Parenteral Nutrition Curriculum

Pediatric

Nassau University Medical Center

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^{*}Note: Direct excerpts have been taken from the ASPEN Core Curriculum book in this document.

Objectives

The participant will be able to:

- 1. Identify appropriate patients who will benefit from parenteral nutrition (PN).
- 2. Identify the most appropriate access to provide PN based upon the patient's nutritional, metabolic and clinical status.
- 3. List the basic components typically incorporated into a PN solution.
- 4. Formulate a basic PN solution, including the appropriate dosing of macronutrients and micronutrients.
- 5. Adjust the PN solution daily based upon laboratory data and physical assessment.
- 6. Describe the clinical and laboratory monitoring required for the use of PN.
- 7. Identify potential complications associated with PN.
- 8. Transition to enteral nutrition (EN) therapy while maintaining adequate nutrition support.
- 9. Discontinue PN therapy.

Introduction

Parenteral nutrition (PN) is a life-saving method of nutrition support when enteral nutrition (EN) support is not an option. PN is the provision of nutrients intravenously. A complete, balanced formulation includes dextrose as the carbohydrate source; amino acids; fat emulsions (lipids) in addition to a variety of electrolytes such as potassium, magnesium, and phosphorus; vitamins; and multiple trace minerals (zinc, copper, manganese, chromium, selenium). It can also be used as a vehicle to provide certain medications. The principal forms of PN are central and peripheral—which describes the venous route of delivery.

Central parenteral nutrition (CPN) is often referred to as "total parenteral nutrition" (TPN), since the entire nutrient needs of the patient may be delivered by this route. It has high glucose content (usually 15% to 25% final concentration) and, along with amino acids and electrolytes, provides a hyperosmolar (1300-1800mOsm/L) formulation that must be delivered into a large-diameter vein, usually the superior vena cava. Central venous access can be maintained for prolonged periods (weeks to years).

Peripheral parenteral nutrition (PPN) has similar nutrient components as CPN but in a lower concentration of dextrose (usually10% final concentration but not more than 12.5%) to create a solution with a lower osmolarity as compared to CPN so it may be delivered via the peripheral vein. Because of its more dilute nature, PPN would have to be administered in larger fluid volumes accompanied by a higher volume of lipid calories to provide a comparable calorie dose as the more concentrated CPN formulation. Since repletion of nutrient stores is usually not a goal of PPN, it is not intended to be used in severely malnourished patients. It may be used for patients with mild to moderate malnutrition to provide partial or complete nutrition support when they are not able to ingest adequate calories orally or enterally. PPN therapy is typically used in patients who can tolerate the fluid load, and is used for short periods (up to two weeks) because of limited long-term tolerance by peripheral veins.

PN is a nutrition option not without risk and should be ordered for the appropriate patients. Risks include those related to infection, access, electrolyte and glycemic management, and vitamin and trace element deficiencies or excesses. A skilled and knowledgeable clinician should be responsible for the management of PN therapy.

Indications for Parenteral Nutrition

Parenteral Nutrition is indicated to prevent the adverse effects of malnutrition when the gastrointestinal tract is not working, not available, or not appropriate.

Condition specific indications for PN:

- Extreme prematurity
- Premature infants weighing < 1500 grams
- Any infant with unstable cardio-respiratory status who cannot be advanced to full enteral feeds in 2 – 3 days
- Congenital intestinal anomalies
- Necrotizing enterocolitis (NEC)
- Neonatal surgical patients: status post surgery for NEC, atresias, bowel obstruction, tracheoesophageal fistula, gastrochesis, omphalocele, imperforate anus
- Failure to thrive
- Mechanical obstruction of the GI tract (without enteral access distal to the obstruction)
- Gastrointestinal (GI) bleeding
- Disordered peristalsis
- Mesenteric ischemia
- Diarrhea
- Severe malabsorption
- GI fistula (when enteral assess is not available posterior to fistula or volume of output is high)
- Inadequate oral or enteral feeding due to intolerance
- Persistent nausea and vomiting
- High aspiration risk (without appropriate enteral access)
- Severe mucositis or esophagitis

Contraindication for Parenteral Nutrition

- Functional gastrointestinal tract capable of adequate absorption of nutrients (excluding neonatal)
- PN therapy anticipated for < 5 days without malnutrition (excluding neonatal)
- Inability to obtain venous access
- Patients whose prognosis does not warrant aggressive nutrition support
- When the risks of PN are judged to exceed the potential benefits

Peripheral Venous Access

One of the easiest and safest ways to access the vascular system is to place a cannula into a peripheral vessel. The adequacy of the vein limits the use of the peripheral system for infusion. It is thought that catheter tips located in a peripheral vessel are not appropriate for the infusion of PN formulas with an osmolarity greater than 900 mOsm/L. Given more recent data, it is likely that the maximum osmolarity tolerated by the peripheral vein is significantly higher than 900 mOsm/L and is likely in the range of 1200 mOsm/L. Low blood flow in combination with hyperosmolar solution is associated with a high risk of thrombosis and thrombophlebitis and is therefore reserved for short-term therapy in individuals with robust veins. Simultaneous infusion of lipid emulsion will dilute the osmotic load and thereby improve tolerance to peripherally administered parenteral nutrition.

Central Venous Access

In general, central venous access is preferred for PN administration since the rate of blood flow rapidly dilutes the hypertonic parenteral feeding formulation to that of body fluids. Insertion of a central line should be considered if it is anticipated that the patient will require PN support for a least 7 days or require PN and cannot tolerate the larger fluid loads required with PPN to meet nutrient needs.

Central venous access is defined as a catheter whose distal tip lies in the distal vena cava or right atrium. Central catheters can be grouped into three broad categories: non-tunneled, tunneled and implanted ports. They can also be single, double or triple lumen. Catheters must be maintained according to strict protocol for safety and to preserve patency. The most common sites of venipuncture for central access include the subclavian (should be avoided in patients with advanced chronic kidney disease due to high risk of central venous stenosis), jugular and femoral (least preferred site because it is virtually impossible to maintain an occlusive dressing in place, thus increasing the risk of sepsis) veins. Central venous infusions are not as limited by pH of the formulation, osmolarity, or volume.

Peripherally Inserted Central Catheter (PICC or PIC line) PIC line is inserted into a peripheral vein, such as cephalic, basilic or brachial vein and then advanced through increasingly larger veins (up the axillary vein into the subclavian vein), toward the heart until the tip rests in the distal superior vena cava or cavo-atrial junction. PICCs are usually inserted by radiologists, physician assistants or certified registered nurses using ultrasound. Chest radiograph is done afterwards to confirm placement. Complications may include catheter occlusion, phlebitis, hemorrhage, thrombosis and infection. However, the complication rate is lower since pneumothorax and vascular injury with hemothorax that can be seen with subclavian and internal jugular line placements are avoided. Other advantages are lower risk of air embolism and catheter related sepsis. PIC lines generally remain in place no longer than 30 days, although longer duration of use is possible. PICCs do not restrict arm movement or normal activity.

BOTH PPN AND CPN REQUIRE ONE LINE OR PORT DEDICATED EXCLUSIVELY FOR THE INFUSION OF THE SOLUTION.

NEVER USE DIALYSIS ACCESS FOR PN ADMINISTRATION.

PN Formulation Components

Components used in formulating PN typically include energy substrates such as carbohydrate, fat and protein as amino acids, as well as electrolytes, vitamins, and trace elements. Sterile water for injection is added to provide necessary volume to the PN formulation. Sulfites are added as a preservative to many PN components and can cause an allergic reaction.

Energy Substrates

In malnourished or critically ill patients gluconeogenesis, from amino acids principally, is the major source of new glucose formation. Amino acids are mobilized mainly from skeletal muscle to support protein synthesis in the other vital organs (such as brain, heart, liver, lungs, and kidneys), thus preserving them at the expense of skeletal muscle and connective tissue. By providing energy source as a mixture of glucose, lipids and amino acids, it has protein-sparing effects.

Dextrose

- Primary fuel source providing 3.4 kcal/g of energy
- Acidic pH (3.5 6.5)
- Available with pre-added electrolytes
- Available in concentrations ranging from 5-70%; however, for compounding purposes usually stock 50% and 70%. Our institution uses exclusively 70% dextrose concentration solution
- Higher dextrose concentrations (usually 10% final concentration but not more than 12.5%) are generally reserved for central venous administration because of propensity to cause thrombophlebitis in peripheral veins
- Excessive dextrose delivery can result in:
 - o Increased CO₂ production
 - o Synthesis and storage of fat
 - o Hyperglycemia
 - o PN associated liver disease (PNALD)
- Dose moderately (50 75% of maximum dose) to avoid potential complication, see table 1 for maximum dosage of dextrose
- Alternative carbohydrate source is glycerol (4.32 kcal/g), less frequently used

Table 1. Maximum Dosages of Dextrose

Age	Maximum Dose
Neonates - < 11 years of age	14 mg /kg /min (20.1 g /kg /d)
11 - 20 years of age	7 mg /kg /min (10.0 g /kg /d)
Adults	5 mg /kg /min (7.2 g /kg /d)

Calculations: calculating calories from % dextrose solution

Step #1 % x volume (ml) = grams Step #2 grams x 3.4 kcal/g = calories

Example 1. Two liters of parenteral solution containing a final concentration of 15%

dextrose (or 150 g/L)

Step #1 0.15 x 2000 ml = 300 grams Step #2 300 g x 3.4 kcal/g = 1020 kcal

<u>Calculations:</u> calculating % dextrose solution from calories

Step #1 kcal / 3.4 kcal/g = grams

Step #2 grams / volume (ml) x 100 = % solution

Example 2. 102 kcal is desired in a parenteral solution of 200 ml. What is the final

dextrose concentration of the solution?

