Abstract

In the late 1970s the age of viability was approximately 28 weeks' gestation. Most infants less than 1,000 grams and some less than 1,500 grams were considered nonviable, therefore, resuscitation attempts were less aggressive. Advancing technology has led to improvements in ventilators, intravenous access materials, and surfactant therapy; have all had an impact on lowering the age of viability. It is not unusual today to resuscitate infants as young as 22 weeks' gestation. One of the major obstacles in the care of babies on the edge of viability is to provide adequate nutritional intake. This article discusses the importance of adequate nutrition, reviews the components of total parenteral nutrition (TPN), and makes suggestions concerning initiation of enteral feedings for premature infants.

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Total Parenteral Nutrition for Premature Infants

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Total parenteral nutrition (TPN) is the intravenous infusion of all nutrients necessary for metabolic requirements and growth. Parenteral nutrition (PN) refers to the supplemental intravenous infusion of nutrients by peripheral or central vein. Enteral nutrition (EN) is provided by oral or gavage feedings. PN is commonly indicated in neonates experiencing congenital malformation of the gastrointestinal tract, gastroschisis, meconium and paralytic ileus, short bowel syndrome, necrotizing enterocolitis (NEC), respiratory distress syndrome, extreme prematurity, sepsis, and malabsorption. The ability to provide PN and TPN over the past four decades has significantly improved the overall survival of newborns when other options of adequate nutritional support were not possible.

The goal of TPN is to initially provide sufficient nutrients to prevent negative energy and nitrogen balance and essential fatty acid deficiency and support normal rates of intrauterine growth of appropriate composition without increased significant morbidity. Fear of toxicity and metabolic imbalance has alerted clinicians to use TPN with caution, especially in the sickest and most premature infants. An increasing number of practitioners appreciate that this cautionary management has resulted in suboptimal nutrition intake of these infants. Practitioners have speculated that this cautionary practice contributed in part to national growth failure outcome statistics published of infants extremely low in birth weight (ELBW; less than 1,000 grams) and appropriate for gestational age (AGA; weight $\geq 10^{\text{th}}$ percentile norm) born from 1995 to 1996. When assessed at discharge (~ 36 weeks' corrected age) 99% of these infants had significant growth failure with weights less than the 10th percentile compared with intrauterine growth standards.¹ Longer-term statistics indicate that a significant percentage of infants born very low in birth weight (VLBW; less than 1,500 grams) may suffer substantial neurodevelopmental deficits in part attributable to inadequate nutritional support in the neonatal period.² In more recent years, the earlier introduction and more aggressive advancement of TPN was shown to be safe and effective, even in the smallest and most immature infants.³⁻⁷

Timely intervention with TPN begins with the provision of glucose as soon as possible after birth with amino acids within the first 12 hours, intravenous fat within the first 24 to 48 hours, and trophic feeding within the first 24 hours.⁸ Optimal use of routine TPN for nutritional support of ELBW and VLBW infants may influence short-term outcomes such as lower propensity to infection and shortened hospital stay, as well as longer-term outcomes such as decreased growth deficits,⁸ improved neurodevelopment, and overall morbidity.⁹⁻¹¹ Indications that are generally recognized as those that necessitate TPN for newborns

Table 1. Indications for TPN Support and Route of Administration for Newborn Infants Who Require Intensive Care

Route of TPN Administration	Indication for TPN
Peripheral	Temporary supply of nutrients < 2 weeks: <ul style="list-style-type: none"> • ↓ Enteral intake • Functional gut immaturity • Temporary feeding intolerance • Medical instability
Central	Prolonged nonuse of the gastrointestinal (GI) tract > 2 weeks: <ul style="list-style-type: none"> • Short bowel syndrome • Surgical GI disorders • Necrotizing enterocolitis • Intractable diarrhea • Meconium ileus • Line access in infants extremely low in birth weight, <1,000 grams

are listed in Table 1. Thorough discussions of the components of TPN solutions and protocols for monitoring the tolerance and safe delivery of them to premature neonates are available in a number of classic and current references.¹²⁻¹⁹

Components of TPN Solutions

TPN provides some or all nutrients of basal metabolism and growth for fluid, energy, macronutrients (protein, carbohydrate, and fat) and micronutrients (electrolytes, major minerals, trace minerals, and vitamins). Recommended intakes for premature and term neonates are summarized in Table 2. An overview of fluid, macronutrient, and micronutrient recommendations follows.

Fluid

On day one of life, maintenance fluids are met with a range between 80 and 140 mL/kg/d if the environment of the baby increases insensible water losses and 60 to 100 mL/kg/d in environments with increased humidity.¹³ Thereafter, fluid volume is advanced as tolerated to 120 to 180 mL/kg/d. Maximal fluid volume varies with individual management. Fluid management considerations for infants who require fluid restriction are discussed later.

Macronutrients

Carbohydrate (dextrose) and fat (lipid emulsions) provide the energy needed to meet the demands of the circu-

latory, respiratory, neurological, and muscular systems and, when provided in adequate amounts, spare protein (amino acids) to support cell maturation, remodeling, growth, activity of enzymes, and transport proteins for all body organs. Energy needs may be increased with infection, chronic lung disease, healing, growth, and in babies who have experienced intrauterine growth restriction (IUGR). Energy needs may be decreased with sedation, mechanical ventilation, and after tracheostomy placement.

Micronutrients

Electrolytes

Sodium, potassium, and chloride are essential to life and requirements are dependent on obligatory losses, abnormal losses, and amounts necessary for growth. Estimated and advisable intakes are based on accretion studies and urinary and fecal losses from balance studies completed in the late 1970s.¹⁴ Sodium and potassium can be given as chloride, lactate, or phosphate salts. Infants who receive electrolytes solely as chloride salts may develop hyperchloremic metabolic acidosis. Sodium can also be given as acetate; a randomized trial in 1997 demonstrated the utility of acetate in parenteral nutrition solutions.¹⁵ Potassium is added when urinary flow is established and sodium is added post-diuresis. Chloride is generally given as sodium chloride. Thorough and up-to-date discussions of fluid and electrolyte management of premature infants are published elsewhere.^{13,16}

Major Minerals

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. As indicated in Table 2, amounts of calcium and phosphorus are initiated at maintenance levels and advanced when energy and protein intakes are adequate to support intrauterine accretion rates of lean tissue.¹⁷ The adequacy of these nutrients from TPN solutions has been studied extensively in the premature population and in-depth discussions appear elsewhere.¹⁸⁻²⁴

Trace Minerals

Recommended amounts for trace minerals are listed in Table 3. The 1988 American Society of Clinical Nutrition (ASCN) guidelines²⁵ are given for term and preterm infants and compared with the 1993 consensus recommendations of an international panel of experts for preterm infants that are defined as transitional (within the first two weeks' of life) and stable (after two weeks' of age).²⁶ Zinc

is universally recommended from day one of TPN, whereas the other trace minerals are generally provided after two, four, or 12 weeks' of TPN without any appreciable enteral feeding. Copper, selenium, molybdenum, and iron can be delivered separately also. Several trace element solutions are available with varying combinations of zinc, copper, chromium, manganese, and/or selenium.¹⁹ Copper and manganese are discontinued from TPN solutions with the complication of cholestasis, and amounts of chromium, selenium, and molybdenum are reduced or omitted when renal output is low.²⁵ Many of the component solutions to TPN are found to be "contaminated" with trace elements and therefore administration before actual need may increase risk for toxicity.²⁷⁻³¹ Some have suggested copper requirements greater than the 20 $\mu\text{g/kg/d}$ recommendation.^{18,25,26,32} Because of the oxidant effect of copper as well as the risk of toxicity from limited excretion in patients with cholestasis, Greene and coworkers²⁵ advise the lower amount. Minimal enteral feedings are also a source of copper within the first two weeks.

Although they may cause allergic reactions, iron dextran and ferrous citrate can be used to supplement TPN solutions. Parenteral iron supplementation may be delayed until two months of age in premature infants and three months of age in term infants and considered for those infants who do not receive regular blood transfusions.¹⁹ Concern for iron overload is related to increased risk for septicemia in malnourished infants with a low serum transferrin as well as an increased need for vitamin E.^{19,25,33}

Even though recommendations for premature infants exist within the first two weeks of life for copper, selenium, chromium, iron, iodide, and manganese, these trace minerals generally are not added to TPN but are provided within minimal enteral feedings. Supplementation with iodide may not be necessary because needs for iodide may be met from the topical absorption of iodide-containing disinfectants, detergents, and other environmental sources.²⁵

Aluminum Toxicity

Rules for manufacturers that address the aluminum content of parenteral solutions were developed by the U.S. Food and Drug Administration^{19,34-37} Many component solutions of TPN solutions (albumin, heparin, calcium, and phosphate salts) contain aluminum. The additive amounts of aluminum place infants on long-term TPN at risk for toxicity because of its tendency to incorporate into body tissues.

Vitamins

MVI Pediatric is the only parenteral multivitamin solution designed for pediatric patients (Astra Pharmaceutical, Westboro, MA). In 1999, a shortage of this preparation

occurred in the United States. Possibly because of this shortage, guidelines subsequently were published to address this issue.¹⁹ The most recent guidelines for parenteral vitamin administration for infants remain those published as the consensus recommendations from an international panel of experts in 1993.²⁶ These are compared in Table 4 to those recommended in 1988 by the ASCN.²⁵ For the most part, recommended intakes are based on serum vitamin concentrations measured in term and preterm infants who received various amounts of different vitamins.²⁵ These studies were primarily completed in infants greater than 1,000 grams at birth. Thus, specific needs of ELBW infants remain unclear.³⁸ The recommended parenteral vitamin intakes can only be approximately delivered from MVI Pediatric. The standard dose of 2 mL/kg/d with a maximum intake of 5 mL/d provides lower amounts of vitamin A and higher amounts of most of the B vitamins (see Table 4). Furthermore, intravenous vitamin delivery may be less due to photodegradation of vitamins A, D, E, K, B₂, B₆, B₁₂, C, and folic acid and adsorption of vitamins A, D, and E into the vinyl delivery bags and tubing.³⁹ Some clinicians have addressed these issues with the protection of delivery equipment from light and the administration of fat-soluble vitamins with lipid.^{40,41} The need for a newly formulated pediatric MVI solution that better meets the premature infant's needs has been discussed and recommendations for its composition have been suggested.^{18,25}

