CHAPTER

49

Parenteral Nutrition

The goal of nutrition management in neonates, especially very low birth weight (VLBW) infants, is achieving postnatal growth at a rate that approximates the intrauterine growth of a fetus and ensuring optimal long-term neurodevelopment.[1] This is best achieved by enteral nutrition. However, parenteral nutrition (PN) is required when enteral nutrition is inadequate or contraindicated. PN is especially crucial for extremely low birth weight neonates and neonates with congenital gastrointestinal anomalies.

INDICATIONS

Parenteral nutrition (PN) should be considered in neonates who are not expected to be on significant enteral feeds for more than 3–5 days or are anticipated to receive less than 50% of the total energy requirement in the next 7 days (Table 49.1).

MACRONUTRIENTS

Energy

The total energy is provided by a combination of macronutrients that include carbohydrates, fats, and proteins. It is preferable

Table 49.1: Indications of parenteral nutrition

- Birth weight less than 1000 g: TPN to be started on day 1 (MEN to be started along with TPN if hemodynamically stable and no contraindication for feeding like A/REDF).
- Birth weight 1000–1499 g and anticipated to be not on significant feeds for 3 or more days.
- Birth weight more than 1500 g and anticipated to be not on significant feeds for 5 or more days.
- Surgical conditions: necrotizing enterocolitis, gastroschisis, omphalocele, tracheoesophageal fistula, intestinal atresia, malrotation, short bowel syndrome, meconium ileus, and others that prevent the initiation of enteral feeds.

to have a balance of energy from carbohydrates (60–75%), fats (25–40%), and proteins (10–15%).[2]

A daily energy intake of 110–120 kcal/kg is needed to meet the metabolic demands of a healthy preterm neonate and to allow for a growth rate comparable to the intrauterine growth rate.[3,4] Energy requirement of term neonates is 90–100 kcal/kg/day. The energy intake of sick neonates (e.g. those with acute respiratory illness, chronic lung disease, necrotizing enterocolitis) is not precisely known; it is likely to be near the upper limits of the energy requirement of preterm infants.

Each gram of dextrose and lipid provides 3.4 kcal and 9 kcal, respectively. If the non-protein energy is insufficient, amino acids are catabolized for energy production. An adequate balance between nitrogen and non-protein energy sources (protein/energy ratio: 3–4 g/100 kcal) is needed to promote protein accretion.[5] However, if the dextrose infusion is initiated at the physiological rate (4–6 mg/kg/minute), starting with even 3–3.5 g/kg/day of amino acids in the first few days of life may be beneficial. There is no concrete evidence for monitoring the P: E; however, pragmatic studies show the benefit of starting with higher amino acids in better achieving lean body mass. A balance between carbohydrates and fat is needed to prevent excessive fat deposition and excessive production of CO_2.

Carbohydrates

Carbohydrates are the primary energy substrate for neonates receiving PN. The amount of carbohydrate delivered as dextrose is commonly initiated at the endogenous hepatic glucose production and utilization rate of 4–6 mg/kg/min. This provides an energy intake of 40–50 kcal/kg/d and preserves carbohydrate stores. Once the glucose infusion rate (GIR) supports acceptable serum glucose values, it is advanced in a gradual, stepwise fashion (2 mg/kg/min/day) to a suggested maximum glucose oxidative rate for neonates of 12–13 mg/kg/min to support growth and maintained there unless serum glucose values change significantly. In the first week of life, it is advisable to be cautious in advancing GIR due to reduced insulin sensitivity and glucose tolerance. Table 49.2 summarizes the GIR recommendations as per various nutrition guidelines:

Insulin infusion should not be routinely used to increase the GIR. However, it can be started if the infant develops high glucose levels despite a GIR of 4–6 mg/kg/minute.

