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دانشیار

TOTAL PARENTERAL NUTRITION

- Total parenteral nutrition (TPN) is the intravenous administration of all nutrients necessary for metabolic requirements and growth .
- The goal of PN in the initial days is to provide adequate calories and amino acids to prevent negative energy and nitrogen balance .
- Goals thereafter include the promotion of appropriate weight gain and growth while awaiting the attainment of adequate enteral intake

- PN is started on the first post natal day (within hours of birth) for infants who are < 1,500 g birth weight and / or < 31 weeks ' gestational age .
- PN is important for term and preterm babies with congenital or acquired gut disorders or critical illness when significant entral feeding is not possible for 3-5 days
- Most institutions initiate PN while establishing full enteral feeds for infants < 34 weeks ' gestational age and / or < 1800 g .

- Indications .
- PN is used as a supplement to enteral feedings or as a complete substitution (TPN) when adequate nourishment cannot be achieved by the enteral route .
- Common indications in infants include extreme prematurity , congenital malformation of the GI tract such as gastroschisis and omphalocele , short bowel syndrome following NEC . congenital heart disease , sepsis , and malabsorption

- PN should be started on the first day of life and as soon as possible in preterm or sick infants to decrease catabolism and to optimize postnatal growth . Early PN is associated with better weight gain and neurodevelopmental outcomes in the VLBW population

- Methods of PN administration.
- Central PN . Central PN is used when infants have central access such as umbilical lines or for those infants requiring long - term parenteral support . PN involves infusion of a hypertonic nutrient solution (12.5 % -25 % dextrose , 5 % -6 % amino acids) into a suitable vessel with rapid flow through an indwelling catheter .

- Two methods are commonly used for long - term infusion of PN .
- 1. Percutaneously inserted central catheter . Positioned in the antecubital , temporal , external jugular , or saphenous vein and advanced into a large vessel outside the heart (eg , superior or inferior venacava)
- 2. Tanneled central catheter (Broviac) . Placed surgically in the internal or external jugular , subclavian , or femoral vein .

- Peripheral PN (PPN) . PPN can be infused via peripheral veins , but the concentrations of the amino acids and dextrose solution that can be infused are limited by the fragility of veins
- The mOsm / L limit for PPN is 900 to 1100 mOsm / L , which limits dextrose to 12.5 % and amino acid concentration to 3 %
- Peripheral infusion of PN carries higher risks of infiltration and phlebitis .

- C. Umbilical catheters . Umbelical venous catheters are commonly used for PN
- PN can be given through an umbilical venous catheter (and occasionally through an umbilical artery catheter in some institutions) after ensuring the catheter is central and not in the liver . Hyperosmolar infusion in the hepatic vessels is associated with portal venous thrombosis and portal hypertension .
- Low lying umbilical venous catheters should be used only temporarily and treated as peripheral vessels and , therefore , limited to concentrations similar to PPN .
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- Caloric requirements and densities .
- Goal caloric intake (including protein calories) for PN remains around 80 to 90 kcal / kg / d
- The optimal amount of energy intake differs for each infant and may be higher for sick and E LBW infants .
- Caloric densities of various energy sources are as follows :
- A. Dextrose (anhydrous) . 3.4 kcal / g .
- B. Protein . 4 kcal / g .
- C. Fat 9 kcal / g

- Composition of solutions
- Fluids .
- Goal fluid parenteral requirements after the first few days of life range from 120 to 150 ml / kg / d for term infants and from 130 to 160 ml / kg / d for pre term infants .
- These can vary based on clinical status .

- Carbohydrates . Dextrose is the only commercially available form of glucose , with concentrations of 5.0 % to 12.5 % dextrose used in peripheral PN and up to 25 % dextrose in central PN .
- Glucose infusion rates (GIR) should be calculated as milligrams per kilograms per minute
- Infants should be started on a GIR of 5 to 8 mg / kg / min to allow for appropriate response of endogenous insulin .