Initiation and Advancement of Macronutrients in TPN Solutions

The use of TPN is suggested to support all ill and premature babies less than 1,500 grams that cannot sustain at least ~ 60 kcal/kg/d enterally and initiation is recommended during the first 24 hours of life to avoid excessive protein losses. The premature infant who is not growing, not septic, and not unduly stressed requires an energy intake of about 50 kcal/kg/d for resting energy expenditure, activity, and occasional cold stress,⁴²⁻⁴⁵ with as little as ~ 1 to 1.5 g protein/kg/d to preserve endogenous protein stores.^{5,46,47} At least 60 kcal/kg/d is thought to meet energy requirements during acute sepsis.⁴⁸ Provision of greater than 70 kcal/kg/d and 2.7 to 3.5 g protein/kg/d has been demonstrated to support growth and positive nitrogen balance in preterm infants.⁴⁴ The TPN script "scenarios," listed in Table 5, approximate amounts of nutrients that meet these recommendations for babies with different clinical situations, fluid management, and glucose tolerance. The nonprotein calorie to nitrogen ratios (NPC:N) are included in the table for information purposes but are not generally used in the clinical manage-

Table 2. Usual Daily Requirements of Nutrients in TPN Solutions for Preterm and Term Infants

Nutrient Additive	Usual Daily Requirements in TPN	
Neonatal amino acid	For maintenance: 1.5-2.5 g/kg/d For ELBW infants, begin at a minimum of 1.5 g/kg/d as soon as possible.	Goals for growth: 3.5 g/kg/d for <1,000 grams 3.0 g/kg/d for 1,000-2,500 grams 2.5 g/kg/d for >2,500 g 4.0 g/kg/d for some infants with greater needs
Cysteine hydrochloride	40 mg/g of amino acids (120 mg/kg maximum) Refer to acetate guidelines for ELBW infants (see below under Excess anions)	
Dextrose	For maintenance: 4-6 mg/kg/min (endogenous hepatic glucose production) 8-10 mg/kg/min (preserves carbohydrate stores) ⁵⁰	Goals for growth: 12-13 mg/kg/min Usual maximum concentration: 12.5% peripheral route 20-25% central route
Lipid (20% emulsion from 100% soy oil)	0.5-4.0 g/kg/d; Begin 0.5-1.0 g/kg/d and advance by 0.5-1.0 g/kg/d Essential fatty acids met with 1.0 g/kg/d and at least 80 kcal/kg/d Delivered as a component to the amino acid–glucose solution (admixture) or as a separate solution	
Energy	Goals for maintenance Preterm/term: 60 kcal/kg/d	Goals for growth Preterm: 90-110 kcal/kg/d Term: 80-90 kcal/kg/d Dextrose (40-60%), lipid (40-50%), protein (10-15%)
Carnitine	2-10 mg/kg/d not to exceed 50 mg/kg/d ¹⁰⁶	
Heparin	1 unit/mL not to exceed 137 units/d 0.5 unit/mL for ELBW infants when volume exceeds 150 mL/kg/d	
Sodium (Na) as chloride or phosphate	2-4 mEq/kg/d	Positive nitrogen balance is critical for growth; ELBW infants may require increased intake
Potassium (K) as chloride or phosphate	2-4 mEq/kg/d	Consider omitting in ELBW infants until renal sufficiency is well established
Chloride (Cl)	2-4 mEq/kg/d	Usual Na:Cl is 1:1
Excess anions Acetate Chloride	Excess anion equivalent = (Na + K) – (Cl + P) Usually provide electrolytes as acetate Always use acetate if adding cysteine hydrochloride for ELBW	
Calcium (Ca) as gluconate	1-3 mEq/kg/d for maintenance	3-4.5 mEq/kg/d for growth (see text for solubility limits) Should be administered through a central line rather than a peripheral line in premature infants
Phosphorus (P) as sodium or potassium phosphate	1.3 mmol/kg/d for maintenance ¹⁷	1.5-2.0 mmol/kg/d for growth
Magnesium (Mg)	0.25-1.0 mEq/kg/d Begin ELBW infants at low end	Increased needs for infants with ostomy losses

Table continued on following page

Table 2. Continued

Nutrient Additive	Usual Daily Requirements in TPN
Vitamins as MVI-Pediatric	Premature: 2 ml/kg/day to a maximum of 5 mL/d Term: 5 mL/d
Zinc (Zn) as sulfate or in pediatric trace element (PTE) solution	400 $\mu\text{g/kg/d}$: Preterm infants and all infants with gastrointestinal losses 250 $\mu\text{g/kg/d}$: Term infants 0-3 months 100 $\mu\text{g/kg/d}$: Term infants > 3 months and all infants with long-term TPN
Copper (as sulfate or in PTE)	Withhold during the first 2 weeks of TPN, then initiate at 20 $\mu\text{g/kg/day}$ Decrease amount or withhold with complication of obstructive jaundice
Selenium in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of renal dysfunction Premature: Begin at 1.3 $\mu\text{g/kg/d}$ and advance to 1.5-2.0 $\mu\text{g/kg/d}$ Term: 2.0 $\mu\text{g/kg/d}$
Chromium in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of renal dysfunction Premature: Begin at 0.05 $\mu\text{g/kg/d}$ and advance to 0.05-0.2 $\mu\text{g/kg/d}$ Term: 0.2 $\mu\text{g/kg/d}$
Manganese in PTE	Withhold during the first 2 weeks of TPN Decrease amount or withhold with complication of obstructive jaundice Premature: Begin at 0.75 $\mu\text{g/kg/d}$ and advance to 1.0 $\mu\text{g/kg/d}$ Term: 1.0 $\mu\text{g/kg/d}$
Iodide (I)	Withhold for the first 3 months of TPN Premature: 1.0 $\mu\text{g/kg/d}$
Molybdenum (Mb)	Withhold for the first 3 months of TPN Decrease amount or withhold with complication of renal dysfunction Premature/term: 0.25 $\mu\text{g/d}$
Iron (Fe) as dextran or ferrous citrate	May withhold until 2 months of age (Premature), 3 months of age (Term) and considered for infants who do not receive regular blood transfusions. Premature/Term: 1.0-2.0 $\mu\text{g/kg/d}$
Fluoride (Fl)	Withhold for the first 3 months of TPN then provide premature with 500 $\mu\text{g/kg/d}$ Solutions may be contaminated with fluoride

ment of premature babies. Instead, adequacy is determined by actual amounts of protein (g/kg) in addition to energy (kcal/kg) as described below.

Carbohydrate

Carbohydrate is delivered in 2.5 to 70% dextrose solutions that provide 3.4 kcal/g. Glucose is the energy source for all cells and is essential for the central nervous system (CNS), erythrocytes, and other tissues. To ensure a stressed premature infant receives an adequate but not excessive amount of glucose, 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;⁴⁹ 8 to 10 mg/kg/min in ELBW infants provides 40 to 50 kcal/kg/d and preserves carbohydrate stores.⁵⁰

Frequently smaller, more unstable premature infants develop hyperglycemia due to decreased insulin production and insulin resistance. Glucose infusion rates (GIR) for these babies may need to be limited to 4 mg/kg/min or less, while larger preterm infants or term infants can often tolerate up to 8 mg/kg/min initially.^{42,51} Once the GIR supports acceptable serum glucose values, it is advanced in a gradual, stepwise fashion (0.5 to 1 mg/kg/min) to a

Table 3. Amounts of Trace Minerals Recommended for Term and Preterm Infants in Total Parenteral Solutions (TPN)^a

Trace Element	Term ($\mu\text{g/kg/d}$) ASCN (1988)	Preterm ($\mu\text{g/kg/day}$)		ASCN (1988)
		Consensus recommendations (1993)		
		Transitional (first 2 weeks of life)	Stable (>2 weeks old)	
Chromium ^b	0.20	0-0.05	0.05-0.2	0.2
Copper ^{c,d}	20	0-20	20	20
Iron ^e	—	0-200	100-200	—
Flouride ^f	—	—	—	—
Iodide	1.0	1.0	1.0	1.0
Manganese ^c	1.0	0-0.75	1.0	1.0
Molybdenum ^b	0.25	0	0.25	0.25
Selenium ^b	2.0	0-1.3	1.5-2.0	2.0
Zinc ^g	250	150	400	400

^aReprinted with permission from Denne et al.⁴² Recommendations are those from the American Society of Clinical Nutrition (ASCN), Subcommittee on Pediatric Parenteral Nutrition Requirements, from the Committee on Clinical Practice Issues, 1988,²⁵ and Tsang et al.²⁶

^bRenal dysfunction can cause toxicity.

^cImpaired biliary excretion can cause toxicity.

^dGreater amount (40 $\mu\text{g/kg/d}$) is suggested for VLBW infants without cholestasis.^{18,32}

^eEstimated daily IV requirement is 100 $\mu\text{g/kg}$ for term infants and 200 $\mu\text{g/kg}$ for preterm infants.

^fOnly consider with TPN longer than 3 months as solutions may be contaminated with flouride; a dosage of 500 $\mu\text{g/kg/day}$ for preterm infants.

^gThe only trace element recommended on day 1 of TPN. When TPN is required >3 months, decrease dosage to 100 $\mu\text{g/kg/d}$.

suggested maximum glucose oxidative rate for neonates of 12 to 13 mg/kg/min to support growth and maintained there unless serum glucose values change significantly.^{39,52}

In most situations, a glucose concentration above 12.5% is not necessary.⁴² However a higher glucose concentration may be needed when fluid intake is severely restricted or when the amounts of protein and/or fat are limited.⁴² Excessive carbohydrate delivery above the amount that can be oxidized for energy and glycogen storage will lead to an increase in basal metabolic rate,⁵³ fat deposition, cholestasis,⁵⁴ hepatic steatosis,⁵⁵ or overfeeding as described by the provision of energy in excess of needs for normal growth.⁵⁵ GIR greater than 26 mg glucose/kg/min may contribute to infiltrates of fat in the liver.⁵⁶ Practically speaking, a premature infant who is able to tolerate a fluid volume of 140 to 150 mL/kg/d will meet macronutrient needs for growth if provided a dextrose concentration of 10% (~10 to 10.5 mg glucose/kg/min) or 12.5% (~12 to 13 mg glucose/kg/min); if the protein and fat intakes are both at least 3 g/kg/d, the solutions will approximate 80 to 95 and 100 to 105 kcal/kg/d respectively. Additional dextrose delivery from intravenous medication needs to be taken into account when calculating the GIR for individual babies.⁵⁷ To optimize the amount of fluid available to provide nutrition to the small premature baby while trying to maintain a euglyce-

mic state, it may be necessary to double-concentrate the continuous infusions that deliver medications and run them at lower rates. Consultation with the pharmacist can ensure that these lower medication infusion rates are adequate for optimum clinical effectiveness of the intravenous drug. If further fluid restriction or dextrose limitation is necessary, other options to optimize delivery of glucose are to (1) minimize the amount of fluids delivered with intravenous medications or needed to keep a line patent and (2) decrease the dextrose concentration of the intravenous medication solution so that slightly more dextrose can be delivered from the TPN solution and/or (3) increase the dextrose concentration of the intravenous medication solution to equal that of the TPN solution while ensuring glucose tolerance.

