to coordinate sucking, swallowing, and breathing, orogastric tube-feeding is necessary. The most common methods used are continuous milk infusion and intermittent (bolus) milk delivery (usually every 3 h). Recent studies have suggested that bolus feeding promotes more "normal" feed-fasting hormonal concentrations that potentially benefit intestinal development and nutrient partitioning, and marked differences are observed in feeding tolerance and growth between continuous *vs* bolus tube-feeding methods<sup>[9-13]</sup>. Since continuous feeding is associated with more significant feeding intolerance, more infants are switched to bolus feeding. Importantly, throughout hospitalization, the continuous feeding method is associated with slower growth compared with the bolus group. Thus, bolus feeding is more advantageous than continuous infusion for premature infants with relatively healthy gastrointestinal tracts.

Current data support the practice of starting GI priming early, which does not add complications of neonatal intensive care<sup>[9,10,12]</sup>. Further studies are needed to determine if early feeding can be advanced in volume

so that the use of PN can be reduced. Bolus feeding results in better feeding tolerance and growth than continuous tube-feeding and also obviates the need for costly infusion pumps and support care. The use of human milk, however, may have the most profound effects because of its association with a decrease in morbidity. The evidence-based guidelines for enteral nutrition in preterm infants are listed in Table 1<sup>[14]</sup>.

## PN

PN can meet neonates' requirement for growth and development when their size or condition precludes enteral feeding. Although feeding through the gastrointestinal tract is the preferred route for nutritional management, there are specific conditions for which PN as an adjunctive or a sole therapy is necessary. In very low birth weight (VLBW) premature infants, enteral feeding cannot be established in the first few days of life, due to the immaturity of the gastrointestinal system. PN can successfully meet the nutritional demands in critically ill neonates, neonates with protracted diarrhea and neonates undergone a major gastrointestinal surgery. The evidence-based guidelines for PN in preterm infants are summarized in Table 2<sup>[14]</sup>.

### Fluids and energy requirements

PN is a fundamental part of neonatal intensive care<sup>[15,16]</sup>. Fluid intake volume varies from 60 to 150 mL/kg per day, depending on maturity of the infant and environmental conditions influencing insensible water loss from the skin. An energy intake of 50 kcal/kg per day is adequate to match ongoing expenditure but an additional energy intake of 70 kcal/kg per day is required to achieve optimal growth. The ideal distribution of calories should be 60% carbohydrate, 10%-15%



Table 2 Evidence-based PN in preterm newborns

Evidence-based PN	
Fluids	D 1: 60-80 mL/kg per day. Infants < 28 wk gestation are nursed in a maximally humidified environment (90% humidity) for at least 7 d. Postnatal weight loss of 5% per day to a maximum of 15% is acceptable, which is achieved by progressively increasing the fluid intake to 120-150 mL/kg per day at 1 wk of age
Energy	An intake of 50 kcal/kg per day is sufficient to match ongoing expenditure, but it does not meet additional requirements of growth. The goal energy intake is 120 kcal/kg per day, which is higher in infants with chronic lung diseases
Protein	Optimal parenteral amino acid intake is 3.5 g/kg per day. Parenteral amino acids can begin from day 1 at a dose of 1.75 g/kg per day
Carbohydrate	From day 1, 6-10 g/kg per day can be infused and adjusted to maintain blood glucose level of 2.6-10 mmol/L. Insulin is only used in infants whose blood glucose level is higher than 15 mmol/L and associated with glycosuria and osmotic diuresis, even after glucose intake has been decreased to 6 g/kg per day. Carbohydrate is given as a continuous infusion commencing at a rate of 0.05 U/kg per hour, and increased as required for persistent hyperglycemia
Fat	Intravenous fat, 1 g/kg per day, can be started from day 1, or when intravenous amino acids are started. The dose of intravenous fat is increased to 2 g/kg and 3 g/kg per day over the next 2 d. Twenty percent intravenous fat is delivered as a continuous infusion via a syringe pump, separated from the infusate containing amino acids and glucose. The syringe and infusion line should be shielded from ambient light
Minerals	Minerals should include sodium (3-5 mmol/kg per day), chloride (3-5 mmol/kg per day), potassium (1-2 mmol/kg per day), calcium (1.5-2.2 mmol/kg per day), phosphorus (1.5-2.2 mmol/kg per day), and magnesium (0.3-0.4 mmol/kg per day)
Trace elements	Trace elements should include zinc (6-8 µmol/kg per day), copper (0.3-0.6 µmol/kg per day), selenium (13-25 nmol/kg per day), manganese (18-180 nmol/kg per day), iodine (8 nmol/kg per day), chromium (4-8 nmol/kg per day), and molybdenum (2-10 nmol/kg per day)
Vitamins	Vitamins must be added to the fat emulsion to minimize loss of vitamins due to adherence to tubes and photodegradation

