

Use of Total Parenteral Nutrition (TPN) in the Newborn

Definition

A continuous infusion of a hypertonic solution of glucose, amino acids, electrolytes, minerals and vitamins as well as lipids to maintain tissues and promote growth in neonates unable to tolerate full enteral feeds.

Indications include:

1. Preterm infants who require extended periods of time to establish full enteral feedings. The most common use of TPN in the newborn nursery.
2. Infants with congenital malformations of the bowel who will be NPO for extended periods of time and may require multiple surgeries. For example, gastroschisis and large omphaloceles.
3. Infants with necrotizing enterocolitis (NEC) who require surgery and/or bowel rest.
4. Preterm infants with the spectrum of "feeding intolerance" to suspicion for NEC. This includes ill infants who may have a primary or secondary ileus from NEC or sepsis.
5. Post-surgical infants who are not able to tolerate enteral feeds.
6. Newborns with intractable diarrhea (rare).

Peripheral vs Central TPN

Peripheral TPN is limited by a glucose concentration of no more than D12.5W. If giving maximum protein and lipids with a maintenance infusion rate of about 150 cc/kg, about 90-100 cal/kg/day can be given by the peripheral route, enough to maintain body stores and promote growth in infants with normal nutritional status. It is indicated if the time to full enteral feeds is expected to be relatively short, i.e. 1-2 weeks. This is adequate for some post-surgical infants, larger preemies who will tolerate enteral feeds relatively quickly and short episodes of feeding intolerance or NEC watch. One drawback is maintenance of a peripheral IV. The decision can always be revised depending on the clinical course of the infant.

Central TPN requires placement of a central catheter with the tip either in the superior vena cava or the inferior vena cava at the junction of the right atrium. Most of the central lines are placed through a peripheral vein (basilic, femoral or saphenous) and can be maintained up to a month or more. The surgeons can also place a Broviac or an Arrow catheter either during surgery or at the bedside. Glucose infusions of D20-25W can be given through a central line and adequate calories to promote growth can easily be obtained with central TPN. Central TPN is indicated in small premature infants who will take more than 1-2 weeks to achieve full enteral feeds, post surgical infants who will be NPO for extended periods of time and infants with complications from NEC. Central lines require meticulous care to reduce the incidence of sepsis and accidental displacement. Even so, catheter related sepsis is a common problem in the NICU with both peripherally placed central catheters, broviacs, and Arrow catheters.

Components of TPN

A. Protein

The goal of protein intake is maintenance of existing tissue and growth (positive nitrogen

balance) with an intake that does not strain metabolic or excretory functions. Standard intake for term infants is based on healthy breastfed infants. Normal values for nitrogen retention, amino acid profiles and growth have been difficult to determine in the preterm infant. Standard values for preterm infants have been based on intrauterine growth rates and/or the growth rates of healthy preterm infants fed adequate amounts of breast milk to mimic intrauterine growth rates. A protein intake of 2.7-3.5 gm/kg/day with at least 80 non-protein calories/kg/day has been shown to mimic intrauterine nitrogen accretion with minimal side-effects (Zlotkin et al., 1981). There is no growth advantage to increasing the amount of protein and adverse effects become more prominent (azotemia, hyperammonemia, increased urine osmolality).

The solution of crystalline amino acids used in the NBSCU is Trophamine (Kendall-McGraw). These special formulations have been developed for the pediatric population to "normalize" amino acid profiles in the blood. The "normal" values are based on 2 hour post-prandial levels in 30 day old term breast fed neonates and may not represent normal values for a preterm infant but these formulations have been shown to improve nitrogen retention and weight gain in full term and premature newborns (Helms et al., 1987, Heird et al., 1987, Heird et al., 1988).

Several amino acids are considered "conditionally essential" in neonates and reflect immature enzyme pathways and/or altered metabolism of parenterally administered amino acids (Table 1). Cysteine is a conditionally essential amino acid in newborns because of low hepatic cystathionase activity; cystathionase converts cystathionine to cysteine. It must be added separately to the TPN solution because it remains stable in solution for only a short period of time. Taurine, a derivative of cysteine, is also low in infants maintained by TPN. It has been added to TPN and commercial formulas because taurine is a component of human milk and newborns have high levels especially in the brain. Cats fed a taurine free diet developed retinal degeneration so it is thought to be important for normal brain development (Hays et al., 1975). Infants on TPN are also unable to maintain plasma tyrosine levels despite adequate phenylalanine intake. The reason for low tyrosine levels is unknown since infants appear to have adequate phenylalanine hydroxylase. Since tyrosine is insoluble, newer pediatric formulations include n-acetyl-L-tyrosine which is soluble.