- Infusion rates can then be increased by 0.5 to 2 mg / kg / min each day as tolerated with the goal of maintaining blood glucoseconcentrations between 50 and 150 mg /DL .
- For most infants , GIR of 12 to 13 mg / kg / min will provide adequate caloric intake in the presence of stable blood glucose levels
- Excess glucose can lead to glucosuria and osmotic diuresis .
- Excess glucose is also converted into lipid via lipogenesis , which is an inefficient process that increases energy expenditure

- Endogenous gluconeogenesis in preterm ELBW infants may be independent of glucose infusion , and therefore , this population frequently experiences hyperglycemia ..
- Other factors contributing to hyperglycemia include elevated birth related catecholamines , use of inotropic drugs , and decreased production of and sensitivity to insulin

- . In the presence of hyperglycemia , glucose infusion rate should not be reduced below a basal rate of 4 mg / kg / min .
- Insulin may be required to maintain adequate blood glucose concentrations but is not recommended for routine use .

- Hyperglycemia in preterm infants is associated with worse outcomes .
- Peripheral uptake and utilization of glucose are improved with simultaneous amino acid infusion because it increases endogenous insulin production

Providing glucose alone in the absence of proteins results in negative nitrogen balance that can be reversed by providing 1.1 to 2.5 g / kg / d of protein with energy intake as low as 30 kcal / kg / d .

Providing 25 to 30 kcal of nonprotein energy per gram of protein optimizes protein deposition .

- Proteins
- In preterm ELBW and VLBW infants , amino acids should be started on day I and is associated with better linear growth and neurodevelopmental out comes .
- Term infants who are likely to have delayed initiation of EN should also be started as early as possible .
- Inadequate protein intake may result in failure to thrive . hypoalbuminemia , and edema .

- Excessive protein can cause hyperammonemia . serum amino acid imbalance , metabolic acidosis , and cholestatic jaundice .
- Early addition of amino acids to PN may also stimulate endogenous insulin secretion .
- Postnatal protein loss is inversely proportional to gestational age .
- LBW infants lose 1 % of endogenous protein daily unless supplemented

- Crystalline amino acid solutions The standard solutions originally designed for adults are not ideal because they contain high concentrations of amino acids (eg , glycine , methionine , and phenylalanine) that are potentially neurotoxic in premature infants
- Pediatric crystalline amino acid solutions (eg . Trophamine , Aminosyn PP) contain less of those potentially neurotoxic amino acids as well as additional tyrosine , cystine , and taurine

- The lower pH also allows for the addition of sufficient quantities of calcium (2 mEq / dl .) and phosphorus (1-2 mg / dl .) to meet daily requirements .
- Furthermore , newer crystalline amino acid solutions are associated with less azotemia , hyperammonemia , and metabolic acidosis than previous formulations .
- Conditionally essential amino acids are arginine , tyrosine , cysteine , glutamine , glycine , and proline.

- Amino acids , Early protein intake of up to 3 g / kg / d within the first 24 hours is safely tolerated in VLBW infants and improves nitrogen balance , increases ability to synthesize protein , and decreases protein catabolism .
- Early amino acid supple mentation may decrease hyperglycemia and hyperkalemia in ELBW infants by promoting insulin secretion .

- In term infants , the starting rate should be at least I to 2 g / kg / d , with increases of 1 g / kgid to a goal of 3 g / kg / d . For preterm infants . begin at 3 g / kg / d and advance by 0.5 to i g / kg / d to a goal of 3.5 to 4 g / kg / d

- Cysteine hydrochloride
- Cysteine is often added separately to TPN solutions because it is unstable over time and is omitted from peeformulated amino acid solutions .
- The premature infant lacks the ability to convert methionine to cysteine ; thus , it is conditionally essential .

- Cysteine is also converted to cystine and to glutathione , an antioxidant that is important in maintaining calcium homeostasis
- Addition of cysteine to TPN lowers the pH of the solution , thereby improving the solubility of calcium and phosphorus
- Cysteine may also decrease hepatic cholestasis . The recommended dose is 30 to 40 mg of cysteine per gram metabolic acidosis of protein (72-85 mg / kg / d) . It should be held or used cautiously in infants with metabolic ascidosis

- Glutamine has been identified as a key amino acid , as respiratory fuel for rapidly proliferating cells such as enterocytes and lymphocytes , as a factor in acid - base balance , and as a nucleotide precursor .
- Glutamine may play a role in maintaining got integrity and may decrease the incidence of sepsis .
- Despite all these theoretical benefits , randomized trials show that glutamine supplementation does not have significant effect on mortality or neonatal morbidities including invasive infection , NEC , time to achieve full EN , or duration of hospital stay .
- There is no commercially available amino acid solution that contains glutamine .