Table 49.2: GIR recommendation as per various nutrition guidelines

	Day 1 (mg/kg/min)	*Advancement (mg/kg/min)*	*Maximum rate (mg/ kg/min)*
NICE	Preterm and term: 4–6.25	–	6.25–11.1
ESPGHAN	Preterm: 4–8 Term: 2.5–5	Advance over 2–3 days	Preterm: 5–10 (max 12) Term: 8–10 (max 12)
ASPEN	Preterm: 6–8 Term: 6–8	Advance over 7–10 days	10–14 (max 14–18)

NICE: National Institute for Health and Excellence; *ESPGHAN:* European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; *ASPEN:* American Society for Parenteral and Enteral Nutrition

Carbohydrates in PN: Evidence

Excessive carbohydrate delivery above the amount that can be oxidized for energy and glycogen storage can increase basal metabolic rate, fat deposition, cholestasis, or hepatic steatosis.[6–8] Use of insulin to achieve a higher glucose infusion rate and promote growth has been associated with lactic acidosis.[9]

LIPIDS

Fats are provided as intravenous lipid emulsions and should be started on the first day at a dose of 1.5 g/kg/d and then increased gradually by 0.5–1.0 g/kg/day stepwise to reach 3.5 g/kg/day.[4] Evidence suggests that early initiation of lipids within the first 48 hours is well tolerated and improves cerebellar volume and retinal growth, in addition to improving the nitrogen balance and linear growth in preterm infants.

Specific concerns with the use of lipids have been observed, including PNALD (parenteral nutrition associated liver disease) and IFALD (intestinal failure associated liver disease). The newer combined lipids with fish oil (SMOF) have been postulated to reduce the associated hepatic damage. In preterm neonates with hyperbilirubinemia in the range of exchange transfusion threshold, lipids may be restricted to minimum amounts (1 g/kg/day) to provide only the essential fatty acids.[10]

Intravenous lipid emulsions are available in two strengths: 10% and 20% (*see* Appendix of this chapter). Using 20% lipid emulsions is preferable to decrease the risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.[11] When lipids are exposed to light, they form potentially toxic lipid hydroperoxides. Hence lipid syringes and tubing should be covered by wrapping them in aluminum foil.

Lipids in PN: Evidence

Even a short delay of 3–7 days in supplying lipids to parenterally fed preterm infants leads to biochemical EFA deficiency.[12]

Type of Lipid Infusions

There have been three generations of intravenous lipid emulsions which have been used to date:

First-generation lipid emulsions: The main component of these lipids (e.g. IntraLipid by Fresenius Kabi) is soyabean oil or safflower oil containing long-chain triglycerides (LCT), defined as having 16–18 carbon atoms. The risk of adverse effects (steatosis, cholestasis) with these long-chain lipids mandated better preparations. The concern of sepsis was also high with these lipid emulsions.

Second-generation lipid emulsions: They were marketed with the intent of reducing the LCT content. These emulsions contain 50% of medium-chain triglycerides (MCT) with 6–12 carbon atoms. These emulsions do not require carnitine to enter the mitochondria and are oxidized easily. Lipofundina (soybean oil and medium-chain triglycerides), Clinoleic (soybean and olive oil), and Structolipid (structured lipids) are some of the lipid emulsions of this generation. None of these is being used in India.

Third-generation lipid emulsions: The main constituent of this generation is the omega-3 fatty acids. Compared to omega-6, omega-3 fatty acids have better immunomodulatory and immunosuppressive effects. SMOFLipid (Fresenius Kabi; Soyabean oil, medium chain triglycerides, olive oil, and fish oil), Omegaven (100% refined fish oil emulsion), and Lipoplus (MCT, soyabean oil, and fish oil) are included in this generation of lipid emulsions. Of these, SMOFlipid is available in India.

SMOFlipid vs. Intralipid: Evidence

A meta-analysis of 14 studies, of which 9 studies compared different types of lipid emulsions, concluded that emulsions that are not purely soyabean oil based might be associated with a lower incidence of sepsis.[13–16] Beneficial effects on growth could not be shown. Some retrospective studies show a lesser incidence of parenteral nutrition-associated liver disease (PNALD), but large-scale RCTs are warranted. The use of SMOF in PNALD has been shown to increase the resolution of abnormal liver function tests compared to soyabean-based emulsions; however, its role in the prevention of PNALD is yet uncertain (Cochrane 2019).