Step #1 102 kcal / 3.4 kcal/g = 30 grams

Step #2 $30 \text{ grams } / 200 \text{ ml } \times 100 = 15\% \text{ final concentration}$

Sample calculations:

- 1. How many calories does 75 grams of dextrose provide?
- 2. What is the final concentration of a solution containing 60 grams in 500 ml?
- 3. How many grams of dextrose is provided in a 2400 ml solution with a final concentration of 25%?
- 4. Is the solution in question #3 appropriate for a 50 kg (110 lb) 16 year old female?
- 5. How many ml of 50% and 70% base solution will be needed to fill the prescription in question #3?

Answers: 1. 255 kcal; 2. 12%; 3. 600 g; 4. No, >10 g/kg/d; 5. 1200 ml, 857 ml

Fat Emulsion

- Intravenous fat emulsion (IVFE) or lipid emulsion is used to provide energy and is a source of essential fatty acids (EFA).
- IVFE components include soybean oil or 50:50 mixes of soybean and safflower oil that are long-chain triglycerides (LCT), egg yolk phospholipids as an emulsifier, glycerol to render the formulation isotonic, sulfites (as a preservative) and sodium hydroxide to adjust the final pH (range 6-9).
- IVFE is white in appearance and provide a small source of phosphorus (15 mmol/L), selenium, vitamins E & K and cholesterol.
- Fat emulsion is calorically dense (9 kcal/g), has a low osmolarity and produces minimal CO₂.
- Helps prevent peripheral vein thrombophlebitis (PVT) if run simultaneously with PPN
 - o Lipid reduces endothelial procoagulant activity.
- Lipids administration aids in prevention of hepatic dysfunction
 - Lipids have a protective effect on hepatic microsomal oxidative enzyme (particularly the cytochrome P450) function which is an important route of drug and nutrient metabolism.
- Formulations available:
 - o 10% (supplies 1.1 kcal / ml)
 - o 20% (supplies 2.0 kcal / ml) only formulation available in our institution
 - o 30% (supplies 3.0 kcal / ml) [only available for bulk mixing]
- The 10% emulsion has a relatively greater amount of glycerol and phospholipids content as compared to 20% and 30% emulsions → elevated triglyceride levels.
- Because of the different glycerol and phospholipids content in formulations, calories supplied from lipid should be based on kcal/ml of the solution. <u>Do not use kcal/g method.</u> This method does **NOT** take into account the calories provided by the glycerol component (4.2 kcal/g) or phospholipids (6 kcal/g), thereby underestimating kcal provided.
- If patients are on propofol, the amount of calories provided by propofol should be taken into the account as well (10% emulsion provides 1.1 kcal/ml).
- The infusion rate should not exceed 0.11 g/kg/hr in children through adults (2.5 g/kg/d if run continuously over 24 hours) to avoid potential complications. See table 2 for maximum doses
- Excessive administration of lipid emulsion can result in:
 - o Hypertriglyceridemia
 - o Infections
 - o Reduced pulmonary diffusion capacity
 - o Reticuloendothelial system (RES) dysfunction and thrombocyte adhesiveness
 - o Fat overload syndrome
- Contraindications to lipids administration:
 - o Triglyceride level > 400 mg/dL; in neonates > 150 mg/dL
 - o Egg allergy

Table 2. Maximum Dosing Guidelines for Fat Emulsion

Age	Maximum Dose			
Infants	3.0 g/kg/d or 60% of total kcal			
Children – Adults	2.5 g/kg/d or 60% of total kcal			

- Because of enhanced microbial growth potential with IVFE when infused separately from dextrose and amino acids formulations, the CDC recommendation is to hang IVFE for no longer than 12 hours. However, if volume considerations require more time, the infusion should be completed within 24 hours. The usual practice of our institution is to infuse IVFE over 24 hours to minimize complications. Signs and symptoms of rapid infusion reaction to lipids include palpitations, tachypnea, wheezing, cyanosis, nausea, pain at injection site, headache, and oily taste in the mouth.
- **BEWARE** of allergic reaction to either the soy, sulfite or egg component! (According to the manufacturers, lipid emulsions do not contain soy protein secondary to processing techniques; however a possibility of minuscule amount of soy protein that is below the level of detection is present). Symptoms of an allergic reaction may include fever, chills, vomiting, urticaria, and pain in the back and chest.

Amino Acids

Protein is a component of skeletal muscle, enzyme systems, circulating transport proteins and vital organs. It is provided in the form of crystalline amino acids (AA) in PN formulations and yields 4 kcal/g if oxidized for energy. The amino acid products have acidic pH and can be standard or specialty. Standard or balanced amino acid products are mixtures of essential and nonessential AA. The stock solutions available range from concentrations of 3% to 20%. Our institution standard AA solution is 20% for adults and 10 % for pediatrics. Modified or specialty amino acid products have a modified amino acid profile to meet age or certain disease specific amino acid requirements. Sulfites are added as a preservative and can cause potential reactions.

Essential amino acids: those that can not be synthesized by the body and therefore must be provided in the diet

Nonessential: those that can be synthesized endogenously

<u>Semi-essential</u>: - those that can not be synthesized endogenously in sufficient quantities to sustain normal growth;

- those that are essential during infancy until biological systems mature;
- those that are essential in specific disease states because of altered metabolism.

Table 3. Classification of Amino Acids

Essential	Nonessential	Semi-essential		
❖ Valine	Alanine	Arginine		
❖ Isoleucine	Asparagine	Cysteine		
❖ Leucine	Aspartate	Glutamine		
■ Phenylalanine	Glutamate	Taurine		
□ Tryptophan	Glycine	Tyrosine		
Histidine	Hydroxyproline	-		
Methionine	Ornithine			
Threonine	Proline			
Lysine	Serine			

Branch chain AA

■ Aromatic AA

Available formulations:

- 1. **Standard** has a balanced profile of essential, semi-essential and nonessential amino acids. It contains higher amounts of glycine, methionine and phenylalanine, and does not contain cysteine or taurine as compared to pediatric AA solutions. May cause hyperglycinemia in neonates, which is deleterious to the brain. This solution is used in pediatric patients > 6 years of age.
- 2. **Specialty** has a modified amino acid profile designed to meet age or disease-specific amino acid requirements
 - a) **Disease specific** modifications (more expensive)

Metabolic Stress (trauma, thermal injury, hypercatabolic states):

- Branch chain amino acid (BCAA) enriched
- Its use is based on the theory that higher BCAAs are beneficial during metabolic stress and improve nitrogen balance in certain groups. However, the evidence does not support improved outcomes.

Liver failure with hepatic encephalopathy:

- Contains increased amounts of BCAAs and decreased amounts of aromatic amino acids (AAA) and methionine
- It is postulated that a decrease in the level of BCAA seen in liver failure facilitates the transport of AAA through the blood-brain barrier where they serve as precursors to neurotransmitters that might be responsible for altered mental status.
- Hypothesized that a 'liver' formulation would correct the abnormal AA profile and as a result will correct neurological dysfunction.
- No difference in efficacy between standard verses 'liver' formulation has been shown; therefore, has very limited indications.
- Consider use only if patient is refractory to standard medical treatment.

Renal failure: (essential amino acids and histidine)

- Based on the theory that nonessential AAs can be physiologically recycled from urea and essential AAs must be provided from the diet.
- Relatively dilute preparations (5.2–6.5%), therefore, fluid restriction and provision of adequate nutritional support can be difficult.
- Offers <u>no</u> significant advantage over standard AA formulation, therefore has very limited indications.
- Recommended not to exceed 0.5 g/kg/day.
- b) **Pediatric** (higher in BCAA, tyrosine, histidine taurine, glutamic acid and aspartate, less glycine, phenylalanine and methionine)
 - Can be used up to 6 years of age
 - Provides a better distribution of amino acids for pediatric patient.
 - Demonstrates improved nitrogen retention as compared to adult formulation.
 - Produces an aminogram in neonates more similar to full term infants.

- Premasol and Trophamine are two AA products available on the market. NUMC currently is using Premasol.
- 3. **Fluid restricted** most dense formulation available is 20%. This is the standard used by NUMC for older pediatric patients > 6 years of age.

Recommended Dosing of Protein in Pediatric Patients:

1. Neonatal

- Positive nitrogen balance, no weight gain: 50 non-protein calories + 2.5 g/kg/d protein
- Weight gain and nitrogen retention similar to intrauterine growth: 70 non-protein calories + 3 g/kg/d protein
- 3-4 g/kg/d protein may be used in special cases like term surgical patients
- Maximum of 4 g/kg/day is recommended
- Protein provision > 4 g/kg/d may cause metabolic acidosis and cholestasis.
- 2. Infants (1-12 months): 2-3 g/kg/d of protein
- 3. Children (>10 kg or 1-10 years): 1-2 g/kg/d of protein
- **4.** Adolescents (11-17 years): 0.8 2 g/kg/d of protein

Cysteine – is a major substrate of glutathione and important in maintaining anti-oxidant activity. Generally very little or no cysteine is added to the amino acid solutions.