protein, and 30% fat. A 10% dextrose solution provides 0.34 kcal/mL, a 10% lipid solution provides 0.9 kcal/mL. Although protein is a potential energy substrate, it should be utilized only for tissue growth. Glucose and lipids can provide sufficient calories to avoid protein catabolism. A preterm neonate needs 100-150 kcal/kg per day, whereas a term neonate needs 100-120 kcal/kg per day.

### Carbohydrate requirements

Glucose is the most widely used intravenous carbohydrate for neonates because it is readily available to the brain. A preterm infant has a higher glucose demand and hence early administration of glucose is vital. It is important to balance non-protein calories between carbohydrates and fats, and a 2:1 ratio is recommended. Excess use of glucose would result in lipogenesis, excess production of CO<sub>2</sub> and hyperglycemia leading to osmotic diuresis. Hyperglycaemia during PN can be minimized by starting glucose infusion at a rate of 4-6 mg/kg per min (6-8 g/kg per day) with progressive increase to 12-15 mg/kg per min (16-20 g/kg per day) for 2-3 wk after birth<sup>[15,16]</sup>.

Treatment of hyperglycemia is initiated with insulin if blood glucose is > 200 mg/dL, although the dextrose infusion is below 5 mg/kg per min. Insulin can be started at a dose of 0.05-0.1 U/kg per hour. Insulin infusion rate should be adjusted to 0.05 U/kg per hour to keep the glucose level at 150-200 mg/dL. When the glucose level decreases to < 100 mg/dL, the glucose is monitored every 4 h once the target level is achieved<sup>[15,16]</sup>. Other causes of hyperglycemia like sepsis, intraventricular hemorrhage, and steroids should be ruled out before insulin is used.

### Protein requirements

The goal of giving proteins is to limit catabolism, maintain endogenous protein stores, and provide

sufficient energy and protein to support growth. It has been reported that early administration of PN is safe and efficacious with no metabolic derangements<sup>[17]</sup>. The concept put forth by the American Academy of Pediatrics that nutrition should support postnatal growth that approximates the in utero growth of a normal fetus should be accepted. Parenteral nitrogen requirement is 30-35 mmol/kg per day, which is equivalent to 3.0-3.5 mg/kg amino acids per day. These solutions contain nine essential amino acids and cysteine, tyrosine, taurine and arginine as the semi-essential amino acids. In the absence of an exogenous protein source, a preterm infant catabolizes 1 g/kg of its own body protein per day to meet its metabolic needs. Excess protein administration causes a rise in blood urea, ammonia and high levels of potentially toxic amino acids such as phenylalanine<sup>[18]</sup>. In our unit, we usually start amino acids (1 g/kg per day) on the second day of life for extremely low birth weight (ELBW) infants and increase to 3 g/kg per day with 1 g/kg daily increments per day. Protein with a maximum of 15% calories should be given.