Amino Acids

PN should provide 3.0–3.5 g/kg/day of amino acids (AA). An optimal amino acid solution should contain essential (valine, leucine, isoleucine, methionine, phenylalanine, threonine, lysine, and histidine) and conditionally essential (cysteine, tyrosine, glutamine, arginine, proline, glycine and taurine) amino acids, should not have an excess of glycine and methionine, and should not contain sorbitol. Depending on practical feasibility, the amino acid infusion should be started on the first day of birth, preferably soon after birth. Providing adequate proteins since day one not only contributes to fat-free mass but also helps in normalizing insulin secretion in ELBW neonates, in whom insulin levels are low.[2]

Proteins in PN: Evidence

The amount started on day 1 of PN has varied from 0.5–3.0 g/kg/day in different studies. A higher intake of 3-3.5 g/kg/day can be safely administered starting from the first day of birth.[2] Early provision of protein is critical to attaining positive nitrogen balance and accretion, as premature babies lose about 1% of their protein stores daily.

MICRONUTRIENTS AND MINERALS

Sodium, potassium, chloride, calcium, magnesium, and phosphorus must be provided in PN solution as their daily needs (Table 49.3). All these minerals are readily available for administration in neonates except for phosphate. Sodium, potassium, and chloride are essential to life, and their requirements depend on obligatory losses, abnormal losses, and amounts necessary for growth. Calcium, phosphorus, and magnesium are the most abundant minerals in the body. They are closely interrelated to each other in metabolism, the formation of tissue structure, and function. Estimated and advisable intakes (Table 49.3) are based on accretion studies and urinary and fecal losses from balance studies.[17]

Calcium and phosphate supplementation: The current recommendation is to provide early and appropriate supplementation of calcium gluconate and phosphate (on day 1) to prevent metabolic bone disease. To promote the highest retention of these minerals, the ideal ratio of calcium: phosphorus (mg: mg) for parenteral nutrition should be 0.8–1.1 on Day 1 and 1.3–1.7:1, subsequently in the neonatal period.[18]

An ideal phosphate preparation (should not precipitate when combined with intravenous calcium preparation) is difficult to procure in India. Many units administer intravenous phosphorus

Table 49.3: Daily requirement of minerals[18]	
Mineral	*Requirement*
Sodium	0–3 mEq/kg/day (1st week of life) 2–3 mEq/kg/day (beyond 1st week in term neonates) 3–5 mEq/kg/day (beyond 1st week in preterm neonates)
Potassium	0–2 mEq/kg/day (1st week of life) 1–3 mEq/kg/day (beyond 1st week)
Chloride	2–3 mEq/kg/day
Calcium	2–4 mEq/kg
Magnesium	0.3–0.5 mEq/kg
Phosphorus	1–2 mEq/kg

(Injection Potphos; NEON Laboratories Ltd; 15 ml ampoule; 89 INR per ampoule) and intravenous calcium gluconate in separate syringes in alternate 4–6 hours cycles to avoid precipitation.

VITAMINS

Vitamins are essential cofactors and coenzymes needed for the metabolism of macronutrients and should be added to PN solution to meet the daily requirement (Table 49.4). Preparations

Table 49.4: Recommended vitamin intake[18]			
Vitamin	*Term (daily dose)*	*Preterm (dose/kg/day)*	*Available MVI (per 1 ml)*
Vitamin A (IU)	2300	1640 (700–1500)	1000
Vitamin D (IU)	400	160 (80–400)	100
Vitamin E (IU)	7	2.8 (2.8–3.5)	0.50 mg
Vitamin K (µg)	200	10	
Vitamin B_6 (mg per kg)	1000	0.15–2	1500
Vitamin B_{12} (µg)	1	0.3	
Vitamin C (mg)	80	15–25	50 mg
Biotin (µg)	20	5–8	
Folic acid (µg)	140	56	
Niacin (mg)	17	4–6.8	10
Pantothenic acid (mg)	5	2.5	2.50
Riboflavin (mg)	1400	0.15–2	1400
Thiamin (mg)	1200	0.35–0.5	5 mg

of fat-soluble and water-soluble vitamins suitable for neonates are not available in India. Multivitamin injection (MVI), when added in a dose of 1.5 ml/kg to lipid solution, meets the need for vitamin A and most other vitamins. Intravenous vitamin delivery may be less due to photodegradation of vitamins A, D, E, K, B_2, B_6, B_{12}, C, and folic acid and adsorption of vitamins A, D, and E into the vinyl delivery bags and tubing. Vitamin K needs to be given separately as weekly intramuscular injections. Although vitamin B_{12} is absent in MVI, its deficiency is not manifested unless the neonate is on long-term PN. The total vitamin E dose from multivitamin infusion should not exceed 11 mg/day.