- Additional L-cysteine is added to the PN solution (40 mg/g protein) for patients < 2 years of age in order to accommodate immature AA conversion pathway & compensate for the little or no added cysteine to the amino acid solution.
- L-cysteine may be added to PN solutions for older pediatric patients to maximize calcium (Ca) phosphorus (P) solubility and therefore provide more Ca and P in solution.
- L-cysteine is relatively unstable in solution, therefore is added at time of solution compounding to be used within 24 hours.

Some commercially available amino acids formulations can also contain various concentrations and combinations of electrolytes and/or buffers, in addition to inherent or endogenous electrolyte content of the individual amino acids. For nitrogen balance calculations amino acids are 16% nitrogen (6.25 g of protein = 1g of nitrogen).

Calculations: calculating protein from % solution

% x volume (ml) = grams

Example Two liters of parenteral solution containing a final concentration of 6%

protein (or 60 g/L)

Step #1 $0.06 \times 2000 \text{ ml} = 120 \text{ grams}$

Sample calculations:

1. What is the final concentration of a solution containing 6 grams protein in 200 ml?

2. How much protein is supplied in 1200 ml with a final concentration of 6.5%?

3. How many ml of 10% and 20% base compounding solution is necessary to fill the prescription in question #2?

Answers: 1. 3%; 2. 78 g; 3. 780 ml, 390 ml

Electrolytes

The amount of different electrolytes that are added to PN formulations depend on the laboratory levels of the electrolytes and the patient's requirements. A source of sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca) and magnesium (Mg) must be provided daily. Standard daily ranges for pediatric patients are listed in Table 4, commercially available parenteral electrolyte salts in table 5.

Table 4. Daily Electrolyte Requirements.

Electrolyte	Preterm Neonates	Infants & Children	Adolescents & Children > 50 kg	Adults
Sodium	2-5 mEq/kg	2-5 mEq/kg	1-2 mEq/kg	Base on desired concentration
Potassium	2-4 mEq/kg	2-4 mEq/kg	1-2 mEq/kg	60-120 mEq/day
Phosphate	1-2 mmol/kg ~1.4-2.8 mEq/kg	0.5-2 mmol/kg ~0.7-2.8 mEq/kg	10-40 mmol/day ~14-56 mEq/day	20-40 mmol/day ~30-60 mEq/day
Calcium	2-4 mEq/kg	0.5-4 mEq/kg	10-20 mEq/day	10-20 mEq/day*
Magnesium	0.3-0.5 mEq/kg	0.3-0.5 mEq/kg	10-30 mEq/day	10-30 mEq/day
Acetate	As needed to maintain	in acid-base balance		
Chloride	As needed to maintain	n acid-base balance		

Task force for the revision of safe practices for parenteral nutrition: Safe practices for parenteral nutrition. JPEN 2004;28(6 suppl):S39-S70.

 Table 5. Commercially Available Parenteral Electrolyte Salts.

Electrolyte	Salt Form
Sodium	Chloride, acetate, phosphate
Potassium	Chloride, acetate, phosphate
Chloride	Sodium, potassium
Acetate	Sodium, potassium
Calcium	Gluconate ^a , gluceptate
Magnesium	Sulfate ^a , chloride

^a Preferred salt form for use in PN formulations.

Chloride and acetate are used to adjust acid-base balance and therefore have no specific ranges. Acetate gets directly converted to bicarbonate in the body and is helpful in correcting acidosis when added. As a result, acetate should be avoided in alkalosis as it worsens the acid-base problem. In alkalosis, chloride-based salts would be more appropriate to use. Chloride-based salts that are commonly used in parenteral nutrition compounding include NaCl and KCl. CaCl is not used due to its instability in a solution.

^{*}Baumgartner T, ed. Clinical Guide To Parenteral Micronutrition. Fujisawa USA, Inc; 1997

Vitamins

Vitamins are an essential component of a daily PN regimen because they are necessary for normal metabolism and cellular function. Parenteral requirements differ from enteral due to differences in efficiency of absorption and utilization. Optimal vitamin requirements in the seriously ill are unknown.

Commercially available vitamin products for PN supplementation include single vitamin products and multivitamin products that contain both fat-soluble and water-soluble vitamins. Pediatric patients receiving PN should receive a standard daily dose of parenteral multivitamins, tables 6 and 7.

Table 6. Composition of Adult Parenteral Multivitamin – Infuvite® (10 ml).

Component / Vitamin	Amount
Vitamin A (Retinol)	1 mg (3300 USP units)
Vitamin D (Ergocalciferol)	5 mcg (200 USP units)
Vitamin E	10 mg (10 USP units)
Vitamin K	150 mcg
Ascorbic Acid	200 mg
Thiamin	6 mg
Riboflavin	3.6 mg
Pyridoxine	6 mg
Niacin	40 mg
Folic Acid	600 mcg
Biotin	60 mcg
Cyanocobalamin	5 mcg
Pantothenic Acid	15 mg

One manufacturer provides a product that is vitamin K free with less vitamin C, thiamin & pyridoxine (MVI 12).

Table 7. Composition of Pediatric Parenteral Multivitamin – Infuvite Pediatric® (5 ml).

Component / Vitamin	Amount	
Vitamin A (Retinol)	700 mcg (2300 USP units)	
Vitamin D (Ergocalciferol)	10 mcg (400 USP units)	
Vitamin E	7 mg (10 USP units)	
Vitamin K	200 mcg	
Ascorbic Acid	80 mg	
Thiamin	1.2 mg	
Riboflavin	1.4 mg	
Pyridoxine	1 mg	
Niacin	17 mg	
Folic Acid	140 mcg	
Biotin	20 mcg	
Cyanocobalamin	1 mcg	
Pantothenic Acid	5 mg	

Additional separate vitamins can be added depending upon disease state. Additional vitamin C may be added for meeting the increased vitamin C requirements of wound healing during critical illness or in the post-op period. Additional folic acid (1 mg/day) can be added directly to PN solutions to meet the increased requirements of accelerated red blood cell production in patients with macrocytic anemia.

Trace Elements

Trace elements are metabolic cofactors essential for the proper functioning of several enzyme systems. Commonly used trace elements in PN formulations include zinc, copper, chromium, manganese, and selenium. Other trace elements that may be supplemented in PN include molybdenum, iodine, fluoride and iron. Optimal trace element intakes in the seriously ill are unknown. The only injectable iron that is approved for addition to PN is iron dextran. However, it can only be added to dextrose-amino acids formulations because the IVFE is disrupted by iron. Our institution does not add parenteral iron secondary to risk of anaphylaxis. Be familiar with the recommended requirements and the available preparations on the market in addition to those used at your facility. See tables 8 and 9 for the requirements and the preparations that are available for pediatric patients.

Table 8. Trace Element Daily Recommended Requirements For Pediatrics & Adults*^f.

Trace Element	Preterm Neonates < 3 kg (mcg/kg/d)	Term Neonates 3–10 kg (mcg/kg/d)	Children 10–40 kg (mcg/kg/d)	Adolescents > 40 kg (per day)	Adults (per day)
Zinc Copper Manganese Chromium Selenium	400	50-250	50-125	2-5	2.5-5 mg
	20	20	5-20	200-500 mcg	0.3-0.5 mg
	1	1	1	40-100 mcg	60-100 mcg
	0.05-0.2	0.2	0.14-0.2	5-15 mcg	10-15 mcg
	1.5-2	2	1-2	40-60 mcg	20-60 mcg

^{*} Assumes normal age-related function and losses.

Table 9. Composition of Adult Trace Element & Pediatric Trace Element Mixture.

Trace Element	Amount Adult 1ml (Mu	Amount Pediatric 1 ml (Pediatric Multitrace-4®)
Zinc	5 mg	1 mg
Copper Manganese	1 mg 0.5 mcg	0.1 mg 25 mcg
Chromium Selenium	10 mcg 60 mcg	1 mcg [None provided, must add separately, see table 8]

f Recommended intakes can not be achieved using a single pediatric trace element product.

Task force for the revision of safe practices for parenteral nutrition: Safe practices for parenteral nutrition. JPEN 2004;28(6 suppl):S39-S70.

Additional separate trace elements that can be added depending upon disease state are: zinc, selenium, chromium, iron, copper. Since the trace element mixture does not contain iron, patients on prolonged PN may develop iron deficiency.

Parenteral Nutrient Preparations

PN can be prepared as a total nutrient admixture (TNA) or as 2 in 1 (dextrose – amino acids) formulation. TNA or 3 in 1 solution provides all the macronutrients (dextrose, amino acids, and lipid emulsion) and micronutrients (electrolytes, vitamins, and trace elements) in one delivery system. This system is presently **NOT** being used at NUMC. Two in 1 solution contains all the same components as TNA except for lipid emulsion, which can be infused separately. Our institution uses 2 in 1 solution and lipid emulsion is infused separately as IV piggyback. Specific advantages and disadvantages are associated with the use of each PN formulation system.

Advantages:

- Can use 30% lipid emulsion in fluid restricted patients.
- Decreased nursing time involved in IV set-up & tubing changes.
- Fewer manipulations decrease the risk of touch contamination.
- Less supply and equipment expense for only one pump and IV tubing.
- Reduced training time for home patients.
- Improved patient compliance due to ease and simplicity of TNA administration.
- More convenient storage and fewer supplies in home care setting.
- Inhibited or slower bacterial growth if contaminated compared to separate lipid emulsion.

Disadvantages:

- Better growth medium for bacteria as compared to 2 in 1 solution.
- The standard 0.22-micron filter can not be used; must use a 1.2-micron or larger filter to avoid particle shearing and instability.
- Visual inspection for particulate matter or precipitate is difficult.
- Emulsion stability is influenced by pH, temperature, time, mixing order, ingredients and electrolyte charge, and is less stable than a 2 in 1 solution.
- TNA is less compatible with medications due to the lipid portion.