Protein

Protein is delivered as free amino acids in solutions developed specifically for pediatric patients with an amino acid profile that is higher in amounts of amino acids believed to be conditionally essential for premature infants (aspartate, glutamate, taurine, and tyrosine) and with lesser amounts of glycine compared with adult solutions. Cysteine is also considered as conditionally essential in premature infants due to a theoretical insufficiency of enzymatic activity for the conversion of methionine to cysteine.

Table 4. Amounts of Vitamins Recommended for Term and Preterm Infants in TPN Solutions Compared to Prescribed Dosages of MVI-Pediatric^a

Vitamin	Term (dose/d)		Preterm (dose/kg/d)		
	ASCN (1988)	MVI-Pediatric (1 vial; 5 ml)	Consensus recommendations (1993)	ASCN (1988)	MVI-Pediatric (40% of vial; 2 ml/kg/d) ^b
Fat soluble					
Vitamin A (IU)	2,300	2,300	700-1,500	1,640	920
With lung disease	—	—	1,500-2,800	—	—
Vitamin D (IU)	400	400	40-160	160	160
Vitamin E (IU)	7.0	7.0	3.5 (max = 7)	2.8	2.8
Vitamin K (μ g)	200 ^c	200 ^c	6-10 (300 at birth)	80	80
Water soluble					
Vitamin B ₆ (μ g)	1,000	1,000	150-200	180	400
Vitamin B ₁₂ (μ g)	1.0	1.0	0.3	0.3	0.4
Vitamin C (mg)	80	80	15-25	25	32
Biotin (μ g)	20	20	5-8	6.0	8.0
Folic acid (μ g)	140	140	56	56	56
Niacin (mg)	17	17	4.0-6.8	6.8	6.8
Pantothenate (mg)	5.0	5.0	1-2	3.0	2.0
Riboflavin (μ g)	1,400	1,400	150-200	150	560
Thiamin (μ g)	1,200	1,200	200-350	350	480

^aReprinted with permission from Denne et al.⁴² Recommendations are those from the American Society of Clinical Nutrition (ASCN), Subcommittee on Pediatric Parenteral Nutrition Requirements, from the Committee on Clinical Practice Issues, 1988,²⁵ and Tsang et al.²⁶ Needs of the Preterm Infant: Scientific Basis and Practical Guidelines. Baltimore, Williams These recommendations are currently not achievable because no ideal IV vitamin preparation is available for preterm infants; 40% of a vial (2 ml/kg/d) of MVI-Pediatric (Armor, USA, Rover, Canada) is the closest intake that can be achieved at this time.

^bMaximum not to exceed a dosage of 5 ml/d.

^cThis does not include the 0.5-1.0 mg of vitamin K given at birth, as recommended by the American Academy of Pediatrics.⁵⁶

Cysteine is not contained in amino acid solutions because of problems with long-term stability and addition as a separate solution as the solution is prepared is compatible and is needed to meet recommendations.⁵⁸ Cysteine hydrochloride supplements may cause metabolic acidosis and therefore TPN solutions may need to be buffered with acetate. The amino acid profiles of Aminosyn PF (Abbott Laboratories, North Chicago, IL) and Trophamine (B. Braun, Irvine, CA), two pediatric solutions available in the United States, are compared with profiles of adult preparations in Table 6. Further discussion about pediatric formulations and specific amino acid needs for premature infants are available.^{42,59-61} Other special amino acid solutions designed specifically for patients with hepatic failure, renal disease, and higher protein needs have not been studied in infants and therefore are not recommended for infants. Amino acid profiles of these solutions are summarized elsewhere.⁶⁰ Amino acid solutions provide 4.0 kcal/g of protein. In neonates, protein accretion is thought to more adequately reflect nutritional status than weight gain.²⁸ Studies in preterm babies who receive TPN suggest that protein accretion occurs by amino acid stimulation of protein synthesis rather than by suppression of protein

breakdown.^{5,62} Protein requirements for the neonate tend to be inversely related to gestational age and size due to more rapid growth rates and greater protein losses in the smaller, more premature infants.⁶³ The early provision of protein is critical to attain positive nitrogen balance and accretion, as premature babies lose ~1% of their protein stores daily.⁶⁴ Studies suggest the provision of at least 1 g/kg/d of amino acids can decrease catabolism.^{4,46,65} ELBW infants can generally receive 2 g/kg/d of amino acids on the first day of life.^{4,66} A classic study by Zlotkin and coworkers⁴⁴ suggests a protein goal of at least 2.7 to 3.5 g/kg/d with adequate energy of greater than 70 nonprotein kcal/kg/d to approximate in utero nitrogen accretion. Studies show that early and aggressive provision of 3 grams protein/kg/d and adequate nonprotein energy within the first few days of life is safe and effective at providing protein to meet accretion needs and facilitate intrauterine growth rates.^{3,42} Protein requirements may be increased to counter catabolic or excretory losses in clinical conditions such as postoperative wound-healing, chronic lung disease treated with steroids, lymphatic injury with a sustained chyle leak, and/or during sustained periods when infants require limited or withheld enteral feeding or higher amounts of protein for catch-up growth.^{35,39,65-67}

Table 5. Examples of Parenteral Nutrition Prescriptions That Include the Percent Dextrose, Daily Volume (mL/kg), Protein (g/kg), Fat (g/kg), Energy (kcal/kg), Glucose Infusion Rate (GIR), Nonprotein Calorie to Nitrogen Ratio (NPC:N), and Percent of Energy from Protein, Fat, and Carbohydrate

7.5% Dextrose @ 120 mL/kg, 3.5 g protein/kg, 3 g fat/kg = 75 kcal/kg GIR of 6 mg/kg/min, NPC:N@110:1; 19% Protein, 40% Fat, 41% Carbohydrate
10% Dextrose @ 100 mL/kg, 3.0 g protein/kg, 3 g fat/kg = 76 kcal/kg GIR of 7 mg/kg/min, NPC:N @ 135:1; 16% Protein, 39% Fat, 45% Carbohydrate
12.5% Dextrose @ 100 cc/kg, 3.0 g protein/kg, 3 g fat/kg = 85 kcal/kg GIR of 9 mg/kg/min, NPC:N @ 150:1; 14% Protein, 36% Fat, 50% Carbohydrate
12.5% Dextrose @ 130 cc/kg, 3.5 g protein/kg, 3.5 g fat/kg = 105 kcal/kg GIR of 11 mg/kg/min, NPC:N @ 160:1; 13% Protein, 34% Fat, 53% Carbohydrate
12.5% Dextrose @ 140 cc/kg, 3.0 g protein/kg, 3.0 g fat/kg = 100 kcal/kg GIR of 12 mg/kg/min, NPC:N @ 185:1, 12% Protein, 30% Fat, 60% Carbohydrate

To date, there is no evidence from randomized trials to support the routine use of parenteral or enteral glutamine supplementation in preterm infants.^{68,69} Studies in critically ill adults suggest that glutamine supplemented amino acid solutions may reduce mortality, improve nitrogen balance, and reduce the incidence of clinical infection.⁵⁵

Fat

Fat is delivered as lipid emulsions of neutral triglycerides (TG), primarily polyunsaturated fatty acids (PUFA) that are essential for normal growth and development, retinal development and function, brain development, and cell structure and function. In the United States, available solutions consist of long chain triglycerides and egg yolk lecithin emulsions derived from either 100% soy oil (Intralipid, Kabivitrum Inc., California and Stockholm and Liposyn III, Abbott Laboratories, Montreal) or a 50% soy and 50% safflower mixture (Liposyn II, Abbott Laboratories). Lipid emulsions provide a concentrated source of energy, 10 kcal/g of fat that enables the provision of nutrient intakes to premature infants within limited fluid volumes to achieve in utero rates of growth. Adequate administration of lipids prevents essential fatty acid deficiency, promotes positive nitrogen balance, and optimizes energy utilization. Solutions with 100% soy oil provide

54% of energy as linoleic acid and 8% as linolenic acid whereas the 50% soy and 50% safflower mixture provides 66% of energy as linoleic acid and only 4.2% of energy as linolenic acid. Recommendations to prevent essential fatty acid deficiency in premature infants are to provide at least 80 kcal/kg/d, which will limit utilization of stored fat for energy and thus preserve docosahexanoic acid (DHA) and arachadonic acid (ARA) stores.^{70,71} An intake of linoleic acid is recommended at 4 to 5% of total calories and that of linolenic acid at 1% of total calories.^{70,72} Based on a minimal intake of 80 kcal/kg, a fat intake of 0.6 to 0.8 g fat/kg will meet linoleic acid recommendations and 1.0 g fat/kg will meet linolenic acid recommendations from a solution that is 100% soy. Because the 50% soy and 50% safflower mixture provides less linolenic acid, the amount required to meet recommendations is 2.0 g fat/kg. Lipid emulsions are available as 10 and 20% solutions; 20% solutions require less fluid volume and provide a lower phospholipid-to-triglyceride ratio and therefore are recommended for premature infants.

