56 Parenteral Nutrition

The goal of nutrition management in neonates, especially very low birth weight (VLBW) neonates, is not only the achievement of postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postmenstrual age, but also ensuring optimal long term neurodevelopment. Although this is best achieved with optimal enteral nutrition, early enteral feeding is limited by immaturity of gastrointestinal motor function or by conditions that preclude enteral feeding. Likewise, establishing an alternative source of nutrition becomes a life-sustaining intervention in surgical neonates with congenital or acquired disease causing gastrointestinal failure.

Importance of nutrition: What is the evidence?

Suboptimal nutrient intake during neonatal period has been associated with increased vulnerability to infections, greater need of ventilatory support, poor growth and neurodevelopment outcome, susceptibility to cardiovascular diseases, reduced cell growth in specific organ systems (heart, kidney and pancreas).[1,2]

Indications

Parenteral nutrition (PN) should be considered in neonates who are not on significant enteral feeds for more than 3-5 days or are anticipated to be receiving less than 50% of total energy requirement by day 7 of life (Table 56.1). None of the studies have identified the ideal candidates or absolute indications for starting parenteral nutrition; benefits versus harm should be viewed in each neonate before initiating PN. Table 56.1 provides broad guidelines for initiation of PN.

Table 56.1: Indications of parenteral nutrition

- Birth weight less than 1000 g : PN to be started on day 1 (MEN may be started along with PN 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, tracheo-esophageal fistula, intestinal atresia, malrotation, short bowel syndrome, meconium ileus and others which prevent initiation of enteral feeds

VLBW neonates are more susceptible for postnatal growth restriction, in view of their increased energy demands because of immaturity, growth needs, and high risk of hypo-and hyperthermia.

Energy

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

Each gram of dextrose and lipid provides 3.4 kcal and 9 kcal, respectively. If sufficient amount of non-protein energy is not provided, amino acids are catabolized for energy production. 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 provided at the physiological rate (4 to 6 mg/kg/minute), it may be beneficial to start with even 2 to 3 g/kg/day of amino acids. Balance between carbohydrates and fat is needed to prevent excessive fat deposition and production of CO_2. The ideal distribution of calories should be 50-55% carbohydrates, 10-15% proteins and 30-35% fats.

Carbohydrates

Carbohydrates are the main energy substrate for the neonates receiving PN. The amount of carbohydrate delivered in the form of dextrose is commonly initiated at the endogenous hepatic glucose production and utilization rate of 4 to 6 mg/kg/min. This provides 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) daily to a maximum glucose of 12-14 mg/kg/min. The GIR is maintained at this rate unless serum glucose values change significantly. Insulin infusion should not be routinely used to increase the GIR. However, if the neonate is having high glucose levels despite glucose infusion rate of 4-6 mg/kg/min, insulin infusion needs to be started.

Carbohydrates in PN: What is the evidence?

Excessive carbohydrate delivery above the amount that can be oxidized for energy and glycogen storage can lead to an increase in basal metabolic rate, fat deposition, cholestasis or hepatic steatosis.[8-10] Use of insulin to achieve higher glucose infusion rate and promote growth has been associated with lactic acidosis.[11]

Lipids

Lipids can be started on first day at dose of 1.5 g/kg/d and then increased gradually by 0.5 to 1.0 g/kg/d daily in stepwise fashion to reach 3.5 g/kg/d.[4] In preterm neonates with hyperbilirubinemia in range of exchange transfusion threshold, lipids may be restricted to minimum amount (1 g/kg/d) that will provide only the essential fatty acids.[12]

Intravenous lipid emulsions are available in two strengths: 10% and 20% (Appendix). Use of 20% lipid emulsion is preferable to 10% solution to decrease the risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.[13] 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: What is evidence?
Even a short delay of 3 to 7 days in supplying lipids to parenterally fed preterm neonates leads to biochemical EFA deficiency.[14]

Type of lipid infusions

Three generations of intravenous lipid emulsions have been used till date:

The first generation lipid emulsions (based on soybean or safflower oil; *Intra lipid by Fresenius Kabi)***:** The main component of these lipids is soyabean oil containing long chain triglycerides (LCT). Adverse effects (steatosis, cholestasis) with these long chain lipids indicated the need for better lipid preparations. Concern of sepsis was also high with these lipid emulsions.

The second generation lipid emulsions were marketed with intent to reduce the LCT content. These emulsions contain 50% of medium chain triglycerides (MCT). These emulsions do not require carnitine to enter the mitochondria and hence are oxidised 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 are being used in India.