- Fats .
- Fats are essential for normal body growth and development , in cell structure and function , and in retinal and brain development
- Because of their high caloric density , intravenous lipids provide a significant portion of daily caloric needs .
- Most lipid solutions are derived from soybean , but newer combination oils with olive oil , MCT , and fish oil are now available (eg , Intralipid , Liposyn II , Nutrilipid , Soyacal , Omegavan , Lipoplus , and SMOF lipid) .
- Omegavan is made exclusively from fish oil and is rich in omega - 3 fatty acids

- SMOF (a third - generation emulsion containing soybean oil , MCT , and fish and olive oil) has an altered ratio of omega - 6 to omega - 3 fatty acids that may decrease the risks of PN - associated liver disease (PNALD) .
- Most intravenous fat solutions are isotonic (270-300 mOsm / L .)

- Lipid emulsions contain linoleic and a - linolenic acid ; the latter can be converted into DHA .
- DHA is accumulated in the third trimester , and preterm infants have limited capacity to convert a - linolenic acid to DHA , which plays a critical role in brain development .
- Delay in initiating lipids can result in biochemical and clinical evidence of essential fatty acid deficiency within 3 days and increase susceptibility to oxidant injury .
- Intravenous lipids at 0.5 to 1 g / kg / d are needed to prevent essential fatty acid deficiency

- Concentrations . Lipid emulsions are usually supplied as 20 % solutions pro viding 20 g of triglyceride per 100 ml .
- Starting lipids at 1 to 2 g / kg / d within 24 hours of birth is well tolerated .
- Advance by 0.5 to 1.0 g / kg / d as tolerated up to 3.0 g / kg / d .
- The infusion is given continuously over 20 to 24 hours , and the rate should not exceed 0.12 to 0.15 g / kg / h .

- To maintain calcium and phosphorous solubility , lipids should be administered separately from proteins because amino acid solutions are acidic .
- Adding lipids to protein solutions increases the pH and precipitates calcium and phosphorus
- The caloric value of 20 % lipid emulsions is 2 kcal / mL (-10 kcal / g) . The use of 20 % emulsions is preferred over that of 10 % emulsions because the higher ratio of phospholipids to triglyceride (TG) in the 10 % emulsion interferes with plasma TG clearance

- Twenty percent emulsions also provide a more concentrated source of calories .
- For these reasons , only 20 % lipid emulsions are used
- Current data suggest that preterm infants are at risk for EFA deficiency that is evident within 72 hours after birth , if an exogenous fat source is not delivered .

- Carnitine supplementation . Carnitine synthesis and storage are not well devel oped in infants < 34 weeks gestation . Carnitine is a carrier molecule necessary for oxidation of long - chain fatty acids . An exogenous source of carnitine is available from human milk and infant formulas ; however , studies have shown that pre term infants on TPN become deficient in 6 to 10 days . Carnitine supplementa tion of 2 to 10 mg / kg / d is recommended for infants on TPN for > 4 weeks .

- Some institutions use carnitine whenever lipid emulsions are used . Carnitine - deficient infants may experience hypotonic , nonketotic hypoglycemia , cardiomyopathy , encephalopathy , and recurrent infections .
- Newborn screening programs now test for carnitine deficiency .