Stability and Compatibility of PN

Stability of PN formulations refers to the extent to which nutritional components retain their original properties. It may also refer to the ability of the added medications to maintain their chemical integrity and pharmacological activity and resist degradation.

Compatibility, in contrast, refers to the ability to combine two or more chemical products such that the physical integrity of the products is not altered. Incompatibility issues with PN formulations generally involve the formation of precipitates.

The major concerns about the stability and compatibility of 3-in-1 PN solutions include: the stability of the lipid emulsion, the potential for calcium phosphate precipitation, the stability of vitamins and trace elements, and the stability implications of adding drugs to PN or giving drugs concurrently via the same tubing as the PN.

Lipid Emulsion

Deterioration or **Breaking** of a TNA solution involves a change in droplet size and dispersion. This process occurs in several steps:

1. **Aggregation:** Fat droplets collect throughout the emulsion, reversible with gentle

agitation.

2. **Creaming:** Fat aggregates of larger size rise to the surface and form a cream layer,

reversible with gentle agitation

3. Coalescence: The aggregates fuse together and become even larger; irreversible and

unusable.

4. Oiling Out: There is a total separation due to continued coalescence; irreversible and

unusable.

Toxicity may occur if undispersed fat aggregates are infused, therefore all TNA need to be visually inspected before being administered.

Calcium and Phosphate

The combination of calcium (Ca) and phosphorus (P) salts in excessive amounts in PN formulations may result in crystalline precipitates and possible pulmonary emboli and catheter occlusion. Calcium phosphate solubility is a major compatibility concern with PN formulations.

The maximum amount of Ca and P that may be added to the PN formulation depends on:

- 1. pH of the final PN solution
 - The lower the pH of the PN admixture, the more Ca and P can be added to the solution secondary to increased calcium phosphorus solubility at low pH.
- 2. Calcium and phosphorus concentrations
 - The concentration or the amounts of calcium and phosphate ions are directly related to the risk of precipitation. As the concentration of either of the ions increases, precipitation is more likely to occur. It is recommended that the sum of the calcium and phosphorus should <u>not</u> exceed 45 mEq per liter in a "2 in 1" solution.
- 3. Calcium salt form
 - The risk of precipitation can be reduced by using calcium gluconate rather than calcium chloride, and by using the more acidic monobasic rather than dibasic phosphate salts.
- 4. Temperature of solution
 - Calcium and phosphorus are *less* soluble at higher temperatures (e.g. if temperature of solution is increased from room temperature, 25°C to body temperature, 37°C)

5. Mixing procedures

• Provided that compounding guidelines are adhered to, the amounts of calcium and phosphate in adult PN should pose little risk of precipitation.

6. AA concentration

• AA decrease the risk of Ca and P precipitation by forming soluble complexes with calcium. AA decrease free calcium available to precipitate with phosphorus.

Vitamins and Trace Elements

Several vitamins are known to undergo substantial degradation after addition to the PN formulation. Photo-degradation caused by light exposure, particularly fluorescent light, results in loss of some vitamins, including B12, folate, vitamin K, pyridoxine, thiamin, riboflavin and retinol. Additional vitamins are lost due to adherence to the tubing of the infusion system. Due to this instability over time, it is recommended that vitamins are added to PN formulations shortly before administration of the solution.

Drugs and PN

Certain drugs can be compatible in dextrose – amino acids solutions but not in TNA formulation. Other medications, usually fat soluble, can be compatible with TNA but not dextrose – amino acids formulations. Usually drugs are not added to 3-in-1 TNA but can be added to "2 in 1" PN solution. Certain drugs that are compatible with the PN can be given via Y-site administration (piggyback drug delivery system). Medications routinely added to "2 in 1" PN solutions include: H-2 antagonists (e.g. ranitidine) and insulin.

Filtering the PN Solution

- Use a 0.22 micron sterilizing filter with 2 in 1 solutions.
 - This will filter out organisms like Staphylococcus epidermis, Escherichia coli and Candida albicans as well as particulate matter. IVFE is connected below the filter.
- Use a 1.2 micron filter with TNA.

This is not a sterilizing filter but will remove large microorganisms like Candida albicans and large particles (like Ca P precipitates) that might otherwise lodge in the pulmonary capillaries if allowed to pass.

Prescribing Parenteral Nutrition

The concentration of the components in the parenteral feeding formulations will determine the osmolarity and whether it can be infused via a central or peripheral vein. A PPN solution may contain up to 10% final concentration of dextrose (with a maximum of 12.5% in certain

situations). Dextrose solutions greater than 10% final concentration should be administered via a central venous access catheter with exception of a solution that contains 12.5% final concentration of dextrose with an amino acid content $\leq 3.5\%$ (or 3-4 g/kg/d in neonates). Pediatric formulations for younger age groups tend to have a lower percentage of protein and other components thereby allowing a greater provision of dextrose that can still be infused via a peripheral vein.

Changes in clinical condition and activity level may require periodic recalculation of calorie and protein requirements. The electrolyte composition of PN may be varied based on the serum electrolyte profile, changes in clinical status, organ function, and medications. PN volume may be concentrated for patients at risk for volume overload or the PN fluid volume may be expanded to meet the needs of patients with increased fluid requirements.

PN Osmolarity

Parenteral feeding formulations are hypertonic to body fluids. The osmolarity is dependent primarily on the dextrose, amino acids, and electrolyte content. The maximum osmolarity tolerated by a peripheral vein has been said to be 900 mOsm/L. However, a higher osmolarity (approximately 1200 mOsm/L) is likely to be tolerated as well and can be provided depending upon the condition of the veins and fluid requirements. Formulas for peripheral vein administration usually require more fluid and a higher content of fat as a calorie source than those for central vein administration. This is so the osmolarity of the formula can be maintained at a value that can be tolerated by the peripheral vein.

Contribution of TNA components to the osmolarity:

- Dextrose: 5 mOsm/g/L or 50 mOsm/ % solution
- Amino Acids: 10 mOsm/g/L or 100 mOsm/ % solution
- Lipid Emulsion 20%: 1.3 1.5 mOsm/g/L or 13 15 mOsm/ % final solution
- Electrolytes: 1 mOsm/mEq/L of individual electrolyte additive

Usually for the compounding purposes, it is assumed that the amounts of individual electrolytes are approximately equal (for simplicity). Electrolytes usually are expressed in milliequivalents (mEq). However, to calculate osmolarity an appropriate formula has to be used. Osmolarity is always based on a liter.

```
mEq/L = mmol/L \ x \ valence

mOsm/L = (number of species in solution \ x \ mEq/L) \ / \ valence

mOsm/L = number of mmoles in solution \ x \ number of species in solution
```

- For monovalent salts (e.g. NaCl, KCl), disassociation in solution is a 1:1 ratio. Therefore, 1 milliequivalent = 1 mmole.
 - o 1 mmol NaCl = 1 mmol of Na⁺ + 1 mmol of Cl⁻ = 1 mEq Na⁺ + 1 mEq Cl⁻
 - o Osmolarity = 1 mEq or 1 mmol of solution of NaCl is equivalent to 2 mOsm
- For divalent salts (e.g. MgSO₄, CaCl₂), the equivalent weight is one-half its molecular weight, since the valence of the divalent component is two. 1 mEq = 0.5 mmol.
 - o 1 mmol MgSO₄ = 1 mmol of Mg²⁺ + 1 mmol of SO₄²⁻¹ = 2 mOsm
 - o Osmolarity of 1 mEq MgSO₄ = $(2 \times 1 \text{ mEq of MgSO}_4) / 2 = 1 \text{ mOsm/L}$

- For trivalent salts (e.g. Na₃PO₄, K₃PO₄), 1 mEq = 0.333 mmol. However, phosphate can exist in different ionic forms H₂PO₄⁻, HPO₄²-, or PO₄³-, and an exact valence can not be given. Valence is approximated at around minus 2. As a result, phosphate is usually expressed in mmoles.
 - o 1 mmol $K_3PO_4 = 3 \text{ mmol of } K^+ + 1 \text{ mmol of } PO_4^{3-}$
 - Standard solution of KPhos = 4.4 mEq/ml of K + 3 mmol/ml of Phos = 7.4 mOsm/ml

Osmolarity calculations are based on a liter!

Example: 2 liter PN with the following components: 4.5 % AA (90 g), 10% dextrose (200 g) with 155 mEq Na, 90 mEq K, 15 mEq Ca and 20 mEq Mg added as salts, with 20% IVFE of 360 ml (72 g).

