Parenteral Nutrition Curriculum

Adults

Nassau University
Medical Center

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Contents

Objectives

The participant will be able to:

1. Identify appropriate patients who will benefit from parenteral nutrition (PN).
2. State the best PN route based on the patient's nutritional, metabolic, and clinical status.
3. List the basic components typically incorporated into a PN formulation.
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 the 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 (10% final concentration) to create a solution with a lesser osmolarity 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 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

- Non functioning gut (e.g. paralytic ileus, mesenteric ischemia, motility disorders) or expected non-functioning gastrointestinal tract in a malnourished or hypermetabolic patient
- Malnourished patients in whom the use of the intestine is not anticipated for >7 days

Condition Specific Indications for PN

1. For cancer patients:
   - PN should be initiated if treatment is expected to cause gastrointestinal toxicities (severe mucositis, esophagitis or radiation enteritis) that will preclude oral intake for >7 days. PN is unlikely to benefit patients whose malignancy has not responded to chemotherapy or radiation therapy.

2. For surgical patients:
   - Pre-operative PN (defined as 7-10 days before surgery) is indicated for severely malnourished patients and in patients undergoing major surgery for cancer of the esophagus or stomach.
   - Post-operatively, PN may be implemented within 3 days after surgery (to assure that the patient is hemodynamically stable) for patients with mild to moderate malnutrition if it is expected that the gastrointestinal tract cannot be used for a prolonged period.

3. In critically ill patients:
   - PN is recommended if hypermetabolism is expected to last more than 4 to 5 days when enteral nutrition is not possible. Special attention should be paid to patients in the Intensive Care Unit (ICU) with systemic inflammatory response syndrome (SIRS) or multiple organ dysfunction syndrome (MODS).

4. For inflammatory bowel disease:
   - PN should not be used routinely in these patients. PN does not influence disease activity in acute exacerbations of ulcerative colitis. Indirect evidence suggests that parenteral nutrition is less effective than steroid therapy in treating active Crohn's disease.

5. In renal failure:
   - Amino acid formulas that contain essential amino acids alone are not recommended for most situations.

6. In hepatic dysfunction:
   - Branched-chain amino acids are not necessary for most patients.

7. In pancreatitis:
   - PN is not the first course of nutrition support. Enteral nutrition support is recommended initially. PN is recommended if abdominal pain or pancreatic fistula drainage is increased by enteral feeding. Lipid emulsions are considered safe in pancreatitis if serum triglyceride levels remain $\leq$ 400 mg/dL during the infusion.

8. For patients with short-bowel syndrome who cannot absorb adequate oral or enteral nutrients:
   - PN should be administered. PN may be needed indefinitely if less than 60 cm of functioning small bowel remains.

9. In patients with eating disorders:
    - PN may be used in patients with eating disorders where severe malnutrition (<65% of ideal body weight or >30% recent weight loss) and gastrointestinal or emotional intolerance to enteral feeding exist. Careful implementation of PN is necessary to avoid refeeding syndrome.

10. In AIDS:
    - PN may be used in AIDS patients who have failed other methods of nutrition support.

Special attention should also be paid to adults who are nutritionally-at-risk. Adults are considered at nutrition risk if they have any of the following:

- Actual or potential for developing malnutrition (involuntary loss or gain of ≥10% of usual body weight within 6 months, or ≥5% of usual body weight in 1 month, a body mass index (BMI) < 18.5 or > 30), presence of chronic disease, or increased metabolic requirements.
- Altered diets or diet schedules (receiving total PN or EN, recent surgery, illness, or trauma).
- Inadequate nutrition intake, including not receiving food or nutrition products (impaired ability to ingest or absorb food adequately) for greater than 7 days.

Contraindications for Parenteral Nutrition

- Functioning gastrointestinal tract capable of adequate absorption of nutrients
- PN therapy is anticipated to be < 5 days without malnutrition
- Inability to obtain venous access
- Patients whose prognosis does not warrant aggressive nutritional support
- When the risks of PN are judged to exceed the potential benefits.

Intravenous Access

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, the maximum osmolarity tolerated by a peripheral vein is likely to be higher than 900 mOsm/L (in the range of 1200 mOsm/L) and is dependent upon the condition of the veins and fluid requirements. Low blood flow in combination with hyperosmolar solution is associated with a high risk of thrombosis and peripheral vein thrombophlebitis (PVT) and is therefore reserved for short-term therapy in individuals with robust veins. Simultaneous infusion of lipid emulsions 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 energy 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) 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.