Outside the United States, lipid solutions are available that contain shorter chain and monounsaturated fats from olive oil and medium chain triglyceride (MCT) oil. When compared with the longer chain triglyceride solutions, those that contain MCT and olive oil provide a greater vitamin E to polyunsaturated fatty acid ratio, lower serum cholesterol, and are hydrolyzed more rapidly, but they may not be as effective in promoting protein accretion.⁷³

A 20% IV fat emulsion is typically started at 0.5 to 1 g fat/kg on the first day of life generally at the same time amino acids are started to prevent the occurrence of essential fatty acid deficiency as well as to provide a more generous source of calories. The lipid emulsion is advanced as tolerated in incremental rates of 0.5 to 1 g/kg/d to a typical maximum of 3 g/kg/d.⁵⁶ In a balanced TPN solution, this generally approximates about 30% of total calories from fat. Fluid-restricted, growth-compromised patients or those limited to peripheral line access may require as high as 3.5 to 4 grams fat/kg/d to achieve adequate energy for growth and protein sparing. This intake is appropriate as long as the fat intake remains less than 60% of nonprotein calories.⁷⁴

In neonates, the maximal removal capacity of plasma lipids was shown to be 0.3 g/kg/h.^{74,75} To minimize the occurrence of hyperlipemia, bilirubin displacement, and respiratory compromise, lipid infusion rates less than or equal to 0.15 g/kg/h are recommended to span over 24 hours. The delivery of 3 g/kg/d of a 20% lipid emulsion equates to an infusion rate of 0.125 g/kg/h.^{56,76} Premature infants have limited fat stores and lipoprotein lipase concentrations that may hinder their ability to clear plasma lipids following infusions of intravenous fat.³ The use of heparin dosing at 0.5 to 1 units/mL of TPN solutions, with

Table 6. Amino Acid Content of Selected Solutions: A Comparison of Estimated Amino Acid Requirements to a Protein Intake of 3.0 g/kg/day^a

Amino Acids	Estimated Requirements (mg/kg/d)	Pediatric Solutions 10%		Adult Solutions 10%	
		Aminosyn PF (mg/kg/d)	Trophamine (mg/kg/d)	Aminosyn (mg/kg/d)	Travasol (mg/kg/d)
Essential term and preterm					
Isoleucine	180-200	228	246	216	180
Leucine	240-400	360	420	282	220
Lysine	120-168	203	246	216	174
Methionine	15-72	54	102	120	120
Phenylalanine	100-144	128	144	132	168
Threonine	60-144	154	126	156	126
Tryptophan	30-36	54	60	48	54
Valine	168-200	202	234	240	174
Histidine	50-58	94	144	90	144
Arginine	122-250	368	360	294	346
Considered essential preterm					
Aspartic acid	—	158	96	0	0
Glutamic acid	12.5-48	186	150	0	0
Cysteine	72-85	0	<5	0	0
Tyrosine	12.5-144	12	72	13	12
Taurine	—	22	7	0	0
Nonessential					
Alanine	100-144	209	162	384	620
Glycine	100-396	115	114	276	310
Proline	50-192	244	204	258	204
Serine	100-166	149	114	126	150

^aAdapted from Sapsford.⁵⁹

a maximum of 137 units/d, can facilitate lipoprotein lipase activity to help stabilize serum triglyceride values.^{39,77}

Lipids may be restricted in patients with hyperbilirubinemia in minimum amounts that will provide only the essential fatty acids. Some clinicians will reduce or withhold lipids if rising bilirubin trends approach levels requiring exchange transfusions. Because both lipids and bilirubin are transported in the blood by albumin, lipids competing for binding sites on albumin may result in insufficient binding of bilirubin to facilitate excretion.⁵⁷ Persistently high bilirubin values may increase the risk of kernicterus from the deposition of bilirubin in brain cells. A free fatty acid to albumin ratio (FFA:albumin) greater than 6:1 is thought to be clinically significant.^{66,78}

Clinical Monitoring of Nutrient Adequacy, Compatibility, and Tolerance of TPN Solutions

Accurate and routine monitoring of growth measures is necessary to prevent over- or undernutrition from TPN support. Further, routine monitoring of solution compatibility and tolerance is required to prevent morbidity.

Growth

Intrauterine growth rates approximate 10 to 21 g/kg/d for weight depending on gestational age, 0.9 to 1.1 cm/wk for length, and 0.7 to 0.9 cm/wk for head circumference.^{79,80} Weekly lengths and head measurements, in addition to daily weights, are important to ensure that overall growth is occurring and not simply weight gain.⁸¹ Although accurate and reproducible lengths are more difficult to obtain among clinicians, they are a better indicator of lean body mass and not influenced significantly by edema.⁸⁰ Head growth correlates with increase in brain mass, therefore it is common to see a rapid increase during catch-up growth.⁸² For infants to grow optimally, ongoing assessment of growth in relation to daily estimates of nutrient intake is necessary. It is critical for practitioners to be cognizant of the actual amount of TPN that is delivered to a patient and not to assume that it approximates 100% of what is ordered. Often, actual nutrient intakes are significantly less than intended intakes because medications that are incompatible with TPN solutions are administered in separate intravenous solutions with TPN delivery inter-

rupted once or several times during the day. Quantification of TPN delivery warrants investigation when babies experience poor growth despite the TPN order that prescribes adequate calories, protein, vitamins, and minerals to support needs. Actual intakes may also be overestimated when TPN scripts are based on body weights that are not current. See the example of actual intake presented in Table 7.

Fluid Restriction

Premature infants with patent ductus arteriosus or other cardiac disease, chronic lung disease, or oliguria require some degree of fluid restriction. This limitation provides a challenge in tinier premature babies born with the lower nutrient stores, who also require more protein and minerals for a greater, more sustained rate of catch-up growth. The use of central lines such as PICCs (peripherally inserted central catheters) and PCVCs (percutaneous central venous catheters) allows clinicians to approach the infants' needs during fluid restriction. In these situations, the TPN solution is often concentrated to the maximum osmolarity and precipitation limits for optimal provision of energy, protein, and minerals to support growth. Restrictions of one or more macronutrients may result in an uneven distribution of calories between protein, carbohydrate, and/or fat. For example: an ELBW infant who requires dexamethasone therapy may experience transient hyperglycemia and necessitate a decrease in carbohydrate with compensatory increases in protein or fat needed to provide sufficient energy. An inappropriate balance of parenteral nutrition can result in inefficient utilization of protein and nutrients.^{42,83} Even with maximally concentrated TPN solutions, nutrient intakes adequate to support growth may not be achieved in some infants. With consistently poor growth over time, either reassessment of total fluid management and/or a change in the composition of fluids is needed from the neonatology team.⁸¹ Routine assessment of weight trends over time and careful monitoring of fluid intake and output that includes electrolyte balance and urine specific gravities will help to fine-tune fluid management. Fistula or ostomy losses increase fluid, mineral, and/or electrolyte needs and may require intravenous replacement.

Overfeeding

Premature infants with chronic lung disease may become stable medically over time and receive TPN in excess of requirements. This results in an increase in fat synthesis.⁸⁴ Although catch-up growth may be a goal of nutritional support in select infants, there are indications that a gradual, cautious approach to the advancing of

Table 7. An Example of How Actual TPN Delivered May be Overestimated

TPN for a 1.8-kg baby who receives:	100% delivery	85% delivery
10% dextrose	150 mL/kg/d	125 mL/kg/d
Energy (kcal/kg)	~95 kcal/kg	~80 kcal/kg
Protein (g/kg)	3.0	2.5
Fat (g/kg)	3.0	2.5
NPC:N of 170:1		

If this same 1.8-kg baby was prescribed TPN based on an initial weight of 1.5 kg and with the assumption of ~85% delivery, the baby's intake of energy and protein would be reduced further to 65 kcal/kg and 2.1 g protein/kg.

parenteral calories may lead to fewer clinical side effects associated with overfeeding. Overfeeding is associated with fatty infiltration of the liver, hyperglycemia, hypertriglyceridemia, increased metabolic rate, and electrolyte imbalance.^{54,77,85,86} In addition, overfeeding of total energy intake and with glucose may increase oxygen uptake and CO₂ production and retention in infants with lung disease^{39,84,87,88} or heart failure.^{39,89} Hypermetabolic and undernourished patients are thought to be most susceptible to these respiratory problems, while metabolically normal and nourished patients are not as adversely affected.⁵⁵

To avoid overfeeding, appropriate nutrition assessment and monitoring is strongly advised to ensure a balanced provision of nutrient needs relative to gestational age, medical presentation and diagnosis, degree of repletion indicated, current metabolic indicators, and prognosis.⁸⁶ Excessive and disproportional gains are likely indicators of overfeeding. Growth should be monitored by measures of weight and length, including board lengths if linear growth and proportional growth are a concern. Calculations of rates of growth compared with normative data, weight in proportion to length, and skinfold measures of subcutaneous fat may be indicated for babies born post-term having chronic conditions.

Tolerance/Complications

Protocols for tolerance assessment of TPN fluids vary among NICUs but each typically offers a suggested schedule for the routine monitoring of physical and biochemical measures. An example of a monitoring schedule is provided in Table 8. Daily weights, volume intake, and calculations of actual fluid and nutrient delivery, urine output, serum electrolytes, glucose levels, blood urea nitrogen (BUN), and serum creatinine provide indicators of substrate tolerance and hydration to aid in day-to-day man-

Table 8. Nutritional Assessment for Low Birth Weight Infants Receiving Total Parenteral Nutrition^a

Variable to be Monitored	Frequency
Fluid intake (mL/kg/d)	Daily
Nutrient intake (U/kg/d)	Daily
Energy intake (kcal)	
Protein intake (grams)	
Specific nutrient (U)	
Anthropometry	
Body weight (grams)	Same time each day
Length (cm)	Weekly
Head circumference (cm)	Weekly
Energy	
Urine glucose	Every void, then serially daily to weekly
Serum triglycerides	After dose changes or stress, then weekly
Protein	
Blood urea nitrogen (BUN)	After amino acid dose changes, then weekly
Albumin	Weekly to every other week
Prealbumin (transthyretin)	If low BUN/albumin
Minerals	
Ca, P, Mg	Ionized Ca daily for 1-3 days, then total Ca weekly Serum P daily until normal, then weekly Serum Mg daily until normal, then weekly
Alkaline phosphatase	Weekly
Na, K, Cl, CO ₂	Daily, then weekly
Other laboratories	
Conjugated bilirubin, alanine transaminase (ALT)	After 2 weeks, start every other week
Other assessments	2 months
Renal ultrasonography	

^aAdapted with permission from Schanler RJ. The low birth weight infant. In: Walker WA, Watkins JB, Duggan C, editors. *Nutrition in pediatrics: basic science and clinical application*. 3rd edition. Hamilton (ON): BC Decker Inc, 2003. p.491–514.¹⁸

agement decisions. Once a baby is clinically stable, electrolytes may need to be checked no more than twice each week.³⁹ Patients with a history of electrolyte instability or requiring chronic diuretic therapy will need more frequent monitoring. Premature infants have a relatively small blood volume (eg, 80 to 100 mL/kg), therefore the potential benefits of the information obtained are weighed against the risk of frequent blood sampling.