- Minerals .
- More than 80 % of bone mineralization occurs in the third trimester .
- Therefore , preterm infants are at increased risk of metabolic bone disease and require supplementation of calcium and phosphorus .
- Delays in reaching full enteral feeds , medications such as diuretics and steroids , and risks of precipitation can limit calcium and phosphorus intake and increase risk of osteopenia of prematurity

- Calcium supplementation is typically provided in PN as calcium gluconate .
- Start at 2 mEq / kg and keep ratio of calcium to phosphorus at 2 : 1 to help prevent precipitation .
- Consider an increase if hypocalcemia or development of metabolic bone disease occurs
- Phosphorus . Phosphorus is typically supplemented in PN as sodium phosphate in the United States . It can be contaminated with aluminum . Start at 1 mEq / kg and keep ratio of calcium to phosphorus at 2 : 1 to help prevent precipitation .
- Additional supplements may be needed with hypophosphatemia or metabolic bone disease

- Vitamins . Multivitamins are added to intravenous solutions in the form of a pediatric multivitamin suspension (MVI Pediatric)
- Preterm infants are especially prone to vitamin deficiencies due to their compromised stores and rapid growth .
- The dose of parenteral vitamins for preterm infants with normal organ function should be 1.5 to 5 mL (1.5 mL when patient weight is < 1000 g . 3.25 ml .
- When patient weight is 1000-3000 g , and 5 mL when patient weight is > 3000 g) .

The 5 - mL reconstituted MVI Pediatric sterile lyophilized powder contains : 2300 IU vitamin A : 400 IU vita min D ; 7 IU vitamin E ; 200 ug vitamin K ; 80 mg ascorbic acid ; 1.2 mg thiamine : 1.4 mg riboflavin ; 17 mg niacin ; 5 mg pantothenic acid ; 1 mg pyridoxine : 1 µg . cyanocobalamin ; 20 ug biotin ; and 140 ug folic acid

Vitamin A delivery can be hampered by binding to plastic tubing

- Trace elements . Supplementation with zinc , copper , manganese , chromium , selenium , and molybdenum is currently recommended in neonatal PN , and deficiencies may occur if these elements are not added when infants are on long - term PN .
- Trace elements are added to the solution based on weight and total volume , with both single - agent and combination products commercially available .
- Increased amounts of zinc (1-2 mg / d) are often given to help promote healing in patients who require GI surgery.

- Electrolytes are not added to PN during the first 2 to 3 days of life , as there are negligible renal losses ; adding early sodium is associated with BPD and early potassium with hyperkalemia . Sodium is started after serum sodium falls to 130 and potassium is started after serum potassium falls to 4 , and urine output is established
- Sodium and potassium concentrations are adjusted daily based on individual requirements
- Maintenance requirements are estimated at approximately 2 to 4 mEq / kg

- Heparin . Heparin should be added to PN (unfractionated heparin 0.5 U / ml . TPN) to maintain catheter patency . In addition , there is a decreased risk for phlebitis use of heparin . and an increase in lipid clearance as a result of release of lipoprotein lipase with use of heparin

- Monitoring of PN .
- Hyperalimentation can cause many alterations in biochemical function .
- Thus , frequent and consistent anthropometric and laboratory monitoring is for all patients , especially ELBW infants .

Table 21.4. Schedule for Nutrition Laboratory Monitoring

	Parenteral Nutrition
Electrolytes	Daily, till stable; then as clinically indicated
Triglycerides	Consider during initiation and/or advancement for extremely low-gestational-age or growth-restricted infants receiving parenteral lipid nutrition
Calcium, phosphorus, alkaline phosphatase	After 14 days of PN and as clinically indicated
Alanine aminotransferase (ALT), direct bilirubin	After 14 days of PN and as clinically indicated

PN, parenteral nutrition.

- Complications of PN
- . Approximately 70 % of infants admitted to the NICU receive some form of PN , with catheter infiltration and infections as the most common com plications .
- Early initiation and rapid advancement of enteral feeds can limit the com plications associated with PN

- Metabolic
- 1. Hyperglycemia . Hyperglycemia can result from excessive glucose intake or change in metabolic rate , such as with infection or glucocorticoid administration .
- Routine insulin infusion to prevent hyperglycemia is not recommended and is associated with increased risks of mortality , hypoglycemia , and ROP .
- Insulin drip may be considered if blood glucose is > 200 to 250 mg / dl despite GIR of < 5 mg / kg / min

- 3. Azotemia .
- Azotemia can result from excessive protein (nitrogen) uptake ; however , aggressive protein intake is safe (see earlier discussion) , and this issue is less likely with current amino acid formulations .
- Elevated blood urea nitrogen may actually indicate better amino acid utilization rather than excessive protein intake

- Hypoglycemia .
- Hypoglycemia can result from sudden cessation of infusion , likely secondary to mechanical issues such as intravenous infiltration .
- Hypoglycemia may occur with insulin administration

- Hyperammonemia .
- Currently available amino acid mixtures contain adequate arginine (> 0.05 mmol / kg / d) .
- Therefore , if there is an increase in blood ammonia secondary to PN , symptomatic hyperammonemia does not occur .