Carbohydrate The most commonly used carbohydrate energy substrate is dextrose, which in its hydrated form provides **3.4 kcal/g**. Another carbohydrate energy substrate used less frequently is glycerol, a sugar alcohol which provides 4.3 kcal/g. Dextrose is commercially available in multiple concentrations ranging from 2.5% to 70%; however, for compounding purposes usually 50% and 70% concentrations are used. Our institution uses exclusively 70% dextrose concentration solution. Dextrose solutions are acidic with a pH ranging from 3.5 to 6.5, and vary in osmolarity depending upon their concentration. Higher dextrose concentrations (greater than 10% final concentration) are generally reserved for central venous administration because of propensity to cause thrombophlebitis in peripheral veins. Excessive dextrose delivery can result in increased carbon dioxide production, synthesis and storage of fat, hyperglycemia and PN associated liver disease (PNALD). In order to prevent overfeeding with glucose, the maximum dose in adults for dextrose administration is 5 mg/kg/min (**7.2 g/kg/d**). For critically ill patients, **4.3–5.8 g/kg/d** is recommended. PN should be initiated at a moderate dose (≥ 4.3 g/kg/d) to avoid potential complications. Provision of > 2 mg/kg/min (2.88 g/kg/d) provides maximal suppression of gluconeogenesis.

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

Calculations: calculating % dextrose solution from calories

Step #1 kcal / 3.4 kcal/g = grams

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

Example 2. 1020 kcal is desired in a parenteral solution of 2000 ml. What is the final dextrose concentration of the solution?

Step #1 1020 kcal / 3.4 kcal/g = 300 grams

Step #2 300 grams / 2000 ml x 100 = 15% final concentration

Sample calculations:

1. How many calories does 200 grams of dextrose provide?

2. What is the final concentration of a solution containing 200 grams in 1500 ml?

3. How many grams of dextrose is provided in a 2400 ml solution with a final concentration of 18%?

4. Is the solution in question #3 appropriate for a 50kg (110 lb) female?

5. How many ml of 50% and 70% base solution will be needed to fill the prescription in question #3?

Answers: 1. 680 kcal; 2. approx 13.5%; 3. 432 g; 4. No, >7.2 g/kg/d; 5. 864 ml, 617 ml

Fat Emulsion Intravenous fat emulsion (IVFE) or lipid emulsion is used to provide energy and is a source of essential fatty acids (EFA). In addition, lipid administration has a protective effect on hepatic microsomal oxidative enzyme (particularly the cytochrome P450) function which is an important route of drug and nutrient metabolism. 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, and sodium hydroxide to adjust the final pH (range 6 – 9). IVFE also provides a small source of phosphorus (15 mmol/L), selenium, vitamins E & K and cholesterol. IVFE are commercially available in 10%, 20%, and 30% concentrations. Each gram of fat provides 9 kcal; however, the glycerol and phospholipids in IVFE add calories so that 10% emulsion supplies 1.1 kcal/ml; 20% emulsion supplies **2 kcal/ml**; and 30% emulsion supplies 3 kcal/ml. Therefore, calories supplied from lipids should be based on kcal/ml of the solution; kcal/g method should not be used since it does not take into account the calories provided by the glycerol component (4.2 kcal/g) or phospholipids (6 kcal/g), thereby underestimating total 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 10% fat emulsion has a relatively greater amount of phospholipids and can raise triglyceride levels to a greater extent as compared to 20% and 30%

IVFE. Our institution uses 20% concentration only. Fat intake should be limited to less than 30% of total kcals. A minimum of 2-4% of total kcals that come from IVFE is required daily to prevent essential fatty acid deficiency.

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. If IVFE is infused as part of admixture with dextrose and amino acids in the same container, then the solution can be administered over 24 hours. The 24 hour hang time and infusion of this formulation is extended compared with the recommended 12 hour infusion of IVFE alone because bacterial growth is inhibited at reduced pH.

Whether infused separately from dextrose and amino acids or as admixture, IVFE infusion rate should not exceed 0.11 g/kg/h (**2.5 g/kg/d**). Greater infusion rates are associated with an increased risk of side effects such as hypertriglyceridemia, infections, reduced pulmonary diffusion capacity, and reticuloendothelial system (RES) dysfunction. During critical illness ≤ **1 g/kg/d** should be provided to minimize potential 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. If the patient's triglyceride level exceeds 400 mg/dl or a patient has an egg allergy, the IVFE should not be given. Fat emulsion should be used cautiously in patients with severe liver disease or dysfunction, or history of hyperlipidemia (e.g. AIDS) as these patients have a decreased capacity to clear the infused fat.

Protein Crystalline amino acids are used in PN formulations to provide protein and yield **4 kcal/g** if oxidized for energy. The amino acid products can be standard or specialty. Standard or balanced amino acid products are mixtures of essential and nonessential amino acids. The stock solutions available range from concentrations of 3% to 20%, however, the most commonly used preparations are 8.5% and 10%. Our institution standard amino acid solution is 20%. Modified or specialty amino acid products have a modified amino acid profile to meet age or certain disease specific amino acid requirements.