Hypoglycemia/Hyperglycemia

Premature babies are at risk of developing hypoglycemia due to limited glycogen reserves, with more premature or growth-restricted infants being at greatest risk.³⁹ Glucose needs are increased due to a relatively large surface area of metabolically active organs requiring energy,³⁹ with glucose infusion delivery rates based on weight and gestational age. Hyperglycemia is also a common occurrence in sick VLBW infants supported by TPN. Hyperglycemia is due in part to insulin resistance or to stress levels of cortisol and glucagon.³⁶ Persistently high serum glucose values can lead to glycosuria with an osmotic diuresis, complicating fluid management. The usual management for these complications is to reduce glucose concentration, although the delivery of adequate calories might be challenged. Due to the risk in variation of response, the use of insulin typically is reserved for those infants who do not respond to a reduction in glucose delivery or continue to experience higher than desired serum glucose levels.⁸³ Insulin given to VLBW and ELBW infants with hyperglycemia, controlled hyperglycemia, increased glucose delivery and energy, and increased weight gain.⁹⁰ Insulin given to infants <1,500 grams with hyperglycemia, controlled serum glucose levels, increased glucose delivery and ELBW infants without hyperglycemia decreases protein breakdown resulting in metabolic acidosis due to increased lactate levels.^{7,91} Therefore careful monitoring of blood glucose and acid-base status is essential when insulin is used.⁹¹ Moreover, bacteremia should be ruled out when hyperglycemia develops in a baby receiving TPN at a dextrose concentration previously tolerated.⁹²

Protein Status

The adequacy of protein intake is often determined with the monitoring of serum proteins; however, their usefulness is somewhat controversial. Through the first three months of life, premature infants have lower serum albumin, prealbumin, and retinol-binding protein levels than term babies.⁹³ Premature babies may experience decreased hepatic synthesis of plasma proteins and increased protein turnover.^{81,94} Furthermore, inadequate intakes of vitamin A and zinc may interfere with the ability of the liver to synthesize adequate retinol-binding protein.⁹⁵ Other influential factors on these acute phase reactants include steroids, acute stress, sepsis, liver disease, the presence of edema, and rapid growth,³⁹ making their interpretation as it relates to nutrition more challenging. If renal function and hydration are normal, BUN levels less than 5 mg/dL may indicate inadequate intravenous protein intake.⁹⁰

Blood urea nitrogen levels within normal limits without

acidosis have been reported with amino acid intakes of 3 g/kg/d.⁵ Urea is a metabolic by-product of protein oxidation and sometimes is used as a marker for amino acid intolerance. Elevated BUN values are thought to be consistent with higher rates of protein turnover and oxidation in premature infants and potentially in ELBW babies who are receiving inadequate calories.⁵ Some authors suggest that increases in BUN values are a direct reflection of increased amounts of available amino acids⁸³ and are evidence of efficient utilization and nitrogen retention.^{3,42}

Hyperlipidemia

Lipid intolerance may occur in infants who are premature, IUGR, septic, have liver disease, or are receiving steroids.⁹⁶ The catabolic effect induced by steroids may cause an increase in serum free fatty acids levels with a concomitant increase in triglyceride synthesis.⁹⁷ Elevations in serum triglycerides may also result from fat breakdown in response to cortisol, catecholamines, and cytokines released in infants who are metabolically stressed.⁸⁴ Although heparin helps to improve high serum triglyceride levels, it does not change the oxidation rate of fatty acids.⁹⁸ Elevations in serum triglycerides generally occur four hours after the initiation or increase in parenteral lipid.^{84,98}

High serum triglyceride levels (greater than 200 mg/dL) that occur with prolonged TPN have also been attributed to carnitine deficiency.⁹⁹ Carnitine is synthesized by the liver from methionine and lysine. Premature infants younger than 34 weeks' gestation have limited carnitine stores. Infants receiving TPN have no dietary source of carnitine. Therefore, these groups of infants may develop carnitine deficiency in as little as five days after birth.⁹⁹

Carnitine facilitates long chain fatty acid transport into the mitochondria for fatty acid oxidation^{100,101} and therefore parenteral supplementation may improve long chain fat metabolism in neonates.¹⁰² Studies suggest increased serum carnitine concentrations,^{103,104} improved lipid tolerance,^{102,104} weight gain, and nitrogen retention¹⁰³ in preterm infants who received 10 to 20 mg/kg/d of carnitine compared with unsupplemented groups. No studies were found demonstrating that carnitine deficiency resulted in lipid intolerance.¹⁰⁵ Higher dosing of carnitine at amounts of 48 mg/kg/d resulted in greater nitrogen excretion and slower growth rates in preterm infants compared with those receiving lower amounts.¹⁰⁶ In a more recent review of all randomized trials involving parenteral supplementation of carnitine in neonates for improvements in growth or lipid tolerance, no evidence was found supporting routine supplementation with carnitine.¹⁰⁷ Improved serum carnitine levels were noted over eight weeks. However, no clinically improved measures of growth, apneic episodes,

or length of hospital stay were observed in 80 premature infants less than 1,500 grams at birth who received intravenous carnitine at a dosage of 15 mg/kg within 96 hours of birth and 100 mg/kg of L-carnitine given enterally in divided doses when feedings were established.¹⁰⁸ The manufacturer of intravenous carnitine (Carnitor, Sigma-Tau, Gaithersburg, MD) suggests dosing between 20 to 50 mg/kg/d, although lower amounts between 2 and 10 mg/kg/d may improve serum levels without adverse clinical symptoms.^{100,106} Supplementation is particularly important with long-term TPN and PN and continued provision is suggested until enteral intake approximates 50% of energy required to support growth.¹⁰¹ A dose of two to five mg carnitine/kg/d is suggested with routine monitoring of serum levels at baseline and quarterly and then annually thereafter.¹⁰⁹ Serum analysis of carnitine includes measuring plasma total and free carnitine concentrations and acylcarnitine fractions. A calculated ratio of acylcarnitine-to-free carnitine greater than 0.4 suggests insufficiency.¹⁰¹

Cholestasis

If it is anticipated that TPN will be needed for longer than two weeks, it is prudent to obtain liver function tests, including a fractioned bilirubin, especially in ELBW infants to establish a baseline and repeat measures to document trends suggestive of cholestasis or liver disease.^{42,110,111} Elevations in serum alkaline phosphatase and direct bilirubin may be observed as soon as two weeks after initiating TPN.⁸⁶ A much earlier, although nonspecific indicator of cholestasis is gamma-glutamyl transpeptidase (GGT),⁸⁶ however its specificity is said to be improved when used with alkaline phosphatase.^{112,113} Rising direct bilirubins and transaminases are later indicators of cholestasis.^{54,85} Risk factors associated with the development of cholestasis include the withholding of enteral feeding, immaturity, sepsis, hypoxia, toxicities of amino acids such as methionine and trace elements including copper, chromium, and manganese,^{61,86,114,115} and excessive energy and dextrose intakes.¹⁰¹ Oxidation of TPN solutions by light,^{41,73,86,116,117} medications, and nutrient deficiencies of taurine, choline, fatty acids, and trace minerals^{86,118} have been associated with increased incidence of cholestasis.

The addition of taurine to pediatric amino acid products may help premature infants in the conjugation of bile salts and bile acid secretion.¹¹⁹ Copper and manganese are excreted in the bile and may contribute to hepatic toxicity when their removal from the liver is impaired due to limited bile flow.^{55,119-121} Because several studies suggest that manganese accumulation contributed to the severity of cholestasis or liver disease, some have not recommended providing manganese until a month following

TPN administration and closely following manganese serum levels.^{29,122} With an elevated direct bilirubin greater than 2 to 3 mg/dL,¹¹³ amounts of intravenous copper and manganese should be reduced or temporarily withheld.⁵⁴ Small amounts of enteral feedings, especially for infants who require long-term TPN, may help prevent cholestasis, since feedings enhance gastric motility and bile flow.^{86,101,123} Also, by offering enteral feedings, trace minerals (ie, copper and manganese) can be eliminated from TPN.

Cycling of TPN is suggested for infants who may require long-term TPN as it may reduce continuous, non-physiologic hepatic stimulation¹²⁴ and may help in visceral protein synthesis.¹²⁵ Periods “off” TPN allow the body to mobilize fat, possibly decreasing the likelihood of fatty liver and essential fatty acid deficiency.¹²⁶ The benefits of cycling TPN to decrease the occurrence of cholestasis is not conclusive^{126,127} and the limited glucose stores and glucose homeostasis in premature infants necessitate that the period of time when TPN is not administered be a maximum of three to six hours, depending on the infant’s size.¹²⁸ The use of choleretics such as Ursodiol (Actigall, Axcon Pharma U.S. Inc, Minneapolis, MN) in young children receiving TPN is suggested as a better treatment of cholestasis than phenobarbital (Luminal sodium, Abbott Laboratories, Abbott Park, IL).¹²⁹ Choleretics do not alter the progression of cholestasis and have not yet been proven to be an appropriate treatment for neonates.⁴² In most cases, the discontinuation of TPN and progression of enteral feedings result in a gradual improvement of cholestasis over weeks to months.

An increased risk for cholestasis in nonsurgical premature babies who received TPN for longer than three weeks was noted in a retrospective study in infants who received Aminosyn PF compared with similar babies who received Trophamine.¹³⁰ Those who received Aminosyn PF also were introduced to enteral feedings earlier and therefore this observation justifies a larger prospective study.

Osteopenia

Osteopenia is reported to be as high as 30% in studies of babies less than 1,500 grams at birth²⁰ primarily supported with prolonged TPN without appreciable enteral feedings. Occurrence results mainly due to the inability to deliver adequate amounts of calcium and phosphorus safely within a limited amount of parenteral volume. Other infants that are at risk include those with fluid or protein restriction during TPN administration, those treated with chronic diuretic therapy, and those with high ostomy output with increased loss of electrolytes and minerals (eg, magnesium, calcium, and sodium) important for adequate bone mineralization.^{12,81,113} An option for these babies

would be to consider the earlier use of separate dextrose and amino acid solutions with fat emulsions administered by “piggy-back” infusions, allowing for more optimal delivery of calcium and phosphorus compared with those in total nutrient admixtures.