Complications from parenteral protein intake have been largely resolved with current formulations. Metabolic acidosis is rarely a problem with the newer amino acid preparations that removed hydrochloric salts of the cationic amino acids and hyperammonemia (> 120 $\mu\text{moles/L}$) is uncommon as long as an adequate amount of arginine (at least 0.5 mmol/kg/day) is included. Protein should be started at 3.0 gm/kg/day and increased by 0.5 to 1 gm/kg/day; ammonia levels do not need to be monitored. Advance parenteral protein intake to 3.5 – 4.0 gm/kg/d for infants ≤ 1500 gm birth weight and to 3.0 – 3.5 gm/kg/d for infants > 1500 gm birth weight. All VLBW infants can start amino acid solutions within 1-2 hours of birth. Even the smallest, sickest preterm infants can tolerate parenteral protein and are more likely to retain positive nitrogen balance if started early (Van Goudoever et al., 1995).

B. Carbohydrate

Basic energy requirements include basal metabolic rate, activity, thermal effect of food (SDA), thermoregulation, and excretion. The best estimate for maintenance is 50-60 cal/kg/day but this will vary from infant to infant (Weinstein and Oh, 1981) i.e. Infants with BPD or CHF will have an increased maintenance energy requirement. Growth will require additional calories. With a protein intake of 3.0-3.5 gm/kg/day, 110-130 cal/kg/day should give a daily weight gain of

10-30 grams/day. Excessive calories and additional weight gain reflect addition of adipose tissue, not lean muscle mass. Non-protein calories are given as glucose or lipids.

Glucose infusions are started at D5 to D7.5W in the smallest premature infants to D10W to D12.5W in the larger premature and term infants. The glucose infusion can be advanced as tolerated. The hepatic output of glucose is 6 mg/kg/min. Infants should receive a minimum of 6-8 mg/kg/min. to prevent hypoglycemia. As the infusion rate exceeds 6 mg/kg/min, many VLBW infants will have problems with hyperglycemia due to a relative insulin resistance and a low renal threshold for glucose. As the glucose infusion is advanced, hyperglycemia and glucosuria appear. This may result in large fluid shifts and dehydration. Treatment consists of limiting the glucose infusion but this also limits calories. Amino acid and lipid infusions only exacerbate the problem (Savich et al., 1988). The use of insulin in VLBW infants has been shown to improve caloric intake and weight gain (Collins et al., 1991). It is administered as a continuous infusion starting around 0.05 - 0.1 u/kg/hour which can be adjusted to response. Insulin use is reserved for infants with glucose intolerance resulting in severe restriction of calories and weight loss. It should be considered after 5-7 days of age when major fluid shifts have resolved; close monitoring is required to prevent hypoglycemia. Early, aggressive administration of parenteral nutrition has reduced the frequency of hyperglycemia.

C. Lipids

Lipids are an excellent source of calories that can be given in a relatively small volume. Adequate weight gain with TPN was not feasible until the addition of a lipid emulsion. Adequate calories can be given with peripheral TPN if lipids are used. Lipids are also a source of essential fatty acids (linoleic and linolenic acid).

The parenteral source of fat used in the NBSCU is a 20% (20 gm/dL) lipid emulsion (Liposyn II, Abbott laboratories, Chicago, IL) which is made from a soybean oil/safflower oil mix with an emulsifying agent of egg yolk phospholipid. After infusion, the triglycerides are hydrolyzed to fatty acids and glycerol by endothelial lipoprotein lipase. Triglyceride levels will remain relatively constant if the rate of infusion does not exceed the rate of hydrolysis. The activity of endothelial lipoprotein lipase increases with gestational age and is inhibited by stress (infection, surgery), theophylline, and malnutrition i.e. SGA infants have less activity (Heird WC, 1991). Insulin increases activity. In general infusions given over 20-24 hours at a rate no greater than 0.2 - 0.25 gm/kg/hour are usually well tolerated (Vileisis et al., 1982). Complications include exacerbation of hyperglycemia, inhibition of white cell function and adverse effects on pulmonary diffusion at higher infusion rates.