Disease specific modifications (more expensive):

1. Metabolic stress (trauma, thermal injury, hypercatabolic states):
   - branch chain amino acid (BCAA) enriched
   - Use is based on the theory that higher BCAA amounts are beneficial during severe metabolic stress by improving nitrogen balance in certain patient groups. However, the evidence does not support improved outcomes.

2. Liver failure with hepatic encephalopathy:
   - Contains increased amounts of branched-chain amino acids (BCAA) 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 the neurological dysfunction.
   - No difference in efficacy between standard verses 'liver' formulation has been shown; therefore, has very limited indications.

- Consider use only in patients that are refractory to standard medical treatment.

3. Renal failure:
   - Composed primarily of essential amino acids and histidine
   - Based on the theory that nonessential AA can be physiologically recycled from urea and essential AA must be provided from the diet.
   - Relatively dilute preparations (5.2% – 6.5%) and as a result fluid restriction and provision of adequate nutritional support can be difficult.
   - Offer no significant advantage over standard AA formulation; therefore has very limited indications
   - Recommended not to exceed 0.5 g/kg/d.

4. Fluid restricted:
   - Most concentrated solution available is 20%

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

Step #1 % x volume (ml) = grams

Example 1. Two liters of parenteral solution containing a final concentration of 6% protein (or 60 g/L)

Step #1 0.06 x 2000 ml = 120 grams

Sample calculations:

1. What is the final concentration of a solution containing 120 grams protein in 1500 ml?

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

3. How many ml of 10% and 15% base/compounding solution is necessary to fill the prescription in question #2?

Answers: 1. 8%; 2. 78 g; 3. 780 ml, 520 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 adults are listed in Table 1.

Table 1. Daily Electrolyte Requirements

Electrolyte	Parenteral Range
Sodium	45 – 145 mEq
Potassium	60 – 120 mEq
Calcium	10 – 20 mEq
Magnesium	10 – 30 mEq
Phosphate	30 – 60 mEq
Chloride	As needed to maintain acid-base balance
Acetate	As needed to maintain acid base balance

Electrolytes are also available in various salt forms, Table 2.

Table 2. 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 salt is not used due to its instability in a solution.

Vitamins

Vitamins are an essential component of a daily PN regimen because they are necessary for normal metabolism and cellular function. Commercially available vitamin products for PN supplementation include single vitamin products and multivitamin products that contain both fat-soluble and water-soluble vitamins. Adult patients receiving PN should receive a standard daily dose of parenteral multivitamins, table 3.

Table 3. Composition of Adult Parenteral Multivitamin Products (in 10 ml dose)

Component / Vitamin	Amount
Ascorbic Acid	200 mg
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
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

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 (Table 4). Other trace elements that may be supplemented in PN include molybdenum, iodine, fluoride and iron. 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 IVFE is disrupted by iron. Our institution does not add parenteral iron secondary to risk of anaphylaxis.

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 zinc per liter of small bowel output fluid loss or 17 mg of Zn per kg of stool or ileostomy output fluid loss should be added to PN formulation. Additional 10 to 20 mcg of chromium may be added to PN formulations per day for patients with intestinal losses in excess of one liter. Provision of additional copper and zinc may be needed in patients with burns to compensate for losses of these elements in burn wound

exudate. With 20% or greater of total body surface area burn, patients can lose 20 – 40% of body copper content within the first week of injury.

Table 4. Trace Elements Daily Requirement for Adults (in 1 ml dose)*

Trace Element	Amount
Zinc	2.5 – 5 mg
Copper	0.3 – 0.5 mg
Manganese	60 – 100 mcg
Chromium	10 – 15 mcg
Selenium	20 – 60 mcg

∗ Assumes normal age-related function and losses.

Parenteral Nutrient Preparations

PN formulations can be of 2 types: commercially available premixed dextrose – amino acids products (i.e., Clinimix) or customized PN formulations compounded from the individual components by a pharmacist. PN can be prepared as a total nutrient admixture (TNA) or as "2 in 1" (dextrose – amino acids) formulation. TNA or "3 in 1" solutions contain all necessary IV macronutrients (carbohydrate source usually in the form of dextrose, fat emulsion, and amino acids) and micronutrients (electrolytes, vitamins and trace elements) together in the same container for final administration. "2 in 1" solutions contain all the same components as TNA except for IVFE, which can be infused separately. Specific advantages and disadvantages are associated with the use of each PN formulation system, table 5.