The presence of bone disease or healing fractures is sometimes discovered on routine radiographs. Rib fractures can precipitate or aggravate respiratory instability^{131,132} and can impact linear growth potential.¹³³ Whereas collagen synthesis and skeleton growth require adequate calories and protein for bone formation, adequate calcium and phosphorus are needed for bone mineralization.¹³⁴ The addition of L-cysteine hydrochloride to acidify amino acid solutions enhances the solubility of calcium and phosphorus, yet does not approach the amounts needed by most premature infants, or approximately 100 mg/kg/d of calcium and 70 mg/kg/d of phosphorus.^{25,26} Parenteral vitamin D intakes of 30 IU/kg/d have been shown to maintain adequate vitamin D status in infants; the direct effect of this vitamin on bone mineralization in parenterally fed infants is not well established.¹³⁵ Medications that are commonly used in premature babies to increase calcium excretion and increase mineral needs include furosemide, xanthines, and dexamethasone.^{16,36,136} Anticonvulsants such as hydantoin and phenobarbital increase the turnover of vitamin D, cause decreased serum levels of calcium and magnesium, and, with chronic use, can lead to bone demineralization.¹³⁷ Disease states such as renal or liver disease increase the risk for osteopenia. To optimize mineral retention parenterally, a ratio of Ca:P of 1.3 to 1.7:1 by weight (mEq:mM) or 1.1 to 1.3 by molar ratio has been advocated.^{21,39,138} When energy and protein intakes support positive weight gain, amounts of calcium and phosphorus can be gradually increased in TPN solutions to meet solubility limits, while mineral intake can be maximized in solutions with an increase in amino acids to greater than 2.5% of the total volume. Mineral intake can also be increased with an increase in the amount of TPN fluids provided if medically feasible. Calcium and phosphorus solubility are discussed later.

A noninvasive wrist or long-bone film can aid in the diagnosis and treatment of osteopenia. Routine blood levels of alkaline phosphatase, phosphorus, and calcium are helpful in detecting signs of metabolic bone disease. Generally, alkaline phosphatase levels will be elevated and serum phosphorus levels will be lower in babies with osteopenia.²² Serum calcium levels are typically maintained within a normal range during osteopenia at the expense of bone,²² although the presence of acute or chronic acid–base disturbances can influence this usually tight control.^{139,140} The acid–base effect on ionized and total serum calcium levels is shown in Table 9.

Table 9. Acid–Base Effect on Ionized and Total Serum Calcium Levels^{139,140}**Total Calcium = Protein bound to Calcium**

80% of calcium is bound to albumin

↓ pH, decreases binding of calcium to serum protein

↑ pH, increases binding of calcium to serum protein

Acid–Base Effect on Ionized and Total Serum Calcium Levels¹⁴⁰ (Marshall, 1976)

Calcium Homeostasis	Ionized Calcium	Total Serum Calcium
Acute acidosis	↑	NL
Chronic acidosis	NL	↓
Acute alkalosis	↓	NL
Chronic alkalosis	NL	↑

Sepsis

Sepsis in premature infants who receive prolonged TPN is a serious risk that contributes to morbidity and mortality.¹¹³ One possible risk factor for coagulase negative staphylococcal bacteremia in NICUs has been attributed primarily to the intravenous administration of lipid emulsions.¹⁴¹ In contrast, other investigations have described sick VLBW infants with a lower incidence of coagulase negative staphylococcal bacteremia and who received significantly larger amounts of lipids and better total energy. These infants received TPN significantly earlier and for longer periods of time and therefore were more likely to be at or greater than the 10th percentile for weight or length by discharge.⁸ Infection appears to be more common with central line delivery; however, these babies tend to be the sickest and require prolonged TPN administration.¹⁴² Propensity for infections is also linked with overfeeding of glucose,¹⁴³ with hyperglycemia being a risk factor in infectious complications.^{55,144} Other risk factors for colonization of neonates in NICUs include the use of central venous catheters and the unclean hands of health care workers. The use of antacids and third generation cephalosporins and a delay in enteral feeding are thought to encourage colonization.¹⁴⁵ Infection is considered when formerly stable babies show clinical or metabolic signs of instability and feeding intolerance.⁵⁴

Flowsheets, Protocols, and Order Sheets

The daily routine of nutrition screening and assessment of infants in a NICU requires ongoing summaries of nutrient intake information, including TPN prescriptions. Trends in growth and current laboratory values and med-

ications help to complete a comprehensive overview of each patient's clinical management and progress. The information for screening can be collected on "worksheets" that allow for routine calculations of current or future projected intakes based on nutrition support orders and current weights. These calculations can then be compared with accepted published recommendations for nutritional intake and growth.^{26,44,46,146-149} The organized format of most nutrition worksheets will allow the clinician to easily identify the need for intervention or further investigation and can be used as a reference when nutrition and growth issues are discussed with the health care team in a busy NICU. These data summary sheets serve as a tool that assists with documentation of nutrient intake and growth in routine chart notes, aids in responding to nutrition consultation, and helps in providing information related to an infant's entire nutritional history to ensure continuity of care.

Raw data also can be summarized for retrospective or prospective evaluation of care to document the ability to meet specific outcomes and identify needed nutrition management changes.¹⁵⁰ Electronic database systems such as Neodata NICU Patient Data System (Metasoft Systems, Inc, Charlottesville, NC), or Neonova Nutrition Optimizer (Ross Products Division of Abbott Laboratories, Columbus, OH) are examples of programs that help organize the presentation of nutrition information and may help to decrease errors in calculations and the reporting of information. Menu-driven, pop-up, or summary screens within these programs allow for the efficient review of macronutrients and additives within TPN fluids for assessment of nutrient intake. These programs may also include graphing capabilities for assessment of growth over time. The effectiveness of any nutrition management changes may lead to the development and use of specific care maps, protocols, and practice guidelines for more predictable delivery of clinical care to achieve best practice outcomes, including those for the ordering, delivery, and management of TPN.

Strategies to decrease variation and improve nutrition outcomes in NICU patients include routine reference to a treatment protocol that serves as an education resource and guideline to clinicians and students for the initiation and advancement of the delivery of TPN on a day-to-day basis. Information that is emphasized in many protocols includes suggestions about site access, central versus peripheral routes, energy and protein goals, and the initiation and advancement of fluid, carbohydrate, protein, and fat components, including specific amounts of electrolytes, major minerals, trace minerals, and vitamins. Other helpful information relates to the discontinuation of certain trace minerals in specific clinical circumstances and factors that affect the solubility limits of calcium and phosphorus. A

guide for laboratory monitoring of TPN solution tolerance as well as general guidelines on when and how to transition to enteral feedings are routine components of feeding protocols.

Calcium and Phosphorus Solubility

The generous calcium and phosphorus requirements of premature infants necessary to mimic accretion rates in utero far exceed compatibility limits of TPN solutions, with precipitation leading to embolisms or death.¹¹⁵ Mineral precipitation is directly affected by solution temperature, hang time, pH, dextrose concentration, the presence of lipids within the solution, and the addition of calcium and phosphorus in close sequence.¹⁵¹ Higher concentrations of amino acids, the addition of cysteine,⁴² and larger volumes of TPN lower the risk of precipitation. Compatibility curves are available to predict the solubility of minerals in TPN solutions with differing amino acid profiles.¹⁵¹⁻¹⁵³ Babies with higher mineral needs are ELBW and VLBW infants who require prolonged periods of TPN, those with osteopenia, healing fractures, or severe and sustained fluid restrictions. For these infants the most optimal delivery of minerals is from a dextrose/amino acid solution separate from a lipid solution that is infused through a different access site. Infusion of lipid emulsions into an amino acid/dextrose mixture via Y-site administration has been reported to increase the risk of calcium and phosphate precipitation as it increases the pH.¹⁵³ The following two-part equation offers a quick and simple method for estimating calcium and phosphorus precipitation factors in total nutrient admixtures based on the concentration of amino acids, volumes to be delivered within a 24-hour period, and moderate magnesium (Mg) dosing:

1. Calculate the final amino acid concentration of the TPN solution:

$$\left[\left(\frac{\text{g/kg/d amino acids}}{\text{mL/kg/day ordered}} \right) \times 100 \right] = \text{ \% }.$$

2. Calculate the calcium (Ca)–phosphorus (P) precipitation (PPT) factor:

- a. $\left[\left(\frac{\text{mEq/kg/d Ca} + \text{mmol/kg/d P}}{\text{mL/kg/d ordered}} \right) \times 1,000 \right] = \text{PPT factor}.$

- b. The following PPT factors are maximum guidelines for given amino acid concentrations.

Amino acid %	PPT factor
≤2.5%	≤26 with Mg < 20 mEq/L
>2.5%	≤35 with Mg < 20 mEq/L

Example. TPN prescription is written to provide 110

mL/kg of 7.5% dextrose with three grams of amino acids and fat/kg; the clinician desires to prescribe 1.8 mEq/kg Ca and 1.5 mMol/kg P.

1. Amino acid concentration: 3 g/kg amino acids/110 mL/kg total solution = 2.7%
2. PPT factor:

$$\frac{1.8 \text{ mEq/kg Ca} + 1.5 \text{ mMol/kg P} \times 1000}{110 \text{ mL/kg}} = 30$$

In this example, the calculated PPT is less than 35, and the amino acid concentration of the solution is greater than 2.5%, therefore the desired calcium and phosphorus amounts should fall within acceptable solubility limits as defined by these guidelines. The need to maintain a neutral final parenteral solution may also limit the amount of calcium and phosphorus that can be added. A solution that has unequal amounts of anions and cations can become unstable. A clinical situation where this becomes an issue is when a baby requires only a small amount of sodium or potassium in the TPN solution (possibly because of the need to better manage serum levels by using IV boluses), but a maximum amount of phosphorus in an attempt to correct hypophosphatemia. An inability to match a small amount of cation to a larger amount of anions in this example would limit the amount of phosphorus available to put in the solution.

Line Access for TPN Delivery

Most premature infants require TPN either peripherally or centrally while enteral feeding is established. Route of TPN delivery depends on energy needs, venous access, anticipated duration of support, and potential risks. Peripheral access can be achieved through a cannula placed in the smaller veins of the scalp, hands, arms, or feet.¹⁵⁴ Peripheral lines are not able to safely accommodate hyperosmolar solutions and therefore limit the amount of energy that can be provided. Peripheral lines are reserved for short-term or supplemental nutrition, generally for as long as two weeks.¹⁵⁵ Peripheral catheters are more prone to infiltration¹²³ and thrombosis.²⁸ Some caregivers advocate heparin administration in peripheral lines for infants younger than 26 weeks' gestation to help maintain patency²⁸ and prevent sclerosis.¹⁵⁶ Central access is used when TPN is needed for a longer or undetermined period of time or when peripheral access is not an option. It is common practice for infants weighing less than 1,200 grams at birth to receive the majority of nutrition support for the first three weeks through a central line.¹ Central lines allow greater ability to provide adequate energy and protein to promote growth and lean body mass accretion.