TRACE ELEMENTS

Eight trace elements (zinc, copper, chromium, iron, manganese, selenium, molybdenum, and iodine) should be part of PN solutions in neonates.[4] Zinc is universally recommended from day one of TPN, whereas the other trace minerals are generally provided after two weeks of TPN without any appreciable enteral feeding. Copper, selenium, molybdenum, and iron can be delivered separately also. Zinc is a critical micronutrient, and zinc deficiency is known if not supplemented, especially in preterm neonates with excessive GI and urinary losses. The dosage is 150–400 microgram/kg/day, but a suitable preparation is difficult to find in the Indian market. Enteral iron is the preferred mode, and the parenteral route for iron is to be considered only in prolonged parenteral nutrition (beyond three weeks). Manganese and chromium are usually present in many parenteral nutrition solutions and need not be replaced. Selenium and molybdenum are required only if prolonged PN beyond 3 weeks is administered. Recommended daily doses of parenteral trace elements are provided in Table 49.5.

WEANING AND DISCONTINUING TPN

There are no clear recommendations on when to start weaning TPN—it depends on the underlying cause of initiating TPN and the neonate's clinical condition. TPN can be gradually weaned off once 50% of total daily needs are tolerated as enteral feeds. Sudden stoppage of GIR may be associated with rebound hypoglycemia. The other components of TPN can be stopped without tapering also. Parenteral nutrition can be stopped once enteral feeds are tolerated at 140–150 ml/kg/day in neonates less than 28 weeks of gestation and 120–140 ml/kg/day in neonates born at or after 28 weeks of gestation (NICE guidelines 2020).

Table 49.5: Recommended daily doses of parenteral trace elements[18]			
Trace element	*Preterm*	*Term*	*Maximum dose per day*
Zinc (µg per kg)	400–500	100–250	5 mg
Copper (µg per kg)	40	20	0.5 mg
Chromium (µg per kg)	0.05–0.3	0.2	5 µg
Iron (µg per kg)	200–250	50–100	5 mg
Manganese (µg per kg)	<1	<1	50 µg
Selenium (µg per kg)	7	2–3	100 µg
Molybdenum (µg per kg)	1	0.25	5 µg
Iodine (µg per kg)	1–10	1	–

SUMMARY: RECOMMENDATIONS

Evidence-based recommendations for the use of PN constituents are summarized in Table 49.6.

DISPENSING PN SOLUTION

In developed countries, the PN solution is prepared by a central pharmacy and delivered ready for use. This facility is usually unavailable in most Indian hospitals, and physicians and nurses must chart and prepare PN. The steps for calculation and preparing PN are as follows (a PN chart is provided in the appendix):

1. Determine the total fluid requirement for the day.
2. Subtract the amount of fluid used for medications (e.g. diluting and infusing antibiotics) and enteral feeds.
3. Plan amino acids, intravenous lipids, and glucose to be given over 24 hours.
4. Load intravenous lipid (IVL) suspension in one syringe and add multivitamins (MVI).
5. Mix amino acids, dextrose, electrolytes, and trace elements in the second syringe.
6. IV L+MVI suspension is infused separately from AA-glucose-minerals solution, although they can be mixed using a three-way adapter at the infusion site.

Osmolarity of PN: Weak and conditional evidence recommends that the osmolarity of PN should not exceed 900 mOsm/L to avoid the potential risk of thrombophlebitis in neonates.