AA: $90 \text{ g in } 2L (45 \text{ g/L}) \times 10 \text{ mOsm/g/L} = 450 \text{ mOsm in } 1L$

or 4.5% solution x 100 mOsm/% solution = 450 mOsm/L

Dextrose: $200 \text{ g in } 2L (100 \text{ g/L}) \times 5 \text{ mOsm/g/L} = 500 \text{ mOsm in } 1L$

or 10% dextrose x 50 mOsm/% solution = 500 mOsm/L

Electrolytes: $(155 \text{ mEq Na} + 90 \text{ mEq K} + 15 \text{ mEq Ca} + 20 \text{ mEq Mg}) \times 2$

(adjustment for total electrolytes) x 1 mOsm/mEq

= 560 mOsm in 2L or 280 mOsm in 1L

Total osmolarity = 450 mOsm/L + 500 mOsm/L + 280 mOsm/L

= 1230 mOsm/L

IVFE will lower the overall osmolarity of "2 in 1" solution if run simultaneously:

Total volume = 2.36 L

AA: 90 g in 2.36 L = 3.8%

3.8% solution x 100 mOsm/% solution = 380 mOsm/L

Dextrose: 200 g in 2.36 L = 8.5%

8.5% dextrose x 50 mOsm/% solution = 425 mOsm/L

Electrolytes: 560 mOsm in 2.36 L = 237 mOsm/L

Lipids: 72 g in 2.36 L = 3%

3% solution x 14 mOsm/% final solution = 42 mOsm/L

Total osmolarity = 380 mOsm/L + 425 mOsm/L + 237

mOsm/L + 42 mOsm/L = 1084 mOsm/L

Table 10. Composition of Common Commercially Available Crystalloid Solutions

IV Fluids	Na ⁺ mEq/L	Cl - mEq/L	K ⁺ mEq/L	Ca ⁺⁺ mEq/L	Lactate mEq/L	Glucose g/L	pН	Osmolarity mOsm/L
Normal Saline (NS)	154	154	_	_	_	_	5.6	310
D5 NS	154	154	_	_	_	50	4.4	560
0.45% NS or ½NS	77	77	_	_	_	_	5.6	155
D5 ½NS	77	77	_	_	_	50	4.4	405
D5 ¹ / ₃ NS	56	56	_	_	_	50	4.4	365
D5 0.2% NS	34	34	_	_	_	50	4.4	320
Lactated Ringer (LR)	130	110	4	3	28	_	6.2	275
D5 LR	130	110	4	3	28	50	4.6	530

^{*}Note: the 50 grams of dextrose in a liter equates to an osmolarity of 250 mOsm/L. However, the dextrose is rapidly metabolized and does not contribute to serum osmolarity unless the patient is hyperglycemic.

Each solution can also come mixed with different concentration of dextrose (e.g. D2.5 NS, D5 LR, D10 ½NS). Commercial solutions also come as D1.5W, D5W (50 g/L of glucose) and D10W.

Parenteral Nutrition Order Writing (see Appendix I and II for sample order forms)

- 1. Determine calorie and protein requirements.
 - Use the recommendations below as a guide. Individual patients may require greater or less than the estimated requirements due to acute illness, therapies or underlying medical conditions. A metabolic cart is available from the Pulmonary Service (extension 2-3320) for actual measurement of calorie needs.

Table 11. Estimated Requirements.

Age	Estimated Calorie Estimated Protein Requirements (kcal/kg) Requirements (g/kg)			
Preterm	90-120	3-4		
< 6 months	85-105	2-3		
6-12 months	80-100	2-3		
1-7 years	75-90	1-2		
7-12 years	50-75	1-2		
>12-18 years	30-50	0.8-2		

^{*} Assumes normal age-related function

f Adapted from JPEN. 2004;28(2 suppl):S39-S70.

2. Determine volume of parenteral solution to be provided.

Table 12. Daily Estimated Fluid Requirements*^f.

Body Weight	Amount
<1500 g	130 – 150 ml/kg
1500 – 2000 g	110 – 130 ml/kg
2 – 10 kg	100 ml/kg
>10 – 20 kg	1000 ml for first 10 kg + 50 ml/kg for each kg >10
>20 kg	1500 ml for first 20 kg + 20 ml/kg for each kg >20

^{*} Assumes normal age-related function

- 3. Determine *moderate* amounts of dextrose, lipid and protein to provide the amount of calories and protein desired.
 - Providing excessive amounts of various fuel sources will increase the likelihood of complications.

Example: 15 year old 60 kg teenager with the following daily requirements: 1800 kcal, 100 g protein, and 2000 ml fluid total.

Calories provided by protein: 100 g protein $\times 4 \text{ kcal/g} = 400 \text{ kcal}$

Calories provided by lipid at 1 g/kg/d: 60 g at 2 kcal/ml of 20% lipid emulsion $60 \text{ g} \times 2 \text{ kcal/ml} \times (1000 \text{ ml} / 200 \text{ g}) = 600 \text{ kcal}$

Calories remaining to be provided by dextrose:

1800 kcal - 400 kcal - 600 kcal = 800 kcal

Amount of dextrose providing 800 kcal: 800 kcal / 3.4 kcal/g = 235 g dextrose

- 4. Determine amount of fluid required to provide the dextrose and protein using the compounding formulations available
 - This step is not always necessary once familiar with the ordering process.
 - Important to calculate in order to assure that the final solution *can be* compounded using the available base solutions
 - o 50% and 70% dextrose
 - o 20% Prosol (standard protein)
 - o 10% Premasol (pediatric protein)

f Adapted from JPEN. 2004;28(2 suppl):S39-S70.

5. Dose the individual electrolytes (see table 4 below).

Electrolyte	Preterm Neonates	Infants & Children	Adolescents & Children > 50 kg	Adults
Sodium	2-5 mEq/kg	2-5 mEq/kg	1-2 mEq/kg	Base on desired concentration
Potassium	2-4 mEq/kg	2-4 mEq/kg	1-2 mEq/kg	60-120 mEq/day
Phosphate	1-2 mmol/kg ~1.4-2.8 mEq/kg	0.5-2 mmol/kg ~0.7-2.8 mEq/kg	10-40 mmol/day ~14-56 mEq/day	20-40 mmol/day ~30-60 mEq/day
Calcium	2-4 mEq/kg	0.5-4 mEq/kg	10-20 mEq/day	10-20 mEq/day*
Magnesium	0.3-0.5 mEq/kg	0.3-0.5 mEq/kg	10-30 mEq/day	10-30 mEq/day
Acetate	As needed to maintain	n acid-base balance		
Chloride	As needed to maintain	n acid-base balance		

Good practice when initiating PN prescription of electrolytes includes trying to minimize the number of salts used for compounding. In general, acetate is provided as Na salt and phosphorus as a potassium salt.

- For sodium (Na)
 - Dose according to the desired concentration. For maintenance begin with 50 77 mEq/L (equivalent to 1/3 to ½ NS Na concentration) or 100 155 mEq of NaCl in a 2L bag. Na concentration can be varied.

- For K, Mg, Ca and P
 - o Provide the average dose for age if the lab results are within normal limits.
 - o Provide high dose range for age if the lab results are low or low normal.
 - o Provide low dose range for age if the lab results are high or high normal.
 - o Omit any electrolyte if the lab result is high.
 - o Add a small amount back to the solution if or when level returns to normal
 - o *Note:* The sum of Ca and P should NOT exceed 45 mEq/L or 90 mEq in a 2L bag (due to risk of precipitation).
- Dose acetate and chloride based on acid-base balance
 - o If mild metabolic acidosis is present, can start with providing $\frac{1}{3} \frac{1}{2}$ of total Na dose as the acetate salt. With more severe metabolic acidosis can provide all of Na dose as the acetate salt.
 - o If further bicarbonate buffering is needed, all of the K (excluding the K given as KPO4) can be provided as the acetate salt.
- 6. Provide standard multivitamin and trace element preparations; see tables 13 and 14 below, and tables 6, 7 and 8, 9.

Table 13. Adult and Pediatric Multivitamins Dosing Guidelines

Age	Dose
11 years of age – Adult	10 ml adult MVI
>2.5 kg – <11 years of age	5 ml pediatric MVI
<2.5 kg	2 ml/kg pediatric MVI

Table 14. Adult and Pediatric Trace Element Mixture Dosing Guidelines*

Age	Dose
>20 kg <20 kg < 3 kg	1 ml adult trace element mixture 0.2 ml/kg pediatric trace element mixture 0.4 ml/kg pediatric trace element mixture

^{*}Provide a source of selenium daily for patients <20 kg as it is not provided in the pediatric mixture.

Additional separate vitamins and trace elements that can be added depending upon disease state or metabolic stress include vitamin C, folate, vitamin K, zinc, selenium, chromium, iron and copper.

Excessive GI losses via drains and stool can result in zinc (Zn), copper (Cu) and chromium (Cr) deficiencies. To avoid zinc deficiency, 12 mg of Zn per liter of small bowel output or 17 mg of Zn per kg of stool or ileostomy output should be added to PN formulation. Older pediatric patients with excessive GI losses may need up to 20 mcg/d of chromium. Provision of additional Cu and Zn may be needed in patients with burns to compensate for losses of these elements in burn wound exudates with \geq 20% total body

surface area burns. Patients can lose 20 - 40% of body Cu content within the first week of injury. Cu and Zn participate in antioxidant defense mechanisms; they are cofactors for superoxide dismutase.

- 7. Complete the order form.
 - Enter the dose of each nutrient into the appropriate section.
 - To calculate the % final concentration: g/volume x 100 = %
 - o 210 g dextrose / 1150 ml = \sim 18 % 25 g protein / 1150 ml = \sim 2.5 %

Alternatively, a premixed solution that is available in our institution (table 15) can be used for older pediatric population. However, caution should be exercised with this solution as it can worsen alkalosis due to its high acetate content and can result in hyponatremia because of its low Na content. Given above problems and a lower dextrose and protein content, Clinimix is not an appropriate substitute for a customized PN in many situations.