Central access implies that the catheter tip is placed in the central circulation, often at the junction of the superior vena cava and right atrium, though exact placement may vary.^{56,154,157} Peripherally placed central catheters are popularly referred to as PICCs and PCVCs. These catheters require insertion using a needle through the skin into a peripheral vein and threaded into the central circulation.¹⁵⁴ PICCs have replaced tunneled and nontunneled catheters for central access, as there have been fewer complications.^{39,54,158,159} Umbilical venous catheters (UVC) and umbilical arterial catheters (UAC) are also used to provide central access and nutrition. Due to risks of infection and formation of thrombi, UVCs are typically removed within a week of placement.³⁹

The most serious complication of central lines is sepsis, specifically with PCVCs. The advantage of PCVCs is that they allow immediate central access with single, double, or triple lumens, making it possible to infuse different solutions or medications simultaneously. This increase in catheter site access also increases the risk for sepsis,¹⁵⁴ with ELBW infants at highest risk.¹⁶⁰ However, the use of PCVCs is not an independent risk factor for bacteremia in VLBW infants.¹⁶¹ Temporary PCVCs may be indicated for short-term use in a hospital setting.¹⁶² PICC lines tend to be a more popular choice in the provision of nutrition to the small premature infant.^{113,163} Complications with these catheters include thrombosis in lines without heparin and skin infiltration. Routine observation and frequent sterile dressing changes help to lower these risks.¹¹³

Osmolarity

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. Osmolality refers to the number of particles per weight of water in kilograms and is typically used to describe enteral feedings and a standard in describing blood.⁸⁵ Osmolarity refers to the number of millimoles of liquid or solid in a liter of solution and is the preferred term for TPN.⁸⁵ To avoid irritation to the veins, The American Society for Parenteral and Enteral Nutrition (ASPEN) recommends limiting the osmolarity of peripheral solutions to 900 mOsm/L to lower the risk of phlebitis due to infiltration.¹⁶⁴ To minimize this risk, peripheral dextrose solutions should be limited to 12.5% or less. Admixtures of lipid emulsion together with the amino acid and dextrose solutions offer additional protection to the peripheral venous endothelium against phlebitis or potential loss of the access site by lowering the osmolarity of the solution.^{156,165} Therefore, more nutrient dense solutions

are possible that facilitate better nutrient intake and growth rates in sick premature infants. With central access, solutions greater than 1,000 mOsm/L are acceptable. The following example uses sample osmolarity calculations of nutrient mixtures and their projected delivery to meet 900 and 1,100 mOsm/L limitations when central access is not an option. Osmolarity can either be measured in a laboratory or estimated using the following guidelines:

- For amino acids: Multiply the percent concentration by 100; (amino acid solutions contribute ~100 mOsm/L for each 1% final concentration in the TPN solution).
- For dextrose: Multiply the percent concentration by 50; (each 1% concentration of dextrose contributes approximately 50 mOsm/L in the TPN solution).
- For lipid and electrolytes: Multiply the number of grams or milliequivalents by the following factors (Lipid $\times$ 1.7 mOsm/g, Calcium $\times$ 1.4 mOsm/mEq, Magnesium $\times$ 1.0 mOsm/mEq, Sodium $\times$ 2.0 mOsm/mEq, and Potassium $\times$ 2.0 mOsm/mEq), then divide by total volume to arrive at percent concentration.
- Convert % concentration of current volume to % concentration/L.
- Sum the osmolarities/L from dextrose, protein, lipid, and electrolytes for an estimated value.

Example. Central TPN solution for a 1.2-kg baby that provides:

12.5% dextrose @ 140 cc/kg/day: 12.5% solution $\times$ 50 mOsm/% = 625 mOsm/L

3.5 g protein/kg: 1.2 kg $\times$ 3.5 g/kg = 4.2 g/168 ml total volume = 0.025 $\times$ 100 = 2.5%; 2.5% solution $\times$ 100 mOsm/% = 250 mOsm/mL

3.0 g/kg fat: 3.0 g/kg $\times$ 1.2 kg $\times$ 1.7 mOsm/g = 6.1 mOsm

1.8 mEq/kg Calcium: 1.8 mEq/kg $\times$ 1.2 kg $\times$ 1.4 mOsm/mEq = 3.0 mOsm

0.25 mEq/kg Magnesium: 0.25 mEq/kg $\times$ 1.2 kg $\times$ 1 mOsm/mEq = 0.3 mOsm

2.0 mEq/kg Sodium: 2.0 mEq/kg $\times$ 1.2 kg $\times$ 2 mOsm/mEq = 4.8 mOsm

2.0 mEq/kg Potassium: 2.0 mEq/kg $\times$ 1.2 kg $\times$ 2 mOsm/mEq = 4.8 mOsm

19.0 mOsm/168 ml total volume = 0.113 $\times$ 1,000 = 113 mOsm/L

Sum: 625 mOsm/L dextrose + 250 mOsm/L protein + 113 mOsm/L lipid/electrolytes ~ 988 mOsm/L

Peroxides

Exposure to endogenous hydroperoxides are increased in premature infants who require TPN for an extended period of time and are related to hypoxia with reperfusion, acidosis,¹⁶⁶ increased oxidative stress from birth, mechanical ventilation, and infection, along with low amounts of

antioxidants.¹⁶⁷ This exposure is thought to have clinical relevance.⁵⁷ Light exposure, especially from phototherapy, generates peroxides and promotes solution degradation in TPN.¹⁶⁸ Animal studies suggest that TPN solutions exposed to light may contribute to liver disease.^{169,170} Lipid emulsions are readily oxidized when exposed to oxygen and light sources due to the high polyunsaturated fatty acid content. In vitro studies have shown vasoconstriction and platelet aggregation that may be a contributing factor to the development of chronic lung disease (CLD), necrotizing enterocolitis (NEC), or retinopathy of prematurity (ROP).^{171,172} Other clinical complications in premature infants linked with increased amounts of lipid peroxides include intraventricular hemorrhage (IVH) and leukomalacia.^{173,174} Currently available fat emulsions contain omega-tocopherol, which offers little protection against peroxidation,⁷³ whereas olive oil-based emulsions contain the more biologically active alpha-tocopherol, a more optimal form of antioxidant. Reports from animal studies suggest that, with increased availability of olive oil emulsions, peroxidation levels may decrease.^{175,176} The lowest levels of peroxidation were found in an emulsion of long chain and medium chain triglycerides.¹⁷⁷ There continues to be an absence of clinically relevant studies with respect to use of these mixtures in the neonate.

Multivitamins are thought to be the main source of peroxides in TPN.¹⁷⁸ Multivitamin preparations contain an unstable 5'-phosphate flavin mononucleotide as vitamin B₂ or riboflavin, which, when exposed to light, generates peroxides.¹⁷⁹ Vitamin levels may decrease due to photodegradation and result in free radical formation.⁵⁴ To minimize the exposure to peroxides, the use of yellow or orange tubing and covering of TPN bags has been suggested.¹⁸⁰ However, large and small bore tubing are not widely available in the United States.¹⁸¹ Some suggest wrapping the tubing and syringes in aluminum foil to shield from both ambient and phototherapy lights,⁷⁶ although others feel this is not practical for routine clinical use.^{180,181} Since ascorbic acid protects against light-induced peroxidation,¹⁶⁸ an alternative option is to provide parenteral multivitamin preparations containing the antioxidant vitamin C with lipid preparations and to administer them from a covered syringe and through dark tubing to prevent lipid peroxidation and minimize vitamin loss.¹⁸¹ Other benefits of adding the vitamins to the lipids include minimizing vitamin loss due to adsorption into the delivery system¹⁸² and the potential increased absorption of fat-soluble vitamins. A possible link between peroxidation of lipids, dextrose-amino acid solutions, or vitamins to morbidity is difficult to determine, however, it warrants further study particularly in ELBW and VLBW infants who are immunocompromised and may receive TPN for a sustained period of time.¹⁸¹ Only prospective trials will

allow clinicians to determine whether protection of TPN solutions from light, with the use of specialized tubing or syringes, will offer clinically important benefits to infants at highest risk to peroxide exposure.

Admixtures or Three-in-One Solutions

Admixtures or three-in-one solutions are TPN solutions that contain dextrose, amino acids, and lipid in the same solution. Advantages are a lower cost,¹⁸³ improved delivery of fat soluble vitamins,⁴⁰ lower osmolarity, and the need for only one line access site. Disadvantages include issues related to nutrient degradation, potential nutrient interaction and precipitation, microbial contamination, emulsion instability, and drug compatibility.¹⁸⁴⁻¹⁸⁸ The amino acids, carbohydrates, and electrolytes are relatively stable in admixtures with the exception of cysteine, which may cause a metal-sulfide complex with copper or calcium. Calcium and phosphorus precipitation have been discussed earlier. Other elements that may precipitate are selenium with ascorbic acid and ferric iron with phosphorus. The opaqueness of an admixture solution may obscure possible precipitations. Solutions become more unstable when they are extremely acidic or alkaline.^{189,190} Contents ranging from 20 to 70 mmol/L sodium, 20 to 50 mmol/L potassium, 2 to 3 mmol/L calcium, 1 to 3 mmol/L magnesium, and up to 9 mmol/L phosphate generally have no adverse effects on the admixtures studied for 24 to 48 hours.¹⁹⁰ An increased temperature may affect the stability of admixtures and cracking the emulsion. All solutions that contain lipid and dextrose require at least 0.5 grams amino acids in 250 mL solution. Because the IV fat particles will not pass through the standard 0.22- μ m filter, a 1.2- μ m filter is used with three-in-one solutions. This larger filter has been shown to be effective in filtering microorganisms.¹⁹¹ A useful summary on the arguments for and against filtration emphasized the positive benefits of precipitate and particulate removal, as well as the potential for microbial contamination and the possible retentive capacity of filters for micronutrients and drugs.¹⁹²

Transition to Enteral Feedings

The delayed introduction of enteral feedings was once a common practice for sick VLBW and ELBW infants in many NICUs. This practice was believed to be the best option, with the widespread use of TPN that permitted premature infants to recover from respiratory or hemodynamic instability from immature physiology. Enteral feedings were withheld to prevent any added risk to the development of NEC that might result from the stress of enteral substrate in an under-perfused gastrointestinal

tract, the use of certain medications, and the use of UACs. It is well recognized, however, that withholding enteral feeding can result in atrophy of the small intestinal mucosa⁸³ and diminished concentrations of gastrointestinal enzymes that accelerate maturation of intestinal motor activity in preterm infants.¹⁹³

Over the past decade, the use of providing small, sustained amounts of enteral feedings soon after birth to sick or stabilizing premature infants, has become a standard of medical, as well as nutritional care in many neonatal nurseries. Studies have shown that early minimal enteral feedings may decrease the time to reach full volume, can result in improved feeding tolerance,¹⁹⁴ and were not associated with an increased incidence of gastroesophageal reflux.¹⁹⁵ Minimal enteral feedings are generally defined between 5 and 25 mL/kg/d as early as the first few days of life that are typically maintained for 5 to 10 days before being advanced in volume. The transition to exclusive oral intake is gradual and may take as long as two or more weeks, depending on the protocol or advancement schedule used by individual nurseries, the management styles of the neonatology team, and individual clinical circumstances surrounding a particular infant. As enteral feedings are tolerated in larger volumes, the rate of TPN is generally decreased by the same volume. One can offer a slight energy and protein benefit if the concentrations of nutrients are maintained and not diluted within the TPN solution delivered at the slower rate.