Table 49.6: Evidence-based recommendations for parenteral nutrition	
Component	*Recommendations*
Fluids	Day 1: 60–80 ml/kg/day (*See* the protocol on 'Fluid and electrolyte management'). Postnatal weight loss up to 3% per day to a maximum of 10–15% is acceptable. This is achieved by progressively increasing the fluid intake to 150 ml/kg/d by the end of first week of life.
Energy	The goal is 100–120 kcal/kg/day (higher in infants with BPD). An intake of 50 kcal/kg/day is sufficient to match ongoing expenditure but it does not meet the additional requirements of growth.
Protein	The optimal parenteral amino acid intake is 3.5 g/kg/day. Parenteral amino acids can begin from day 1 at 1.5–2 g/kg/day.
Carbohydrates	From day one, 6 mg/kg/min can be infused, increased by 2 mg/kg/min every day to 12–14 mg/kg/min, and adjusted to maintain euglycemia. Insulin is only used in infants who continue to have hyperglycemia associated with glycosuria and osmotic diuresis even after the glucose intake has been reduced to 4–6 mg/kg/min. Insulin is given as a continuous infusion commencing at a rate of 0.05 units/kg/h, increasing as required for persistent hyperglycemia.
Fat	Intravenous fat, 1.5 g/kg/d can be started from day 1, at the same time as when intravenous amino acids are started. This is increased to 2 g/kg/day and 3 g/kg/day over the next two days, maximum of 3.5 g/kg/day. It is delivered as a continuous infusion of 20% intravenous fat via a syringe pump, separate from the infusate containing the amino acids and glucose. The syringe and infusion line should be shielded from ambient light.
Minerals and trace elements	Minerals should include sodium, chloride, potassium, calcium, phosphorus, magnesium. Trace elements should include zinc, copper, selenium, manganese, iodine, chromium, iron and molybdenum.
Vitamins	Vitamins must be added to the fat emulsion to minimize loss during administration due to adherence to tubing and photodegradation.

ROUTE OF ADMINISTRATION

PN can be delivered through **peripheral or central venous lines**. Short-term PN can be given through the peripheral venous line.

Peripheral access offers the advantage of a lower risk of infection due to the greater distance of the catheter from the central circulation and fewer mechanical complications.

However, nutrition delivery is limited with peripheral lines due to constraints created by a solution's osmolarity. The limiting factor in deciding the delivery route is the AA-glucose solution's osmolarity, which depends on dextrose concentration. A dextrose concentration greater than 12.5% has an acidic pH and causes irritation to the peripheral veins. In addition to dextrose, electrolytes and minerals added to the solution also increase the osmolarity. Hypertonic solutions should ideally be administered through the central venous line.

The use of peripherally inserted central catheters (PICC) has facilitated the administration of PN while avoiding many potential complications of surgically inserted central lines. Another attractive option in neonates is a central line inserted through the umbilical vein. An umbilical venous catheter can be used for up to 14 days, after which the risk of complications increases.[15,16]

MONITORING AND COMPLICATIONS

Meticulous **monitoring** is needed in a neonate receiving PN (Table 49.7). Monitoring should be more frequent in the initial stages. Once a steady metabolic stage has been achieved, monitoring can be reduced to once a week.

Complications of PN can be nutrient-related or venous access-related.

Nutrient-related complications include hypoglycemia (plasma sugar <50 mg/dl) and hyperglycemia (plasma sugar >150 mg/dl), azotemia and metabolic acidosis (protein-related), hypertriglyceridemia (triglyceride >200 mg/dl; lipid-related), cholestasis, and trace element deficiency. Most of these complications can be avoided by adequately monitoring and providing nutrients.

Parenteral nutrition-associated liver disease (PNALD) is a commonly encountered complication of prolonged parenteral nutrition. The most widely used definition of PNALD requires a direct bilirubin (DB) concentration of 2 mg/dl with no other cause of liver disease. It presents initially with biochemical evidence of cholestasis, clinical evidence of jaundice, and failure to thrive. The reported incidence of PNALD varies from 25% to 60% in infants receiving long-term PN, depending on the criteria used to diagnose PNALD.