Table 15. Available Premixed PN Solution

Component	Clinimix E
Dextrose	10% (340 kcal/L)
Amino acids	4.25% (42.5 g/L)
Sodium	35 mEq/L
Potassium	30 mEq/L
Chloride	35 mEq/L
Acetate	70 mEq/L
Calcium	4.5 mEq/L
Phosphate	15 mmol/L
Magnesium	5 mEq/L
pН	6.0
Osmolarity	1070

Initiation of PN

Neonatal Guidelines

Neonatal PN is separated into 3 groups: starter PN, customized PN for infants \leq 1500 grams, and customized PN for infants > 1500 grams.

1. Starter PN: For infants 32 weeks or younger, or 1500 grams or less

Start as close to birth as possible:

- Fluid: Keep PN at 50 ml/kg/day
- Dextrose: D5W D10W < 1000 g - D5W > 1000 g - D10W
- Protein: 2 g/kg/day, advance by 0.5 g/kg/day until 3 g/kg/day is achieved

- Lipid Emulsion start lipid emulsion on **day 3** with 1 g/kg/day, advance by 1 g/kg/day until 3 g/kg/day is achieved
- Calcium: 2 mEq/kg/day
- MVI: 2 ml/kg/day

NO electrolytes, trace elements or cysteine at this time.

Monitor dextrose and adjust dextrose in PN.

Monitor electrolytes, when required give in separate IV piggyback fluid.

Monitor lipid profile prior to increase; keep triglycerides at 150 mg/dL or less.

2. Customized PN for Infants $\leq 1500 g$

Start on day 4 of life.

- Fluid: Base PN on total fluids/kg/day.
- Dextrose: D5W D12.5W PPN

> D12.5W CPN

(base on glycemic control)

- Protein: 3 g/kg/day
- Lipid Emulsion: 3 g/kg/day (keep triglyceride level ≤ 150 mg/dl)
- Sodium: 2 4 mEg/kg/day
 - o Sodium acetate may be used if there is metabolic acidosis, adjust chloride acetate balance as acidosis improves.
- Potassium: 1 2 mEq/kg/day
- Calcium: 2 3 mEq/kg/day
- Magnesium: 0.3 0.5 mEq/kg/day
- Phosphorus: $\sim 1.4 2.8 \text{ mEq/kg/day}$
- Cysteine: 40 mg/g of protein
- MVI: 2 ml/kg/day
- Trace Elements: 0.4 ml/kg/day

3. Customized PN for Infants > 1500 g

Customized PN may be used from birth. Initiate as early as possible. May be run in place of IVF.

- Dextrose: D10W (based on glycemic control)
- Protein: 2 g/kg/day
- Lipid Emulsion: begin with 1 g/kg/day, advance in 1g/kg/day increments to 3 g/kg/day as tolerated
- Sodium: 2 4 mEq/kg/day
 - o Follow basic metabolic panel (BMP), add Na when Na levels are low normal.
- Potassium: 1 2 mEq/kg/day
 - o Provide K as KPO₄ when K levels are normal and the patient has good urine output.
- Calcium: 2 mEq/kg/day
- Magnesium: 0.3 0.5 mEg/kg/day
- Phosphorus: $\sim 1.4 2.8 \text{ mEq/kg/day}$
- Cysteine: 40 mg/g of protein
- MVI: 2 ml/kg/day, not to exceed 5 ml/kg/day
- Trace Elements: 0.4 ml/kg/day

Pediatric Guidelines (excluding neonatal)

1. **Infants** CARBOHYDTATE – begin with 10% dextrose, advance as tolerated daily

in 2.5% increments in infants and 5% in children until goal is achieved.

& Children

<u>PROTEIN</u> – begin at goal. Add L-cysteine when appropriate.

<u>LIPIDS</u> – begin with 1 - 2 g/kg/d and advance by 1 g/kg daily until goal is

achieved. (There is no evidence that a gradual increase improves fat

tolerance.)

2. **Teenagers** CARBOHYDTATE – begin with 10% dextrose and advance in 5 - 10%

increments daily to goal.

PROTEIN – begin at goal.

<u>LIPIDS</u> – begin at desired goal.

Adult Guidelines

Begin dextrose, protein and fat at goal unless patient is at \underline{high} risk of refeeding syndrome or suboptimal tolerance is anticipated (e.g. brittle diabetic) where on the first day the PN solution should contain less calories from dextrose (50 – 75% of estimated calorie requirements).

Monitoring Patients on PN

The potential for serious complications with PN is high and requires careful monitoring by experienced clinicians. A suggested protocol for monitoring PN is included in Table 16.

Table 16. Suggested Monitoring for PN

Parameter	Baseline	Critically III Patients	Stable Patients
Basic Metabolic Panel	Yes	Daily	Twice weekly
BUN, Creatinine	Yes	Daily	Twice weekly
Calcium	Yes	Daily	Twice weekly
Phosphorus	Yes	Daily	Twice weekly
Magnesium	Yes	Daily	Twice weekly
Liver Function Tests	Yes	Daily	Twice weekly
Neonates	Yes	Weekly	Weekly
CBC with differential	Yes	Daily	Weekly
PT, PTT	Yes	Weekly	Weekly
Serum triglycerides	Yes	Weekly	Weekly
Albumin	Yes	Daily	Weekly
Prealbumin (except neonates)	Yes	Weekly	Weekly
Glucose	Yes	Q6 hours or as needed	Daily (if controlled)
Neonates	Yes	Q6 hours	Q6 hours
Weight	Yes	Daily	3 times weekly
Neonates	Yes	Twice daily	Daily
Intake and output	Daily	Daily	Daily
Nitrogen balance	As needed	As needed	As needed

The monitoring should be tailored to the patient's medical condition.

BE AWARE OF REFEEDING SYNDROME!

Discontinuation of PN

To reduce the risk of rebound hypoglycemia in susceptible patients, a 1 to 2 hour taper down of the infusion may be necessary. If a PN solution must be discontinued suddenly or unexpectedly, 10% dextrose containing IV fluid should be infused for 1 or 2 hours following PN discontinuation to avoid a possible rebound hypoglycemia.

To wean PN in a patient receiving and tolerating enteral feeding:

Neonatal

• As soon as the neonate is clinically stable, start enteral feeding and advance as tolerated. As enteral feedings are increased, PN must be weaned accordingly. For every increase in feeding of 1 ml q3h, decrease PN by 0.3 ml/hr so that the total fluid intake is kept at the prescribed amount. When the neonate is tolerating enteral feedings up to 100 ml/kg/day, PN may be discontinued. May supplement with IV fluids to maintain total fluid intake.

Pediatrics

- Tube feedings once patient is receiving tube feedings (TF) at 50% of goal rate with good tolerance, the PN may be reduced and then weaned off as TF rate advances to goal.
- PO diet once patient is orally consuming 50% of estimated needs the PN may be reduced and then weaned off per clinician judgment when intake is ≥ 85% of estimated requirements.

Example:

15 year old female is receiving 1.7 L CPN containing 6% AA and 14% dextrose infusing at 70 ml/hr with IVFE 20% infusing as piggyback at 13 ml/hr providing a total of 1824 kcal and 100 g protein.

To taper PN:

Start Jevity Plus tube feeds via NGT at 200 ml q6 hrs. Decrease CPN rate to 50 ml/hr, 20% lipid at 10 ml/hr.

If tolerance of tube feeds is demonstrated, further taper:

Decrease CPN rate to 25 ml/hr, discontinue lipid emulsion. Increase intermittent TFs to goal of 360 ml q6 hrs. If TFs tolerance is demonstrated over 6-8 hr, discontinue CPN solution (or allow to run to completion not to exceed 24 hr hang time).

Complications

PN has a unique set of potential complications, some of which can be serious or even life threatening. PN should be monitored by health care professionals trained to recognize, prevent and treat the infectious, mechanical and metabolic complications.

Infections

Infectious complications are the most frequently observed complication associated with intravascular catheters and are associated with increased morbidity and mortality. Therefore, appropriate use of aseptic technique by trained personnel is essential to maintain an acceptable sepsis rate.

Mechanical

Usually vascular access devices or catheter related and include catheter occlusion, thrombosis and breakage. Thrombotic occlusions can be caused by intraluminal clot, fibrin sleeve or sheath formation, mural thrombus or thrombosis of the vessel. Fibrin sheath can encase the catheter and distal catheter tip and prevent withdrawing blood from the catheter but will usually allow nutrients to infuse. To minimize thrombophlebitis, several techniques have been tried including addition of heparin or small amounts of hydrocortisone to PPN or the use of a nitroglycerin patch or NSAID product at the venous insertion site. Running lipid emulsion simultaneously with PPN will also offer protection against peripheral vein thrombophlebitis. Nonthrombotic catheter occlusion can be caused by external clamps, kinking of the catheter, occluded port needles and constricting sutures.

Etiologic factors in the development of Peripheral Vein Thrombophlebitis (PVT):

- Cannula size, material, colonization
- Site of cannula placement, trauma at venipuncture
- Nature of infusion solution, particulate matter in solution, duration of infusion
- Drug additives, vein size

Metabolic Complications

Macronutrient –Related Complications

<u>Hyperglycemia</u> – is the most common complication associated with PN administration. Risk factors for hyperglycemia include metabolic stress, severe prematurity, medications, obesity, diabetes, and excess calorie (dextrose) administration.

Suggested prevention of hyperglycemia with PN includes:

- Frequent glucose monitoring with initiation of PN. Maintain good glycemic control.
- Insulin can be added to the PN solution to aid in glycemic control. Note that insulin is not 100% available (may range from 50-95%) due to adhesion to the bag and tubing and dependence upon other components of the solution (i.e., multivitamins and trace elements may enhance availability to 95%).
- An initial regimen of 0.05 0.1 units regular insulin per gram dextrose is common, 0.15 0.2 units/g dextrose if already hyperglycemic.