- Abnormal serum and tissue amino acid pattern .
- Infants on TPN may have falsely abnormal newborn metabolic screening results due to multiple minor amino acid abnormalities a protocol of interrupting TPN for 3 hours and replacing the infusion with dextrose 10 % in water before newborn screening collection can result in a 74 % reduction in false - positive results

- Mild metabolic acidosis
- Metabolic acidosis in preterm infants is more likely a result of lack of urinary acidification and severity of illness leading to hypotension and poor perfusion than a result of PN itself (low pH) .
- Acidosis can be buffered by titrating acetate concentrations in daily PN

- Systemic
- Parenteral Nutrition Associated Liver Disease (PNALD) . With prolonged administration of intravenous lipids , dextrose , and protein in the absence of enteral feeding , cholestasis usually occurs as evidenced by a direct hyperbilirubinemia .
- Even in the presence of normal bilirubin levels , evidence of liver disease such as fibrosis may be apparent by histopathologic examination after administration of PN

- The incidence ranges from as high as 80 % in VLBW infants receiving TPN for > 30 days (with no enteral feeding) to 15 % in infants weighing > 1500 g receiving TPN for > 14 days .

- Monitoring for abnormalities in liver function and the development of direct hyperbilirubinemia is important in long - term TPN IUGR infants and those with congenital GI diagnoses are at high risk of developing cholestasis .
- Fish oil - based lipid emulsions (Omegavan) and combination emulsions (SMOFLipid) have been used in prevention and treatment of TPN - induced cholestasis

- Omegavan is available in Europe but can be used in the United States
- SMOF Lipid is an FDA - approved product in adults that has been occasionally used in the NICU ; however , there is limited research on its use in neonates .
- Fish oil - based lipid emulsions may also decrease the risk of ROP
- Starting with even minimal amounts of enteral feeds , decreasing lipid dose to 1 g / kg and cycling lipid infusions (over 12-18 hours) help to decrease PNALD .
- Copper and manganese should be withheld in the presence of hepatic dysfunction .

- Complications of fat administration .
- Hypertriglyceridemia may occur.
- periodic determination of blood triglyceride levels is recommended to maintain plasma triglyceride levels 200 mg / dl .
- Lipid infusion should be decreased or stopped when these levels are exceeded .

- Lipid infusion can be associated with platelet dysfunction , acute allergic reactions , deposition of pigment in the liver , and lipid deposition in the blood vessels of the lung .
- Most metabolic problems apparently occur with rapid rates of infusion and are not seen at infusion rates of 0.12 g / kg / h

- hypertriglyceridemia Free fatty acids (FFA) produced from lipid breakdown compete with bilirubin for binding with albumin , resulting in elevated free bilirubin The FFA - to albumin ratio should be kept at below 6
- lipid infusion should not exceed 1 g / kg / d with plasma bilirubin > 10 mg / dl . and albumin levels of 2.5 to 3.0 g / dL
- Exposure of lipids to light , especially phototherapy , may cause increased production of toxic hydroperoxides

- . The addition of multivitamins and use of protective or dark delivery tubing decrease peroxide formation and limit vitamins loss . Steroids cause elevated triglyceride levels
- whereas sepsis decreases peripheral utilization of lipid

- Additional complications include
- Thrombocytopenia ,
- Increased risk of sepsis ,
- Alteration in pulmonary functions
- Hypoxemia , and increased pulmonary vascular resistance .