Table 49.7: Monitoring schedule for a neonate on parenteral nutrition	
Parameter	*Frequency*
Blood sugar	2–3 times a day while increasing glucose infusing rate Once a day while on stable glucose infusion rate
Urine sugar	Once per nursing shift
Serum electrolytes	Twice a week initially, then weekly
Blood urea	Twice a week initially, then weekly
Calcium, magnesium and phosphorous	Weekly
Packed cell volume	Weekly
Liver function tests	Weekly
Serum triglycerides	Weekly
Anthropometry	
Weight Head circumference Length	Daily at the same time Weekly Weekly
Nutrient intake calculation	Energy in kcal per kg day Proteins in grams per kg per day

Management strategies include two methods: Lipid replacement and lipid restriction. Soyabean-based lipid composition (Intralipid) contains phytosterols which are implicated in PNALD. Replacing Intralipid with SMOFlipid has been shown to have liver-protecting properties in older children receiving PN; however, lipid restriction and lipid replacement in neonates with PNALD is still controversial and requires further studies.[19,20] There are currently no recommendations for restricting the amino acid component of the TPN. The best protective strategy for PNALD would be to minimize the duration of parenteral fluids and switch over to enteral feeds as early as possible.

Intestinal failure-associated liver disease (IFALD):[21] Preterm neonates with gastrointestinal pathologies like necrotizing enterocolitis (NEC) or surgical intestinal conditions and are on PN are predisposed to develop IFALD. The clinical and pathological features are similar to PNALD, with progressive cholestasis, biliary fibrosis, and steatohepatitis. The etiology is multifactorial, with genetics, the role of soyabean oil in PN, and alteration of gut microbiome being implicated to a certain extent in the development

of IFALD. Restriction of soyabean oil based PN and transition to enteral feeds have been associated with a gradual reduction of symptoms of IFALD in some reports.

Neonatal refeeding syndrome:[18] Inappropriate rates of minerals, electrolytes, and amino acids (low electrolytes and high amino acids) can lead to increased uptake of phosphate, potassium, and magnesium into cells for energy and protein synthesis, thus leading to the neonatal refeeding syndrome characterized by low serum phosphate, potassium, and magnesium and high serum calcium, glucose, and sodium. This can trigger white matter injury and chronic lung disease.

Venous access-related complications include occlusion, dislodgement, and infection.

PREVENTION OF INFECTION[22–24]

Healthcare-associated infection (HAI) is a significant complication of PN. All efforts should be made to avoid HAI:

- Aseptic precautions during the preparation of PN
- Use of laminar flow for preparation of parenteral fluid solutions
- No compromise on disposables
- Trained staff
- No reuse of the PN solutions
- No interruption of the venous line carrying PN
- Use of bacterial filter

APPENDIX

See Tables 49.8 and 49.9

Table 49.8: Sources of parenteral solutions

Component	*Commercial preparation*	*Concentration*
Proteins	Aminoven Primene	10% (0.1 g/ml)
Lipids	Intralipid	10% (0.1 g/ml) 10% PLR (phospholipids reduced) 20% (0.2 g/ml)
Glucose	Dextrose	5% (0.05 g/ml) 10% (0.1 g/ml) 25% (0.25 g/ml) 50% (0.5 g/ml)

(*Contd.*)

Table 49.8: Sources of parenteral solutions (*Contd.*)		
Component	*Commercial preparation*	*Concentration*
NaCl	NaCl	0.9% (0.009 g/ml = 0.15 mEq/ml) 3% (0.03 g/ml = 0.5 mEq/ml)
KCl	KCl	15% (0.15 g/ml = 2 mEq/ml)
Calcium	Calcium gluconate	10% (9 mg/ml of elemental calcium)
Multivitamin	Adult MVI	–
Trace elements	Celcel 4 (Claris) Celcel 5 (Claris)	–
Magnesium sulfate	Magnesium sulfate	50% (0.5 g/ml = 4 mEq)

Table 49.9: Cost and availability of common parenteral fluids			
Name of the fluid	*Concentration (%)*	*Manufacturer*	*Cost (INR)*
Aminoven	6 10	Fresenius Kabi	220 (100 ml) 280 (100 ml)
Primene (Amino acid)	10	Baxter	288 (100 ml)
Intralipid	10 20	Fresenius Kabi	255 (100 ml) 520 (250 ml)
SMOF lipid emulsion	20	Fresenius Kabi	690 (250 ml)
Calcium gluconate	10	Biostan	12 (10 ml)
Magnesium sulphate	50	Ravi Pharma	8 (2 ml)
MVI	–	Psychotropics India (Multizac) NBZ Pharma Infuvite Pediatric (Baxter)	15 (10 ml)

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