Parenteral Nutrition

The goal of nutrition management in neonates, especially very low birth weight (VLBW) infants is the achievement of postnatal growth at a rate that approximates the intrauterine growth of a normal fetus at the same postmenstrual age. Although, this is best achieved with optimal enteral nutrition, early enteral feeding is commonly limited by immaturity of gastrointestinal motor function, manifested principally as delayed stomach emptying, gastro-esophageal reflux, abdominal distension, and infrequent stooling. 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 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]

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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 1).

Table 1: Indications of parenteral nutrition

- Birth weight less than 1000 g
- Birth weight 1000-1500 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 in neonates: Necrotizing enterocolitis, Gastroschisis, Omphalocele, Tracheo-esophageal fistula, Intestinal atresia, Mal-rotation, Short bowel syndrome, and Meconium ileus

Energy

A daily energy intake of 110-120 kcal/kg is needed to meet the metabolic demands of a healthy premature neonate and to allow for growth rate comparable to intrauterine growth rate.[3,4] Energy requirement of term neonate is 90-100 kcal/kg/day. 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 upper limits of the energy requirement of preterm infant.

10% dextrose solution provides 0.34 kcal/ml. 10% lipid solution provides 0.9 Kcal/ml and 20% lipid solution provides 1.1 Kcal/ml. 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] Balance between carbohydrates and fat is needed to prevent excessive fat deposition and excessive

production of CO_2. The ideal distribution of calories should be 50-55% carbohydrate, 10-15% proteins and 30-35% fats.

Amino acids

PN should provide 3.0-3.5 g/kg/day of AA. An optimal AA solution should contain essential (valine, leucine, isoleucine, methionine, phenylalanine, threonine, lysine and histidine) and conditionally essential (cysteine, tyrosine, glutamine, arginine, proline, glycine and taurine) AAs, should not have excess of glycine and methionine and should not contain sorbitol. Depending on practical feasibility, AA 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.

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

Proteins in PN: what is evidence?

The amount started on day 1 of PN has varied from 0.5 to 3.0 g/kg/d in different studies.[6] Although, intake of about 1.5 g/kg/d is needed to prevent negative nitrogen balance, higher intake of 3-3.5 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, as premature babies lose about 1% of their protein stores daily.[7]

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 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. Insulin infusion should not be used to increase the GIR. However, if infant is developing high glucose levels despite glucose infusion rate of 4-6 mg/kg/minute, insulin infusion can be started.

Glucose is available as 5%, 10%, 25% and 50% solutions.

Carbohydrates in PN: What is 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 1.0 g/kg/d and then increased gradually in stepwise fashion to 3.0 g/kg/d.[4] In preterm neonates with hyperbilirubinemia in range of exchange

transfusion threshold, lipids may be restricted to minimum amounts (1 g/kg/d) that will provide only the essential fatty acids.[12]

IVL emulsions are available in two strengths: 10% and 20% (Appendix). Use of 20% lipid emulsion is preferable to a 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 it 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 infants leads to biochemical EFA deficiency.[14]

Minerals

Sodium, potassium, chloride, calcium, magnesium and phosphorus need to be provided in PN solution as per their daily needs (Table 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. 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 2) are based on accretion studies and urinary and fecal losses from balance studies.[15]

Table 2: Daily requirement of minerals

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	150-200 mg/kg/day
Magnesium	15-25 mg/d
Phosphate	20-40 mg/kg/d

Vitamins

Vitamins are added in PN solution to meet the daily requirement (Table 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 need of vitamin A and most other vitamin. Furthermore, intravenous vitamin delivery 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 is not manifested unless the neonate is on long-term PN.

Table 3: Recommended vitamin intake		
Vitamin	**Term (daily dose)**	**Preterm (dose/kg/day)**
Vitamin A (IU)	2300	1640
Vitamin D (IU)	400	160
Vitamin E (IU)	7	2.8
Vitamin K (µg)	200	80
Vitamin B6 (µg)	1000	180
Vitamin B12 (µg)	1	0.3
Vitamin C (mg)	80	25
Biotin (µg)	20	6
Folic acid (µg)	140	56
Niacin (mg)	17	6.8
Pantothenic acid (mg)	5	2
Riboflavin (µg)	1400	150
Thiamin (µg)	1200	350

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 without any 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.

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. Fluid therapy is regulated by monitoring hydration status of the infant (weight gain/loss, serum sodium, urinary specific gravity, urine output and osmolality of plasma and urine).

Evidence-based recommendations

Evidence-based recommendations for use of PN constituents are summarized in Table 4.