Numerous studies over the past 15 years have examined the effects of minimal (eg, trophic) enteral feedings as an adjunct to TPN, with none suggesting an increased incidence in NEC, even with a UAC in place.¹⁹⁶⁻¹⁹⁸ Instead, the early exposure to enteral feedings suggested a decrease in the amount of time to reach full feedings, a decrease in the number of days that feedings were held due to clinical signs of feeding intolerance, a reduction in total hospital length of stay,^{39,198} and faster growth due to better total caloric intake compared with those who received TPN without enteral feedings. Fewer total days of administered TPN resulted in lower bilirubin levels and a decreased incidence of cholestasis.¹⁹⁹ Improved calcium and phosphorus retention and the maintenance of lower alkaline phosphatase levels have been found in premature infants fed small amounts of enteral nutrition compared with similar babies who remained NPO on TPN alone.¹⁹⁶ Another benefit of introducing small amounts of enteral feedings early in the nutritional management of the premature infant is that of a minimized incidence of metabolic bone disease. This practice is best considered as an induction of gut maturation and function rather than as a source of nutrition for the purpose of sustaining growth.¹⁹⁹

A more recent, randomized, controlled study suggested that the use of small feeding volumes decreased the oc-

currence of NEC in VLBW infants.²⁰⁰ The study protocol maintained feedings of 20 mL/kg/d for 10 days and then advanced volumes by 20 mL/kg each day thereafter until a volume of 140 mL/kg was reached. Parenteral nutrition was gradually decreased as enteral feedings increased. Infants less than 32 weeks' who were advanced more rapidly in feeding volumes experienced a higher risk for NEC compared with similar infants who were maintained with the low 20 mL/kg/d enteral volume during the first 10 days of feeding. Although larger enteral volumes led to greater amounts of plasma concentrations of gastrin and motilin, hormones important in gastrointestinal maturation, they did not speed the maturation of gastric motility. The absolute number of days to reach full enteral feedings and the incidence of feeding intolerance between the two groups did not differ.²⁰⁰

Choice of Enteral Feeding

The use of water as the initial feeding establishes gut motility, but does not provide a fed response.¹⁹³ Gastric inhibitory peptide, thought to exert trophic effects on the gut mucosa, did not increase in amount to feedings of water as it did formula.¹⁹⁴ Small intakes of sterile water have been utilized as early as one day after birth to prepare the gut for its intended use.¹⁹⁹ On occasion, pediatric oral electrolyte solutions are substituted as initial feedings, however, these contain approximately the same osmolality as full strength feedings without the benefit of enteral protein, and at an energy deficit to human milk or even half-strength premature formula. The advantages of using human milk versus commercially available premature formula for the premature or sick neonate are well known. Although limited nutritionally for the small premature infant, human milk has unique nonnutritive qualities that make it a superior choice. Human milk contains hormones, growth factors, antiviral and antiinflammatory agents, and other properties that help decrease the probability of sepsis and help to establish a healthy gastrointestinal flora.^{201,202} In contrast to human milk, commercial formulas designed for the hospitalized premature infant contain more protein, calcium, phosphorus, vitamins, and trace minerals compared with standard formulas designed for term infants. The amount of whey protein in these formulas approaches that of human milk, which is thought to help eliminate the occurrence of lactobezoars.²⁰³ Forty to 50% of the fat is in the form of medium chain triglycerides that are absorbed efficiently without the need for lipase or bile salts.

Protein hydrolysate feedings designed for term babies have in the past been used sparingly because of reduced bioavailability of nitrogen and minerals^{204,205} as well as lower amounts of vitamins and trace minerals compared

with preterm formulas. Hypoallergenic feedings facilitate faster gastric emptying,²⁰⁶ making these semielemental, lactose-free formulations an attractive option for ELBW infants, sicker babies, or those that have a history of feeding intolerance. A randomized study of premature babies fed either a hydrolyzed cow milk protein formula or premature formula suggested higher urea nitrogen levels in the hydrolysate group and similar growth and calcium and phosphorus values, suggesting no short-term impact on protein or mineral nutriture.²⁰⁷ The same investigators studied the use of hydrolyzed protein feedings and their impact on feeding tolerance as defined by duration to reach full feedings compared with a similar group of infants fed premature formulas. The results suggest that babies who received semielemental feedings reached full volume faster, despite more stooling and no difference in residuals.²⁰⁸

Until more randomized, prospective studies are done that carefully consider effects in protein and mineral status over longer periods of time, it is suggested that the use of semielemental feedings be transitional in nature or used as a stepping stone toward premature formulas and only in babies with demonstrated feeding intolerance. Continuation of a semielemental feeding in a premature baby for a sustained period of time will necessitate the assessment of nutrient adequacy. Factors to consider include gestational age and birth weight, nutrition history, current nutritional status, and volume of intake. Intakes of protein, calcium, phosphorus, vitamins including folic acid, and zinc would need to be assessed and supplementation options considered to meet recommended enteral intakes for premature babies.^{26,46}

Regardless of which feeding is selected, the goals of supporting premature infants' nutritional needs remain the same: to provide adequate protein, energy, vitamins, and minerals to allow for normal metabolism, composition of growth, and physical development comparable to that of their peers in utero. Many factors must be considered in making the best choices.

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Objectives: At the end of this article the readers will be able to: 1) Identify current recommendations for TPN in preterm neonates. 2) Identify strategies to improve neonate tolerance of TPN. 3) Identify complications of TPN use in the preterm neonate.

Article: Total Prenatal Nutrition

- The recommended maintenance fluid requirement for the neonate in a humidified environment is
 - 60-100 cc/kg/day
 - 80-120 cc/kg/day
 - 100-140 cc/kg/day
- Macronutrients include
 - calcium
 - glucose
 - sodium
- Energy needs are increased in the neonate who is
 - appropriate for gestational age (AGA)
 - large for gestational age (LGA)
 - small for gestational age (SGA)
- For the purpose of adding trace minerals to hyperalimentation, transitional premature infants are defined as those who are within the first
 - 72 hours of life
 - 7 days of life
 - 14 days of life
- The recommendation for adding zinc to hyperalimentation is
 - on the first day
 - after 2 weeks of total parenteral nutrition (TPN)
 - after 1 month of total parenteral nutrition
- A trace mineral that should be eliminated from TPN in the neonate with cholestasis is
 - chromium
 - manganese
 - selenium
- A trace mineral that should be eliminated from TPN in the neonate with renal disease is
 - copper
 - molybdenum
 - zinc
- The addition of iron to TPN can be delayed in the premature infant for
 - 4 weeks
 - 6 weeks
 - 8 weeks
- Overloading the under nourished neonate with iron increases the risk for
 - hyperbilirubinemia
 - polycythemia
 - septicemia
- Components of TPN that contain aluminum include
 - heparin sodium
 - potassium acetate
 - sodium chloride
- Compared to the preterm infant who weighs 1100 grams, the specific recommendation for vitamin supplementation in TPN for the very low birth weight (VLBW, <1000 grams) is
 - increased
 - the same
 - unknown
- An intervention to prevent the photodegradation of intravenous vitamins in TPN is the use of
 - fat soluble vitamins with lipids
 - microbore intravenous tubing
 - triple mix (protein, dextrose and lipids mixed in the same bag)
- A strategy to avoid excessive protein losses in the low birth weight (LBW) infant is the initiation of TPN within
 - 1 day of life
 - 3 days of life
 - 7 days of life
- The use of TPN is recommended in all preterm infants who cannot sustain a minimum of
 - 40 kcal/kg/day
 - 60 kcal/kg/day
 - 80 kcal/kg/day

15. Growth of the preterm infant is supported when the TPN provides

<u>Energy (kcal/kg/day)</u>	<u>Protein (grams/kg/day)</u>
A. 50	3.5
B. 70	3
C. 90	2.5

16. The overwhelming majority of glucose provided in TPN is consumed by the

A. brain
B. heart
C. red blood cell

17. The hepatic glucose production rate in the preterm neonate is

A. 4-6 mcg/kg/day
B. 6-8 mcg/kg/day
C. 8-10 mcg/kg/day

18. Compared to adult TPN amino acid solutions, the amount of glycine in pediatric solutions is

A. higher
B. lower
C. the same

19. A conditionally essential amino acid for preterm infants is

A. glycine
B. lysine
C. tyrosine

20. The amount of energy (kcal/kg/day) needed per day to prevent essential fatty acid deficiency in preterm infants is

A. 40
B. 60
C. 80

21. Adding heparin to TPN increases the preterm infant's ability to metabolize

A. glucose
B. fatty acids
C. protein

22. Assuming normal hydration and renal function, insufficient protein intake from TPN in a preterm neonate is indicated when the blood urea nitrogen (BUN) is between

A. 1-5 mg/dL
B. 6-10 mg/dL
C. 11-15 mg/dL

23. Carnitine facilitates fatty acid metabolism by increasing

A. absorption of fat soluble vitamins
B. lipoprotein lipase activity
C. transport into the mitochondria

24. Animal studies suggest that TPN solutions exposed to light may cause damage to the

A. brain
B. kidney
C. liver

25. The recommended intravenous filter size for three-in-one TPN solutions is

A. 0.22 micron
B. 1.2 micron
C. 2.2 micron