Glutamine, one of the most abundant amino acids in both plasma and breast milk, is not included in amino acid preparations for PN. Glutamine, which is unstable in solution, is usually regarded as a non-essential amino acid. However, glutamine provides an important metabolic fuel for rapidly dividing cells of the gastrointestinal tract and immune system, and is an intermediate in a large number of metabolic pathways, and a precursor that donates nitrogen for the synthesis of purines, pyrimidines, nucleotides and amino sugars. In addition, glutamine plays a key part in acid-base balance by acting as the most important substrate for renal ammonia production. It was reported that glutamine supplementation may decrease sepsis and mortality in critically ill adult patients<sup>[19]</sup>. In view of the

important metabolic roles of glutamine, further clinical evaluation is required in neonates.

### Lipid requirements

Lipid is a major source of non-protein energy and has a nitrogen sparing effect. Serving as a source of essential fatty acids and LCPUFA, lipid is a major source of non-protein energy and has a nitrogen-sparing effect. The commercial intravenous lipid emulsions are aqueous suspensions containing neutral triglycerides derived from soybean, safflower oil and egg yolk to emulsify and adjust glycerin tonicity. Hydrolysis of triglycerides by hepatic and lipoprotein lipase results in formation of free fatty acids. Circulating free fatty acids can be used as an energy source or they enter adipose tissue where they are re-esterified to form triglycerides<sup>[15,16]</sup>.

Parenteral fat is introduced at 1 g/kg per day, and gradually increased to 3 g/kg per day, given as a continuous infusion. In our unit, we usually start lipids on the third day of life in ELBW infants when the most acute phase of respiratory distress or other life-threatening events are controlled. We start 1 g/kg of lipids per day and increase it to 3 g/kg per day. At present, a 20% lipid emulsion is preferred over 10% emulsion, because the higher phospholipid content in 10% solution impedes plasma triglyceride clearance, resulting in higher concentrations of triglyceride and plasma cholesterol. Also, combined MCT/long-chain triglyceride (LCT) and lipid emulsion is preferred over LCT emulsion in preterm and critical neonates, because MCT/LCT is more easily metabolized. Advantages of lipid emulsions over concentrated glucose solutions include their isotonicity and greater energy density, the latter means that a low volume is required per calorie<sup>[15,16]</sup>.

### Minerals, trace elements and vitamins

Minerals and trace elements delivered with PN are calculated to meet in-utero accretion rates. Sodium, potassium, chloride, calcium, magnesium and phosphorus levels need to be closely monitored and the infusion needs to be prescribed accordingly. Neonates on long-term TPN may develop trace element deficiencies which should be checked regularly. TPN can provide the daily requirements for water and fat-soluble vitamins. The dose of water-soluble vitamins is 1 mL/kg per day, which should be added to the dextrose-electrolyte solution. The dose of fat-soluble vitamins is 1 mL/kg per day, which should be added to the lipid emulsions<sup>[14-16]</sup>.

### PN-associated cholestasis

In neonatal intensive care units where appropriate medical, nursing, pharmacy and laboratory experts are available, the potential benefits of PN outweigh its hazards. However, PN-associated cholestasis, onset of hyperbilirubinemia with direct bilirubin > 2 mg/dL within 2 wk after starting PN, are the common complications of PN, along with hepatomegaly, and mild elevation of conjugated bilirubin, alkaline phosphatase and transaminases<sup>[20,21]</sup>. Liver function generally becomes

normal within 1-4 mo after stopping PN, but prolonged liver dysfunction and even fibrosis have been reported in certain cases<sup>[20,21]</sup>. The following factors may contribute to PN-associated liver diseases, including prolonged duration of PN therapy, sepsis, low serum albumin, excessive caloric load, enteral fasting, deficiency in nutritional taurine, carnitine, manganese, oxidative stress and hormonal factors such as elevated insulin/glucagon ratio, gut hormones and biliary stasis. Simple interventions such as minimizing the duration of therapy, early detection and treatment of sepsis, and choosing enteral nutrition rather than PN whenever possible, can minimize liver injury<sup>[20,21]</sup>. Ursodeoxycholic acid (UDCA) is used in the treatment of cholestasis<sup>[20]</sup>, because it increases the hydrophilic non-hepatotoxic bile acid pool, decreases hepatocyte display of histocompatibility antigens and gives direct cytoprotection. The dose of UDCA is 20-30 mg/kg per day.

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