- Can add 2/3 of the total amount of sliding scale insulin coverage received over the past 24 hr to the next days PN solution to aid in optimizing glycemic control.
- Consider use of an insulin drip if glucose levels are erratic or a patient has high insulin requirements.
- Hyperglycemia can be due to a chromium deficiency in rare cases. (Insulin will be ineffective in controlling glucose levels in these patients.)

<u>Hypoglycemia</u> – can occur from excess insulin administration via the PN solution, IV drip or subcutaneous injection. Abrupt discontinuation of PN solutions has been associated with rebound hypoglycemia. Because of the high glucose and amino acid load in PN, pancreatic hormones (especially insulin) are produced in moderate to-high quantities. If the nutrient load is suddenly stopped, the hormones are still produced and active for some time resulting in a hypoglycemic state. Obtaining blood glucose 30 minutes to 1 hour after the PN solution is discontinued will help identify rebound hypoglycemia.

Essential Fatty Acid Deficiency (EFAD) – lipid free PN may cause essential fatty acid deficiency with in 1^{st} few days of life in a neonate and within a week in children. Two polyunsaturated fatty acids, linoleic and alpha-linolenic, can not be synthesized by the body and are considered essential. A minimum of 2-4% of total kcal from lipid should be given daily to prevent an EFA deficiency. At least 1 g/kg/d of lipid emulsion is necessary to prevent essential fatty acid deficiency in the neonate.

Clinical manifestations of EFAD can include:

- Alopecia, scaly dermatitis (dry, thick and desquamating skin)
- Diarrhea, fat malabsorption
- Hepatomegaly, hepatic dysfunction due to fatty liver
- Anemia, thrombocytopenia, enhanced platelet aggregation
- Diminished wound healing
- Impaired chylomicron synthesis
- Growth retardation in infants

To biochemically diagnose EFAD, the **Holman Index** should be used.

- A triene:tetraene ratio of > 0.4 is diagnostic of EFA deficiency where a ratio of 0.2 is the upper limit of normal.
 - o triene mead acid or 5,8,11-eicosatrienoic acid tetraene arachidonic acid or 5, 8, 11, 14-eicosatetraenoic acid

In patients who are intolerant to fat emulsion, a topical skin application or oral ingestion of oil (2-3 mg oil/kg/d) can be tried to alleviate the EFA deficiency if it develops.

<u>Hypertriglyceridemia</u> – may be due in part to medications (e.g. steroids, propofol), an improper blood drawing technique (where a blood sample is drawn just distal to the IVFE or propofol infusion) or can occur with dextrose overfeeding or with rapid administration rate or an excessive dose of IVFE. Reducing the dose or lengthening the IVFE infusion time will help minimize these side effects.

The long-chain triglycerides (LCTs) are degraded peripherally by lipoprotein lipase; however, there is also uptake by the reticuloendothelial system (RES) which can interfere with RES function when the lipid load is large. Provision of lipids in smaller amounts does not interfere

with RES function. Heparin aids in triglyceride clearance via stimulation of lipoprotein lipase (LPL). Addition of heparin ($\frac{1}{2} - 1$ unit/ml of solution) to PN can be tried in certain situations. LPL resides in the capillary bed. Malnourished patients have less capillary mass and therefore slower rates of lipid clearance. Acceptable serum triglyceride concentration is $\leq 400 \text{ mg/dl}$ ($\leq 150 \text{ mg/dl}$ in infants and neonates).

Fat overload syndrome is a rare complication of IVFE therapy and is potentially lethal. It is characterized by lipemic serum, massive fat deposition in the lungs, liver, and spleen, reticuloendothelial blockade, immune suppression, and coagulopathy with abnormal platelet function. To avoid the fat overload syndrome, the dose for IVFE administration should not exceed the maximum dosing guidelines.

Carnitine deficiency can result in high triglyceride levels. Carnitine is required for the transport of long chain fatty acids (LCFA) into the mitochondrial matrix for oxidation. It also stimulates medium chain fatty acids (MCFA) oxidation in skeletal muscles. Carnitine is made from lysine & methionine (with niacin, vitamin C, B6 and iron as cofactors) in the liver and kidney. Carnitine is not present in any component of PN formulations, however, an IV form of L-carnitine is commercially available and can be added for selected patients (at 2-5 mg/kg/d that is similar to normal oral intake) who have documented deficiency or are susceptible to a deficiency.

Patients at risk for carnitine deficiency include:

- neonates
- inborn error of metabolism
- carnitine-free diet in combination with significant trauma / infection, cardiac, liver or kidney disease
- hemodialysis patients

Micronutrient –Related Complications

Electrolytes

Hyponatremia – frequently noted in PN patients. The most common cause of hyponatremia is administration of excessive hypotonic fluid. Based on the etiology, hyponatremia is usually treated with fluid restriction or if sodium intake is inadequate and clinical condition warrants, additional sodium may be administered.

Hypernatremia – occurs infrequently. Possible causes of hypernatremia include inadequate free water administration, excessive water loss (as with fever, burns, hyperventilation), or excessive sodium intake. Hypernatremia is usually treated by increasing fluid intake; less often it is treated by reducing sodium intake.

Hypokalemia – may be caused by inadequate potassium intake or excessive losses with diarrhea or intestinal fluids (e.g. nasogastric suction, intestinal fistulas) or as a result of refeeding syndrome. Hypomagnesemia may also give rise to hypokalemia. Hypokalemia may be treated by increasing the potassium content of the PN, by providing it through a peripheral vein, or by the gastrointestinal route. Hypomagnesemia should be corrected concurrently with hypokalemia.

Hyperkalemia – may be caused by administration of excessive potassium especially in setting of

- renal dysfunction, metabolic acidosis, severe prematurity or potassium-sparing medications. If hyperkalemia is present, potassium in the PN formulation should be reduced or discontinued.
- Hypocalcemia may be attributed to decreased vitamin D intake or citrate binding of calcium with blood product administration, or hypoalbuminemia. Hypomagnesemia may also contribute to hypocalcemia. Hypocalcemia that is independent of hypoalbuminemia may be treated with calcium supplementation. It is very common in premature infants due to low intrauterine calcium accretion, therefore calcium needs to be added to the PN solution on day 1.
- Hypercalcemia may be attributed to administration of excess vitamin D or prolonged immobilization and stress. With hypercalcemia, calcium in the PN formulation should be decreased or discontinued.
- Hypomagnesemia may be attributed to refeeding syndrome, diuretic use, prolonged nasogastric suction, increased stool output, diabetic ketoacidosis, or magnesium wasting medications. Parenteral magnesium supplementation should be used to treat severe hypomagnesemia. If intestinal absorption is adequate, oral magnesium can be used to treat mild hypomagnesemia.
- Hypermagnesemia may be seen with excessive magnesium intake in renal insufficiency. Hypermagnesemia is usually treated by decreasing or discontinuing magnesium in the PN formulation. Severe hypermagnesemia may necessitate dialysis. This also may be seen in infants born to mothers receiving Mg during labor. Avoid adding Mg to the PN solution until the Mg level is normal.
- Hypophosphatemia may be seen with refeeding syndrome, and with inadequate phosphorus intake. Hypophosphatemia may be treated with phosphate supplementation or can be increased in the PN formulation. In neonates phosphorus is provided in PN on the third or fourth day of life when K is also included.
- Hyperphosphatemia may be seen with administration of excess phosphate especially in patients with renal insufficiency. Hyperphosphatemia may be treated by decreasing or stopping phosphorus intake or with enteral phosphate binders.

Vitamins

Excessive intake of lipid-soluble vitamins A, D, E, and K has the potential for accumulation and, therefore, the potential for toxicity. Also, inadequate addition of water-soluble vitamins can result in deficiency states.

Trace Elements

Parenteral nutrition provides a limited range of nutrients and bypasses GI homeostatic mechanisms leaving patients at risk for deficiencies and toxicities of trace elements.

Manganese (Mn) and copper (Cu) are excreted in bile; therefore, their levels should be monitored in patients with liver disease. Mn levels should also be monitored for patients on PN >

30 days due to frequent contamination of PN solutions. Mn accumulation seen with cholestasis may result in cerebral Mn deposition causing weakness, irritability, aggressiveness, headaches, muscle rigidity, facial spasms & paralysis, staggered gait, fine tremors and hallucinations. Excessive GI losses via drains and stool can result in zinc, copper and chromium deficiencies. Deficiency symptoms for zinc, copper and chromium include:

- Zinc deficiency can result in diarrhea, depression hypogeusia, anorexia, hypogonadism, anemia, growth retardation, hepatosplenomegaly, impaired wound healing and geophagia.
- Cu deficiency can result in impaired bone formation, osteoporosis, leucopenia, neutropenia & microcytic anemia.
- Cr deficiency can result in impaired glucose tolerance, peripheral neuropathy, ataxia and confusion.

Burn victims can develop copper and zinc deficiencies from losses in burn wound exudate. The trace element mixture does not contain iron, and as a result a patient on prolonged PN may develop iron deficiency.

Refeeding Syndrome

Starved or severely malnourished patients can undergo life-threatening fluid and electrolyte shifts following the initiation of aggressive nutritional support therapies. This phenomenon is known as the "refeeding syndrome" and can occur in patients receiving either enteral or parenteral nutrition support.