The third generation lipid emulsions: The main constituent of this generation is the omega 3 fatty acid. Compared to omega 6 fatty acids, omega 3 have a better immunomodulatory and immunosuppressive effect and hence this generation of lipid emulsions not only achieves the nutrient effect but also has significant immunological contribution.

SMOF (Soyabean oil, medium chain triglycerides, olive oil and fish oil), Omegaven (100% refined fish oil emulsion) and Lipoplus (Medium chain triglycerides, soyabean oil and fish oil) are included in this generation of lipid emulsions.

Of these, SMOF lipid is available in India and is being marketed by Fresenius Kabi.

What is the evidence in favour of SMOF lipid as compared to Intralipid 20%?

The ASPEN (2016) and ESPHAGN (2005) guidelines do not mention any advantage of one lipid emulsion over another type. A metaanalysis of 14 studies, of which 9 studies compared different types of lipid emulsions, concluded that newer emulsions that are not purely soyabean oil based might be associated with a lower incidence of sepsis.[15-18] Beneficial effects on growth could not be shown. Some retrospective studies show a lesser incidence of parenteral nutrition associated liver disease (PNALD) with the newer generation lipid emulsions.

Amino acids

PN should provide 3.0-3.5 g/kg/day of amino acids (AA). An optimal aminoacid solution should contain essential (valine, leucine, isoleucine, methionine, phenylalanine, threonine, lysine and histidine) and conditionally essential (cysteine, tyrosine, glutamine, arginine, proline, glycine and taurine) aminoacids, should not have excess of glycine and methionine and should not contain sorbitol. Depending on practical feasibility, aminoacid infusion should be started on the first day of birth preferably soon after birth. To avoid negative protein balance, one should start with at least 1.5 g/kg/d and then increase by 1 g/kg/d to maximum of 3.5 g/kg/d to 4 g/kg/day. Providing adequate proteins since day one not only provides the contribution to fat free mass but also helps in normalising insulin secretion in ELBW neonates, in whom insulin levels are low.[2]

AA solutions are available as 10% and 20% preparations (Appendix).

Proteins in PN: what is the evidence? The amount started on day 1 of PN has varied from 0.5 to 3.0 g/kg/d in different studies.[6] Though intake of about 1.5 g/kg/d is enough to prevent negative nitrogen balance, higher intake of 3 to 3.5 g/kg/d can be safely administered starting from first day of birth.[2] Early provision of protein is critical to attain positive nitrogen balance and accretion because preterm neonates lose about 1% of their protein stores daily.[7]

Minerals

Sodium, potassium, chloride, calcium, magnesium and phosphorus need to be provided in PN solution as per their daily needs (Table 56.2). Except phosphate, all these minerals are easily available in India. Sodium, potassium, and chloride are essential to life and requirements are dependent on obligatory losses, abnormal losses, and amounts necessary for growth.[19] Calcium, phosphorus, and magnesium are the most abundant minerals in the body. They are closely interrelated to each other in metabolism, formation of tissue structure, and in their functions.

Table 56.2: Daily requirement of minerals[20]

Mineral	Requirement
Sodium	0-3 mEq/kg/d (1st week of life) 2-3 mEq/kg/d (beyond 1st week in term neonates) 3-5 mEq/kg/d (beyond 1st week in preterm neonates)
Potassium	0-2 mEq/kg/d (1st week of life) 1-3 mEq/kg/d (beyond 1st week)
Chloride	2-3 mEq/kg/d
Calcium	2-4 mEq/kg
Magnesium	0.3-0.5 mEq/kg
Phosphorus	1-2 mEq/kg

Calcium and phosphate supplementation to prevent metabolic bone disease: The current recommendation is to provide early and appropriate supplementation of calcium gluconate and phosphate (on day 1) to prevent metabolic bone disease. The ideal ratio of calcium: phosphorus (mg:mg) for parenteral nutrition, in order to promote highest retention of these minerals, is 1.3 to 1.7:1.[20] An appropriate phosphate preparation (concern of alumunium toxicity with available preparation) is currently not available in Indian market, thus limiting its use in PN.

Vitamins

Vitamins are added in PN solution to meet the daily requirement (Table 56.3). Separate preparations 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 needs of vitamin A and most other vitamins. However, intravenous vitamin delivery to the neonate may be less due to photo-degradation 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 not present in MVI, its deficiency does not manifest unless the neonate is on long-term PN.