Intravenous lipids should be initiated within 24 hours of birth if possible, but by day 2 of life. Preterm infants are more likely to have problems with the hydrolysis step; therefore, lipids should be started at 0.5 gm/kg/day for the smallest premature infants and up to 1.0 gm/kg/day for the larger premature infants. Near term and term infants can start at 2 gm/kg/day and all infants can advance to 3 gm/kg/day as tolerated. Essential fatty acid (EFA) deficiency appears rapidly in newborns especially preterm infants and an infusion of 0.5 gm/kg/day will meet the EFA requirement and can be tolerated by almost all infants. Lipids can be advanced by 0.5-1.0 gm/kg/day if the serum triglyceride level remains below 150 mg/dL.

A theoretical concern with lipid infusion is hyperbilirubinemia. Free fatty acids (FFA) bind to albumin and could displace bilirubin. The level at which FFAs displace bilirubin is unknown but in practice, this does not seem to be a major complication. Rubin et al. (1995)

found that preterm infants given lipids in the first week of life had the expected fall in serum bilirubin levels despite an elevated triglyceride level. Therefore, initiating lipids should not be withheld for routine jaundice. However, lipids should be used carefully or held temporarily in infants near exchange levels. Lipids should also be used cautiously in infants with documented sepsis and/or high oxygen requirements.

The 10% lipid solution is not used in the newborn nursery. Studies in neonates have shown that the 10% solution results in higher triglyceride levels which leads to the accumulation of phospholipids and cholesterol in LDLs. 20% lipids had a more efficient clearance of triglycerides even at higher infusion rates (Haumont et al., 1989 and 1992).

D. Electrolytes, vitamins and minerals

Electrolyte requirements may vary somewhat and serum levels should be carefully monitored when initiating TPN. Electrolyte intake should be limited for the first 1-2 days of life, especially in the ELBW preterm infant due to a physiologic excess of total body sodium and water. A diuresis/natriuresis with accompanying weight loss is expected (Lorenz et al., 1995). Costarino et al (1991) found that holding sodium during the first five days of life did not prevent the physiologic diuresis/natriuresis and the infants were less likely to develop hyponatremia and did not require a high fluid intake. In addition, these infants were less likely to develop BPD. Serum electrolytes can be followed carefully and TPN can be ordered with or without electrolytes as needed. Some amount of sodium acetate will be required as a buffer (see Table 4 for a suggested "ideal" initiation of fluids and electrolytes in preterm infants).

Calcium (50-60 mg/dL), phosphorus (40-45 mg/dL) and magnesium (6-7 mg/dL) at an infusion rate of 120-150 cc/kg/day appears to be an adequate intake to maintain mineral homeostasis in preterm and term infants. However, VLBW infants may have a higher calcium requirement for growth (most calcium is acquired during the third trimester and the fetus deposits on average 100 mg/kg/day during the third trimester. TPN can only deliver calcium at about 60-70% of that rate due to precipitation of calcium phosphate crystals in the TPN solution. Lowering the phosphorus to increase the calcium results in hypophosphatemia). The smallest preterm infants on long term TPN are at risk for bone demineralization and "rickets of prematurity" which is caused by inadequate intake of calcium and phosphorous not vitamin D deficiency. This problem is aggravated by fluid restriction and use of loop diuretics (lasix) such as in BPD.

Vitamin and mineral requirements are best estimates based on limited data (see Tables 2 and 3). Table 2 lists the vitamin content in 5 mL of reconstituted MVI-Pediatric. Full term to near-term infants who weigh greater than three kg will receive a daily dose of 5 mL. Infants 1-3 kg will receive 65% of that daily dose (3.25 mL/day) and infants less than 1 kg receive 30% of that daily dose (1.5 mL/day).

Trace elements are added to the TPN solution by adding 0.5 ml/L of Multitrac IV (includes zinc, copper, manganese and chromium). Intake is standard for all infants (Table 3) except zinc which is supplemented in the premature infant. Trace mineral should be added to TPN by the first week of life, especially zinc because there are high requirements for growth in the premature/term infant and deficiency states can develop quickly. Iron (as iron dextran) is not added routinely but should be considered in long term use and should be given to infants receiving erythropoietin. The dose is 1.0 mg/kg/day added directly to the bag.