- Deficiency of essential fatty acids (EFAs) .
- EFA deficiency can occur within 72 hours in preterm infants if exogenous fatty acids are not supplemented .
- EFA deficiency is associated with decreased platelet aggregation (thromboxane A , deficiency) , poor weight gain , scaling rash , sparse hair growth , and thrombocytopenia .
- Use of only safflower oil to provide lipid emulsions may result in deficiency of omega - 3 LCPUFAS EFAs are essential to the developing eyes and brain of infants
- Photoprotection of parenteral nutrition .
- Photoprotection helps decrease vitamin loss and oxidative damage to amino acids and decreases generation of hydrogen peroxides and free radicals

- Photoprotection limits alterations in vasomotor tone via generation of lipid peroxides , decreases nitric oxide production , and improves tolerance to minimal EN .
- Additionally , it has been found to decrease risk of death and chronic lung disease due to lower triglyceride levels .

- Vitamins , trace elements , and iron should not be added together in the parenteral solution to decrease the risks of lipid peroxidation .
- Increased lipid peroxidation products may adversely influence neurodevelopment .

Mineral deficiency .

- Most minerals are transferred to the fetus during the last trimester of pregnancy .
- The following problems may occur if not adequately supplemented
- Osteopenia , metabolic bone disease , and pathologic fractures
- Zinc deficiency can occur if zinc is not added to TPN after 4 weeks .
- Cysteine and histidine in PN solution increase urinary losses .

- Zinc deficiency results in poor growth , diarrhea , alopecia , increased susceptibility to infection , and skin desquamation surrounding the mouth and anus (acrodermatitis enteropathica) .
- Zinc losses are increased in patients with an ileostomy or colostomy .

- Copper deficiency
- Long - term PN puts infants for copper deficiency , which can result in osteoporosis , hemolytic anemia , neutropenia , and depigmentation of the skin
- Manganese , selenium , molybdenum , and iodine deficiency . Trace element deficiency may occur if not supplemented after 4 weeks .

- Iron Adding iron to PN should be considered for infants on long - term PN who have not received recent blood transfusions , with rhEPO administration , and if ferritin levels fall below 100 ng / mL .
- Dose is 3 mg / kg / wk given once per week , preferably without vitamins and other trace elements for that day

- Mechanical . Complications associated with placement of central catheters occur in approximately up to 10% of patients and include pneumothorax , pneumomediastinum , hemorrhage , and chylothorax (caused by injury to the thoracic duct) .
- Thrombosis of the vein adjacent to the catheter tip , resulting in superior vena cava syndrome (edema of the face , neck , and eyes) , may be seen .
- Pulmonary thromboembolism may occur .

- Malpositioned catheters can result in pleural or pericardial effusion and ascites as well cardiac arrhythmias and tamponade .
- Initial x - ray should show the tip outside the heart , and periodic x - rays may be required to identify catheters at risk of migration . Additionally , infiltration and fragility of their vessels.
- Phlebitis can occur more easily and frequently in infants due to the size and fragility of their vessels

- Infectious . Sepsis can occur in infants receiving central PN . The most common organisms include coagulase - positive and coagulase - negative Staphylococcus , Streptococcus viridans , Escherichia coli , Pseudomonas spp . , Klebsiella spp . , and Candida albicans .
- Infection may exacerbate cholestatic liver disease , leading to further morbidities .

- Cost .
- The costs of PN should be weighed against its risks , particularly when the anticipated need for PN is short term (< 5 days) .
- Complications such as CLABSI greatly increase the morbidity , mortality , and length of stay for infants in the NICU .
- Feeding protocols that encourage initiation and advancement of enteral feeds can help limit the morbidities associated with PN

- Transitioning to enteral feeds .
- As enteral feeding volumes are increasing and volume of PN is decreasing , PN may need to be concentrated to prevent a decrease in caloric intake at the same fluid intake .
- Condensing PN to 80 to 90 ml / kg / d when enteral feeds reach 60 ml / kg / d helps maintain appropriate caloric intake at goal fluid volumes of 140 to 150 ml / kg / d . This can be accomplished by decreasing lipids to 1 g / kg / d , continuing full goal protein , and leaving dextrose concentration the same
- PN can be discontinued when entral feeds reache 100 -120 ML/KG/D