Table 56.3: Recommended vitamin intake[20]

Vitamin	Term (daily dose)	Preterm (dose/kg/day)	Available MVI (per 1 mL)
Vitamin A (IU)	2300	1640	1000
Vitamin D (IU)	400	160	100
Vitamin E (IU)	7	2.8	0.50 mg
Vitamin K (µg)	200	80	
Vitamin B6 (µg)	1000	180	1500
Vitamin B12 (µg)	1	0.3	
Vitamin C (mg)	80	25	50 mg
Biotin (µg)	20	6	
Folic acid (µg)	140	56	
Niacin (mg)	17	6.8	10
Pantothenic acid (mg)	5	2	2.50
Riboflavin (µg)	1400	150	1400
Thiamine (µg)	1200	350	5 mg

Trace elements

Trace elements like zinc, copper, manganese, selenium, fluorine and iodine should be provided in PN solutions.[4] Zinc is universally recommended from day one of TPN, whereas the other trace minerals are generally provided after 2 weeks of TPN with no appreciable enteral feeding. Copper, selenium, molybdenum, and iron can be delivered separately also. Dosage of zinc to be provided is 150-400 microgram/kg/d even with

short-term PN, but a suitable preparation is difficult to find in Indian market. Iron is to be considered only in cases of prolonged parenteral nutrition (beyond 3 weeks).

Fluids

Intravenous fluid is the carrying medium for PN. It is started at 60-80 mL/kg/d and advanced by 15-20 mL/kg/d to maximum of 150 mL/kg/d by end of first week of life (see protocol on 'Fluid and electrolytes management').

Weaning and discontinuing TPN

TPN can be gradually weaned off once the enteral feeds are tolerated at 50 mL/kg/day. Sudden stoppage of GIR may be associated with rebound hypoglycemia. The other components of TPN can be stopped without tapering. Parenteral nutrition can be stopped once enteral feeds are tolerated at 100 to 120 mL/kg/day.

Dispensing PN solution

In developed countries, PN solution is prepared by central pharmacy and delivered ready to be used. But this facility is not available in most Indian hospitals, and physicians and nurses have to chart and prepare PN. Steps for calculation and preparing PN are as follows (a PN chart is provided in appendix):

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

Route of administration

PN can be delivered through peripheral or central venous lines. Short-term PN can be given through peripheral venous line. Peripheral access offers the advantage of a lower risk of infection and mechanical complications.

However, nutrition delivery is limited with peripheral lines due to constraints created by the solution's osmolarity. The limiting factor in deciding the route of delivery is the osmolarity of the AA-glucose solution which is dependent on dextrose concentration. Dextrose concentration greater than 12.5% has an acidic pH and can be irritating to the peripheral veins. In addition to dextrose, electrolytes and minerals added to the solution increase the osmolarity of the solution. Hypertonic solution need to be administered through central venous line.

Increasing use of peripherally inserted central catheters (PICC) has facilitated administration of PN while avoiding many potential complications of surgically inserted central lines. Another attractive option in neonates is central line inserted through umbilical vein. Umbilical venous catheter can be used for up to 14 days after which the risk of complications increases.[17,18]

Monitoring and complications

Meticulous monitoring is needed in a neonate receiving PN (Table 56.4). 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 and hyperglycemia (plasma sugar > 150 mg/dL) (glucose-related), 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 proper monitoring and provision of nutrients.

Catheter-related complications include occlusion, dislodgement and infection.

Parenteral nutrition associated liver disease (PNALD)

It is one of the commonly encountered complications of prolonged parenteral nutrition. The most widely used definition of PNALD requires a serum 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 establish the diagnosis PNALD.

Management strategies include two methods: lipid replacement or lipid restriction.

Soybean based lipid composition contains phytosterols which are implicated in PNALD. Replacing this with SMOF has been shown to have important liver protecting properties in a few studies in older children receiving PN; however, lipid restriction and lipid replacement in neonates with PNALD is still controversial and requires further studies.[21] There are currently no recommendations of restricting the amino acid component of the TPN.

The best protective strategy for PNALD would be to minimize the duration of parenteral fluids and to switch over to enteral feeds as early as possible.

Table 56.4: Monitoring schedule for neonates on PN

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 (kcal/kg/d) and proteins (grams kg/d) daily

Prevention of infection

Hospital-acquired infection (HAI) is a major complication of PN. All efforts should be made to avoid HAI. The steps to prevent HAI include:

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

Appendix

Table: Sources of parenteral solutions		
Component	**Commercial Preparation**	**Concentration**
Proteins	Aminoven Primene	6% (0.06 g/mL) and 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)
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)

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 (Aminoacid)	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	15 (10 mL)

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