E. Recommendations for Water and Electrolyte Administration in Preterm Newborn Infants

(See Table 4)

Complications of TPN

1. Catheter
 - a. Infection (25-30%)
 - b. Malposition/dislodgement
 - c. Thrombus of line - treat with TPA. Thrombus of SVC or IVC
 - d. Peripheral catheters - extravasation and skin sloughs. Thrombophlebitis and infection (rare).

2. Metabolic
 - a. Electrolyte abnormalities - Na/K/acid-base disturbances
 - b. Mineral abnormalities - Ca/P/Mg
 - c. Hyper/hypoglycemia, osmotic diuresis
 - d. Hepatic dysfunction - infants on prolonged TPN (>10-14 days) can develop cholestasis. The reason is unknown. Typical lab results show a rising bilirubin with a increased direct component and mildly elevated transaminases. Even small enteral feeds may help this problem. Other causes for a direct hyperbilirubinemia should be considered (TPN cholestasis is a diagnosis of exclusion).
 - e. Hyper/hypovitaminosis (should be avoided with proper use of MVI.
 - f. Essential fatty acid deficiency (avoid with small infusion of lipids)
 - g. Trace mineral deficiency (avoid with addition of trace minerals)

Monitoring

Careful monitoring, especially during the initiation of TPN should prevent or detect most problems. Maintenance of the catheter requires competent nursing care and constant surveillance for catheter placement, normal infusion and signs of local irritation or infection. If an infant with a central line is thought to be infected, blood cultures should be obtained from both the line and from a peripheral vein. All infants with a central line and suspected sepsis are treated with vancomycin (for *S. epidermidis* coverage) as well as an aminoglycoside for gram negative coverage. Vancomycin use is pre-approved for 72 hours for neonates with suspected sepsis.

Metabolic complications can occur especially during initiation so monitoring is more frequent during this period. Once the infant is in a steady state, monitoring becomes less frequent. The table that follows represents a guideline for monitoring the use of TPN in a stable infant. The clinical condition will determine additional tests as needed.

	Baseline ¹	Stabilization ²	Maintenance ³
Weight #	x	daily	daily
Height #	x	weekly	weekly
Head circ. #	x	weekly	weekly
Electrolytes (Na/K/Cl/HCO ₃)	x	daily	weekly
Acid-base status	x	daily	weekly
CBC	x	-	weekly
Renal function (BUN/Cr)	x	-	biweekly
Ca/P/Mg	-	-	biweekly
Lipid level	-	**	biweekly
Liver function	-	-	***
Urine for glucose	x	routine [@]	routine
Dextrostix	x	routine [@]	routine

#Measurements of weight, height and head circumference are routine in the nursery. Each infant should have all three measurements plotted on a growth curve every week to monitor proper growth.

*It is not necessary to monitor ammonia levels as protein is initiated and increased to maintenance.

**The serum lipid level should be determined after lipids reach 3 gm/kg/d. This is particularly important in ELBW infants.

***Screening of liver function consists of measuring a direct bilirubin only to start after the infant has been on TPN for 10 days to two weeks and continuing biweekly. If the direct bilirubin is greater than 2.5 mg/dL, then check transaminases and alkaline phosphatase. A basic work-up for direct hyperbilirubinemia should also be initiated. Infants with evidence of liver disease (clinical jaundice, hepatomegaly) should be worked up immediately. Some groups also check albumin on a biweekly basis as part of routine monitoring.

@Since hyper/hypoglycemia is a common problem, urine is routinely checked for glucose and blood glucose is monitored with the bedside glucometer frequently during initiation of TPN. As the infant matures and is in a steady state, urine is checked 1-2x/day and blood glucose 1-3x/day.

¹ - baseline is just prior to initiating TPN

² - stabilization includes the time to achieve maintenance TPN and includes 2-4 days after achieving maintenance TPN.

³ - maintenance is once the infant has been stabilized on TPN

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Additional Resources

1. Greene HL, Hambidge KM, Schanler R, Tsang RC (1988) Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition [published errata appear in *Am J Clin Nutr* 1989 Jun;49(6):1332 and 1989 Sep;50(3):560]. *Am J Clin Nutr* 48:1324-42
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Table 1

Classification of Amino Acids*

Essential	Nonessential	Conditionally Essential
Isoleucine	Alanine	Cysteine
Leucine	Arginine	Histidine
Lysine	Asparagine	Taurine**
Methionine	Asparate	Tyrosine
Phenylalanine	Glutamate	
Threonine	Glutamine	
Tryptophan	Glycine	
Valine	Proline	
	Serine	

- Based on Irwin MI, Hegsted DM: A conspectus of research on amino acid requirements in man. J Nutr 1971: 101:539-566.