Table 4: Evidence-based recommendations for parenteral nutrition	
Component	**Recommendations**
Fluids	Day 1: 60-80 mL/kg/d. Postnatal weight loss up to 3% per day to a maximum of 10 to 15% is acceptable. This is achieved by progressively increasing the fluid intake to 120-150 mL/kg/d by one week of age.
Energy	An intake of 50 kcal/kg/d is sufficient to match ongoing expenditure, but it does not meet additional requirements of growth. The goal energy intake is 100-120 kcal/kg/d (higher in infants with chronic lung disease)
Protein	Optimal parenteral amino acid intake is 3.5 g/kg/d. Parenteral amino acids can begin from day 1 at 1-1.5 gm/kg/d
Carbohydrates	From day one, 6 mg/kg/min can be infused, increased by 2 mg/kg/min/d 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 dieresis even after the glucose intake has been

	reduced to 4 to 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 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/d and 3 g/kg/d over the next two days. 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, and molybdenum.
Vitamins	Vitamins must be added to the fat emulsion to minimize loss during administration due to adherence to tubing and photo-degradation.

Dispensing PN solution

In developed countries PN solution is prepared by central pharmacy and delivered ready to be used. But this facility is usually not available in most of 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 AA, IVL and glucose to be given over 24 h
4. Take IVL suspension in one syringe and add MVI in to it.
5. In second syringe mix AA, dextrose, electrolytes and trace elements
6. IVL+MVI suspension is infused separately from AA-glucose-minerals solution, although they can be mixed at the site of infusion using a three-way adapter.
7. For calculating amount of each PN component, use following formula:

$$Amount\ of\ PN\ component\ = \frac{Amount\ to\ be\ given\ per\ kg\ body\ weight\ \times Body\ weight}{Strength\ of\ solution}$$

For example, for a baby weighing 1.5 kg to be given 3 mEq/kg of sodium, amount of 3% NaCl to be used is:

$$Amount\ of\ 3\%\ NaCl\ = \frac{3\ meq/kg \times 1.5\ kg}{0.5\ meq/ml} = 9\ ml$$

Computer assisted prescribing of PN should be encouraged, as this can save time, improve the quality of nutritional care and reduce errors.[16] All PN solutions should be administered with accurate flow control. The infusion system should undergo regular visual inspection. Peripheral infusions should be checked frequently for signs of extravasation. The pump should have free flow prevention if opened during use, and have lockable settings.

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 due to the greater distance of the catheter from the central circulation as well as a smaller risk of mechanical complications.

However, nutrition delivery is limited with peripheral lines due to constraints created by a solution's osmolarity. The limiting factor in deciding route of delivery is osmolarity of the AA-glucose solution which is dependent on dextrose concentration. A 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 risk of complications increases.[17,18]

Position of central line should be confirmed by X-ray before starting infusion through it. To avoid risk of pericardial tamponade, tip of the central catheter should lie outside the pericardial sac (on the chest x-ray is at least 0.5 cm outside the cardiac outline). In comparison to catheters made of stiffer material (polyvinylchloride, polypropylene, polyethylene), softer catheters (silicone and polyurethane) are less thrombogenic and less traumatic, and are, therefore, preferable for long-term use. The venous access used for PN should not be interrupted for giving antibiotics or other medications. For this a separate intravenous line should be established.

Monitoring and complications

Meticulous monitoring is needed in a neonate receiving PN. Monitoring protocol and its rationale is summarized in Table 5. 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 < 54 mg%) 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. PN-related cholestasis is usually complication of long-term PN and can be avoided by provision of at least minimal-enteral nutrition. Catheter-related complications include occlusion, dislodgement and infection.

Table 5: 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
Serum albumin	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

Prevention of infection

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

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

Quality improvement

Following process and outcome indicators should be audited in neonatal units which use parenteral nutrition:

1. Incidence rate of central catheter-associated blood stream infection (per 1000 catheter days)
2. Incidence rate of central catheter occlusion necessitating catheter removal
3. Incidence rate of parenteral nutrition-associated cholestasis
4. Proportion of eligible neonates who receive parenteral nutrition.

Appendix

Table: Sources of parenteral solutions		
Component	**Source**	**Concentration**
Proteins	Aminoven Primene	6% and 10%
Lipids	Intralipid	10%, 10% PLR (phospholipids reduced), 20%
Glucose	Dextrose	5%, 10%, 255, 50%
NaCl	NaCl	0.9%, 3%
KCl	KCl	15%
Calcium	Calcium gluconate	10%
Multivitamin	Adult MVI	-
Trace elements	Celcel TMA	-
Magnesium sulfate	Magnesium sulfate	50%

TPN worksheet

An example worksheet provided below can be used to calculate and chart parenteral nutrition therapy. Steps of charting parenteral nutrition include:

1. Determine birth weight, present weight and weight change since 24 h previous to start of parenteral nutrition therapy. Birth weight is used to plan nutrient and fluid intake till baby starts gaining weight and weight on the day of calculation exceeds birth weight. Thereafter weight on the day of therapy is used for all calculations.
2. Depending on day of birth and fluid status of the neonate, determine total fluid to be administered over the 24 h period. Of the total fluid calculated amount to be used for giving parenteral nutrition is determined by subtracting fluid to be administered as enteral feed and as diluent for intravenous drugs (e.g. antibiotics).
3. Plan amino acids, lipids, glucose and electrolytes (sodium and potassium) to be given over 24 h.
4. For calculating amount of each PN component, use following formula:

$$Amount\ of\ PN\ component\ = \frac{Amount\ to\ be\ given\ per\ kg\ body\ weight\ \times Body\ weight}{Strength\ of\ solution}$$