Risk factors for refeeding syndrome are anorexia nervosa, classic kwashiorkor and marasmus, chronic alcoholism, chronic malnutrition-underfeeding, prolonged IV hydration, morbid obesity with massive weight loss, and prolonged fasting.

This syndrome may involve hemolytic anemia, respiratory distress, paresthesias, tetany, and cardiac arrythmias.

The physiological basis of the "refeeding syndrome" is believed to stem from the following:

- Carbohydrate repletion and insulin release enhance cellular uptake of glucose, phosphate, potassium and magnesium. Since total body stores of these minerals are depleted, blood levels fall.
- Rapid expansion of the extracellular fluid volume occurs with carbohydrate refeeding and may predispose patients to fluid overload.
- The reduction in cardiac mass and high energy phosphate reserves associated with malnutrition lead to cardiac insufficiency during fluid resuscitation. Alterations in cardiac function and arrythmias also occur as a result of severe hypophosphatemia, hypokalemia and hypomagnesemia.
- Respiratory muscle, reduced in mass and ATP content by malnutrition, is unable to respond to the increased workload imposed by aggressive nutrition support leading to hypercarbia and in some cases respiratory failure.
- Alterations in red blood cell shape and function occurs in hypophosphatemia which is believed to contribute to tissue hypoxia and increased respiratory drive.
- Deficiency of B-vitamins, especially thiamin, are speculated to have a role in the refeeding syndrome since these vitamins are required in carbohydrate metabolism.

To avoid the development of the refeeding syndrome in these patients deemed at risk the following measures includes:

- Repletion of serum potassium, magnesium, and phosphorus concentrations via intravenous fluids before initiating PN.
- Limiting initial total calories provided (predominantly from carbohydrates) to 50 75% of estimated calorie requirements.
- Including adequate amounts of potassium, magnesium, phosphorus, and vitamins in initial PN
- Increasing carbohydrate-dependent minerals (potassium, magnesium and phosphorus) in proportion to increases in carbohydrate when PN is advanced.
- Initiating and advancing PN slowly.

Hepatobiliary Complications

PN associated liver disease (PNALD) results from a complex set of risk factors present in patients receiving PN. There are three types of hepatobiliary disorders associated with PN therapy: steatosis, cholestasis and gallbladder sludge/stones; however, these disorders may coexist. Steatosis, or hepatic fat accumulation, is predominant in adults and is generally benign and reversible. Mild elevations in transaminase concentrations may occur without ill effect within days to weeks after initiation of PN. Liver enzyme levels may return to normal while the patient is still on PN but almost always normalizes when PN is stopped. Steatosis seems to be a complication of overfeeding and nowadays not as common. The administration of excessive calories from either dextrose or lipids is thought to promote hepatic fat deposition.

PN-associated cholestasis (PNAC) is a condition that occurs predominantly in infants and children, but may also occur in adults receiving long-term PN. It results from the lack of enteric stimulation that occurs with long-term PN therapy. PNAC is a serious complication because it may progress to cirrhosis and liver failure. Lastly, gallbladder stasis during PN therapy may lead to the development of gallstones or gallbladder sludge with subsequent development of cholecystitis.

Another factor that may contribute to the risk of liver complications is the phytosterol content of IVFE. Phytosterols are inefficiently metabolized to bile acids by the liver, and it has been postulated that they may impair bile flow and cause biliary sludge and stones.

Deficiencies in taurine, cysteine, choline, lecithin, carnitine, glutathione and glutamine have all been implicated as contributing factors in PNALD as well since they are not a part of the standard PN solution. Methionine is an essential amino acid and an important precursor to cysteine, taurine, choline, carnitine and glutathione in the body. In neonates and infants the conversion pathway may be immature and or the parenteral form inefficiently converted resulting in these deficiencies.

Management of PN-induced hepatobiliary abnormalities usually includes decreasing dextrose and lipid calories, cycling the PN so that the patient is off PN 8 to 10 hours per day, and using enteral nutrition to stimulate bile flow and to avoid gut mucosal atrophy and bacterial translocation. Lipid emulsion with a fish oil component is being used in the US on a compassionate use basis in neonates for the treatment of PNALD.

Metabolic Bone Disease

Osteoporosis and osteomalacia are associated with long-term PN use and is common in infants supported by PN alone. Osteopenia and rarely rickets may also be seen in infants. It is important to provide adequate amounts of calcium and phosphorus since patients receiving PN are particularly vulnerable to negative calcium balance because of limited intake and increased urinary calcium loss. A number of factors have been associated with increased urinary calcium excretion: higher protein doses in PN formulations, chronic metabolic acidosis and cyclic PN. Those risk factors should be corrected when possible and weighted against other possible benefits. Both vitamin D deficiency and vitamin D toxicity can result in bone disease. However, excessive doses of vitamin D should be avoided as it can cause PTH suppression and directly promote bone resorption.

Osteomalacia had been associated with PN formulations that in the past had significant aluminum (Al) contamination. Nowadays, aluminum contamination of PN formulations is significantly lower; however, it is still a concern. In addition to PN solutions, aluminum contamination is present in parenteral products such as albumin and blood products, and certain medications (e.g. heparin, IV calcium). The aluminum content of parenterals increases over time due to leaching from glass and elastomeric closures. The kidneys are the primary elimination route for unbound aluminum ($\sim 60\%$ of infused Al); the remainder is deposited in the tissues such as brain, bones, liver, and lungs. Aluminum toxicity in addition to bone disease also can result in progressive dementia and iron/erythropoetin resistant microcytic anemia from deposition of the aluminum in the corresponding organs. Patients at risk for aluminum toxicity are those with significant renal dysfunction, high intake of parenteral products and iron deficiency.

Magnesium deficiency can also contribute to the development of bone disease by decreasing mobilization of calcium from bone and by inhibiting PTH release resulting in hypocalcemia. If hypocalcemia is present, magnesium deficiency has to be ruled out. Copper deficiency is not common but it can impair bone formation and cause osteoporosis.

Strategies to prevent and treat osteoporosis should be considered in all patients who require long-term PN therapy. PN formulation should be designed to minimize hypercalcuria, provide adequate magnesium, calcium, and phosphorus, avoid metabolic acidosis, provide vitamins and trace elements, and minimize aluminum contamination.

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Appendix 1. Sample PN order form for pediatric patients.

NASSAU UNIVERSITY MEDICAL CENTER 2201 HEMPSTEAD TURNPIKE • EAST MEADOW, NY 11554

CPN Diagnoses:	#	
AMINO ACIDS	☐ standard ☐ specialty specify:	<u></u> 8
DEXTROSE		<u>8</u>
ELECTROLYTES	Sodium Chloride Acetate Phosphate	mEq/day mEq/day mEq/day
	Potassium Chloride Acetate Phosphate	mEq/day mEq/day mEq/day
	Calcium Gluconate	mEq/day
	Magnesium Sulfate _	mEq/day
MULTIVITAMINS	□ adult □ pediatric _	ml/day
TRACE ELEMENTS	☐ adult ☐ pediatric _	ml/day
OPTIONAL ADDITIVES vitamin C vitamin K folate zinc	_mg/day	
TOTAL SOLUTION VOLUM	ME _	ml/day
INFUSION RATE	_	ml/hour
LIPID EMULSION:	<u> </u>	ml over 24 hou
Parenteral solution	on and lipid supplies:	nonprotein Kca grams protein
DATE/TIME ORDERED	PRESCRIBING MD'S	SIGNATURE & ID N
		PHYSICIAN'S NAME

Appendix 2. Sample PN order form for neonatal patients.

NASSAU UNIVERSITY MEDICAL CENTER 2201 Hempstead Turnpike, East Meadow, NY 11554

PPN	Allergies:		
CPN	Diagnoses:		
	Diet:		
	Wt:	Kg	
			MD WORKSHEET
AMINO AC		_	1
	ediatric plus	 *	g/Kg
L	-cysteine		40 mg/g protein
DEXTROSE			g/Kg
ELECTROL	VTPS		
		mEq/day	mEq/Kg
Deara	Acetate	mEq/day	mEq/Kg
	Phosphate	mEq/day	mEq/Kg
		——————————————————————————————————————	
Potas	sium Chloride	mEq/day	mEq/Kg
	Acetate	mEq/day	mEq/Kg
	Phosphate	_mEq/day	mEq/Kg
Calci	um Gluconate	mEq/day	mEq/Kg
,			10.
Magne	sium Sulfate	mEq/day	mEg/Kg
MULTIVIT			
X	ediatric	ml/day	
TRACE EL	EMENTS	Į.)	56
X	ediatric	ml/day	ml/Kg
OPTIONAL	ADDITIVES		
□ 1	eparin	units/day	
r	reg. insulin	units/day	
□ _			
SYYEAT TA	IFUSED VOLUME	ml/day	ml/Kg
		i i	
INFUSION	RATE	ml/hour	
		,	352751 35 \$205
ПЪП	EMULSION:		Solution & lipid suppli
	10% 🗂 20%		g protein
_	ml		nonprotein Kca nonprotein Kca
	g		lonprocern Kee
-	g/Kg		
ATE/TIME	ORDERED	PRESCRIBIN	G MD'S SIGNATURE & ID 1
	و جدوب المحافظة المتحديد و المحافظة المتحدد و المتحدد		vivina vivina (1998 – 1990) proporti vivina (1998) proporti vivina (
		ATTE	NDING PHYSICIAN'S NAME
enteral N	Autrition Orders M	UST Be Receive	ed In Pharmacy By 1:0