** Not a protein constituent

Table 2

Vitamin A, µg	700
Vitamin E, mg	7
Vitamin K, µg	200
Vitamin D, µg	10
IU	400
Infants	
Ascorbic acid, mg	80
	µg/kg/day)
Thiamin, mg	1.2
Riboflavin, mg	1.4
Pyridoxine, mg	1.0
Niacin, mg	17
Pantothenate, mg	5
Biotin, µg	20
0.20	
Folate, µg	140
Vitamin B ₁₂ , µg	1.0
0.25	

These amounts are provided by 5 mL of Reconstituted MVI-Pediatric (Armour Pharmaceutical Co.).

Table 3

Recommended Parenteral Intakes of Trace Minerals**

Trace Mineral	Preterm Infants	Term
	µg/kg/day	
Zinc	400	250 ⁺
Copper	20	20
Selenium	2.0	2.0
Chromium	0.20	
Manganese	1.0	1.0
Molybdenum	0.25	
Iodide	1.0	1.0

Table 4: Recommendations for Water and Electrolyte Administration in Preterm Newborn Infants

- Goals:**
1. Expect weight loss during first 3-5 days of life
 2. Maintain normal serum electrolyte concentrations:

Sodium	135 – 145 mEq/L
Potassium	3.5 – 5.0 mEq/L
Chloride	98 – 108 mEq/L
 3. Avoid oliguria < 0.5 – 1.0 mL/kg/h for 8 – 12 hours

Phase 1: TRANSITION* during the first 3-5 days of life is characterized by: (1) large transcutaneous water evaporation, and (2) renal diuresis of a large surfeit of extracellular salt and water.

Birthweight (grams)	Expected Weight Loss (%)	Water Intake** (mL/kg/day)	Sodium Intake*** (mEq/kg/day)	Chloride Intake (mEq/kg/day)	Potassium Intake (mEq/kg/day)
< 1,000	15-20	90-140	0.0	0.0	0.0
1,000-1,500	10-15	80-120	0.0	0.0	0.0

- The end of transition is recognized by: (1) Urine volume < 1.0 mL/kg/h, and urine osmolality > serum osmolality; (2) Fractional excretion of sodium diminishes from > 3% to ≤ 1 %; and (3) Urine specific gravity above 1.012.

** Water intake volume should be 10-20% less, with humidified incubator or artificial plastic shielding placed over the infant to conserve insensible water evaporation.

*** Often 0.5 – 1.5 mmol/kg/day sodium is administered to these infants inadvertently with transfusions, medications, and line infusions.

Phase 2: STABILIZATION at euvoletic weight for ≤ 10-14 days. Weight gain is not a priority as parenteral and enteral nutrition are cautiously advanced. Transcutaneous water evaporation is diminishing as the neonatal epidermis cornifies.

Birthweight (grams)	Weight Change (%)	Water Intake** (mL/kg/day)	Sodium Intake*** (mEq/kg/day)	Chloride Intake (mEq/kg/day)	Potassium Intake (mEq/kg/day)
< 1,000	0	80-120	2.0-3.0	2.0	1.0-2.0
1,000-1,500	0	80-100	2.0-3.0	2.0	1.0-2.0

Phase 3: ESTABLISHED GROWTH past two weeks of postnatal life in all weight categories to match intrauterine growth rate is the objective. Oral enteral intake is eventually ad libitum.

Weight gain (g/kg/day)	Parenteral Volume (mL/kg/day)	Enteral Volume (mL/kg/day)	Sodium Intake (mEq/kg/day)	Chloride Intake (mEq/kg/day)	Potassium Intake (mEq/kg/day)
15-20	140-160	150-200	3.0 –5.0	3.0-5.0	2.0-3.0

From: Nutritional Needs of the Preterm Infant: Scientific Basis and Practical Guidelines (1993).
In: Tsang RC, Lucas A, Uauy R, Zlotkin S (eds). Williams & Wilkins, Baltimore (pp. 11-12).