For example, for a baby weighing 1.5 kg to be given 3 mEq/kg of sodium, amount of 3% NaCl to be used is:

$$Amount\ of\ 3\%\ NaCl\ = \frac{3\ meq/kg \times 1.5\ kg}{0.5\ meq/ml} = 9\ ml$$

5. Take lipid suspension in one syringe and add MVI in to it. To account for some volume loss in dead space of the syringe and fluid administration set, one can take additional 20% amount in syringe (overfill). Rate of administration can be calculated by dividing total volume (before overfill) by duration of administration (24 h).
6. In second syringe amino acids, dextrose, electrolytes and trace elements are mixed together. In this solution also, to account for some volume loss in dead space of the syringe and fluid administration set, one can take additional 20% amount of each constituting. More than one syringe can be used if volume to be administered exceeds syringe capacity.
7. Lipids, amino acids and electrolytes to be used are calculated based on formula given above. After taking into account fluid allowance consumed for each component, remaining fluid is used for administration of glucose. Total grams of glucose to be administered can be calculated by multiplying glucose infusion rate with birth weight and 1.44. Different glucose strength solution can be used to provide the amount of dextrose in the allocated fluid (left after taking into consideration all other constituents of parenteral nutrition).
8. Lipid + MVI suspension is infused separately from amino acid-glucose-minerals solution, although they can be mixed at the site of infusion using a three-way adapter.

Name		**Date of birth**		**Age**	
B. wt		**Weight**		**Gain/loss**	
Total fluid rate(ml/kg/day)			Net fluid(ml)		
Feed volume(ml)		Other medications (ml)			
Parenteral fluid (ml)					
	Strength (%)	**gm/kg/day**		**mEq/kg/d**	**Strength**
Lipid planned			**Sodium**		
Amino acid planned			**Potassium**		
GIR planned					
		Multiply with 1.2 for overfill			
Lipid volume required (ml)					
MVI (ml)					
Total lipid solution (ml)					
Fluid rate (ml/hr)					
Amino acid (ml)					
10% Calcium gluconate (ml)					
Sodium chlroride					
Potassium chloride					
TMA					
Magnesium					
Others				Energy	Kcal/kg
				Carbohydrate	
				Protein	
Net (ml)				Fat	
				Total	
Fluid left for Glucose					
Total grams of glucose to be given					
5% dextrose (ml)					
10% dextrose (ml)					
25% dextrose (ml)					
50% dextrose (ml)					
Net (ml)					
Glucose fluid rate					

Research question	Subjects	Study design	Intervention	Outcomes to be measured
1. Can parenteral nutrition be delivered through peripheral venous catheter	Preterm neonates needing parenteral nutrition	Randomized controlled trial	Peripherally inserted central catheter versus peripheral venous catheter	1. Energy, amino acids, lipids delivered 2. Weight gain 3. Rate of hospital-acquired blood stream infections
2. Umbilical venous catheter can be used for what duration without increasing risk of infection?	Preterm neonates needing parenteral nutrition	Randomized controlled trial	7 versus 14 days	1. Rate of hospital-acquired blood stream infections
3. What are complications of parenteral nutrition in SGA neonates?	Preterm SGA and AGA neonates	Prospective cohort study Retrospective case-control study	No	Rate of complications: 1. Neonatal cholestasis 2. Age at full feeds 3. Weight gain 4. Rate of hospital-acquired blood stream infections
4. What are benefits and harms of giving aggressive nutrition?	Preterm neonates needing parenteral nutrition	Randomized controlled trial	Starting full dose parenteral nutrition immediately after birth versus gradually building up the dose administered	1. Energy, amino acids, lipids delivered 2. Weight gain 3. Rate of hospital-acquired blood stream infections 4. Metabolic profile: serum ammonia, blood pH, triglycerides
5. Should dose of lipids be restricted in neonate	Preterm neonates needing parenteral nutrition and with	Randomized controlled trial	Lipid restricted to 1-1.5 g/kg day versus full dose 3 g/kg/d	1. Free bilirubin 2. Concentration of free radicals/oxidative metabolites

s under phototherapy?	significant hyperbilirubinemia			3. Brainstem auditory evoked response
6. What is quality of delivery of parenteral nutrition	Neonates needing parenteral nutrition as per unit protocol	Prospective cohort study	None	1. Proportion of neonates who get parenteral nutrition as per evidence-based unit protocol 2. Rate of catheter related complications 3. Rate of parenteral nutrition related complications 4. Energy and metabolite actually administered

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