Table 5. Advantages and Disadvantages of the Total Nutrient Admixture System

Advantages

- All components aseptically compounded by the pharmacy
- Fewer manipulations decrease the risk of touch contamination during administration
- Decreased nursing time needed in IV set-up and tubing changes, and no piggyback IVFE
- Less supply and equipment expense for only one pump and IV tubing
- Can apply in fluid restricted patients because IVFE 30% is restricted to use in TNA
- Inhibited or slower bacterial growth if contaminated compared to separate IVFE
- Reduced training time for home patients
- Improved patient compliance due to ease and simplicity of TNA administration
- More convenient storage, fewer supplies, easier administration in home care settings

Disadvantages

- Better growth medium for bacteria as compared to 2 in 1 solution
- Larger particle size of admixed IVFE precludes use of 0.22 micron (bacteria-eliminating) filter, and requires larger pore size filter of 1.2 microns
- Emulsion stability is influenced by pH, temperature, time, mixing order, ingredients and electrolyte charge, and is less stable than a 2 in 1 solution
- Difficult to visualize precipitate or particulate material in the opaque admixture
- Certain medications are incompatible with IVFE portion of admixture

Our institution uses exclusively "2 in 1" solutions and IVFE are infused separately as IV piggyback.

Stability and Compatibility of PN

The 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

IVFE are most stable at pH range of 6 to 9. Additives that lower pH below 5 (e.g. dextrose) or increase pH above 10 may destabilize or "crack" the emulsion in TNA. Breaking of an emulsion involves a change in droplet size and dispersion resulting in the oil phase separating from the water phase and it ranges from subtle changes in the uniformly white appearance of the emulsion that may progress to yellow water streaks throughout the bag and finally complete separation of an oil and water phase by forming layers. At this point, TNA becomes unsafe for administration. Excess of any cation amounts, especially divalent cations such as calcium or magnesium can destabilize the IVFE in TNA. Trivalent cations such as iron have even greater destabilizing effects and should not be added to the IVFE-containing TNA.

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, 25C° to body temperature, 37C°)

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.

Filters

The need for filtration of PN at bedside is great. Filters can remove precipitates (e.g. calcium phosphate), and particular matter (e.g. plastic fragments from the bag) from a PN formulation. Filters that are recommended for use are 0.22 micron and 1.2 micron. A 0.22 micron sterilizing filter should be used with 2-in-1 solutions. This will filter out organisms like *Staphylococcus epidermidis*, *Escherichia coli* and *Candida albicans* from a PN administration line. However, because fat particles are larger than 0.22 microns, the use of this filter with IVFE containing solutions is inappropriate. Currently 1.2 micron filters are used with TNA to avoid particles shearing and instability. This is not a sterilizing filter but will remove large microorganisms including *Candida albicans*. An occluded filter should never be removed to allow a PN

formulation to infuse freely. Filter should be used to reduce infusion of particulates, microprecipitates and microorganisms.

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.

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 is known to be 900 mOsm/L (a higher osmolarity of up to 1200 mOsm/L is likely to be tolerated as well). 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. Dextrose solutions greater than 10% final concentration may not be infused into peripheral veins and should be administered via a central venous access catheter.

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 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 appropriate formulas have 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.
    - 1 mmol NaCl = 1 mmol of Na^+ + 1 mmol of Cl^- = 1 mEq Na^+ + 1 mEq Cl^-
    - Osmolarity = 1 mEq or 1 mmol of solution of NaCl is equivalent to 2 mOsm
- For divalent salts (e.g. $MgSO_4$, $CaCl_2$), the equivalent weight is one-half its molecular weight, since the valence of the divalent component is two. 1 mEq = 0.5 mmol.

- 1 mmol $MgSO_4$ = 1 mmol of Mg^{2+} + 1 mmol of SO_4^{2-} = 2 mOsm
- Osmolarity of 1 mEq $MgSO_4$ = (2 x 1 mEq of $MgSO_4$) / 2 = 1 mOsm/L

- For trivalent salts (e.g. Na_3PO_4, K_3PO_4), 1 mEq = 0.333 mmol. However, phosphate can exist in different ionic forms $H_2PO_4^-$, HPO_4^{2-}, or PO_4^{3-}, and an exact valence can not be given. Valence is approximated at around minus 2. As a result, phosphate is usually expressed in mmoles.
  - 1 mmol K_3PO_4 = 3 mmol of K^+ + 1 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 g in 2L (45 g/L) x 10 mOsm/g/L = 450 mOsm in 1L
or 4.5% solution x 100 mOsm/% solution = 450 mOsm/L

Dextrose: 200 g in 2L (100 g/L) x 5 mOsm/g/L = 500 mOsm in 1L
or 10% dextrose x 50 mOsm/% solution = 500 mOsm/L

Electrolytes: (155 mEq Na + 90 mEq K + 15 mEq Ca + 20 mEq Mg) x
x 2 (adjustment for salt component) 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 6. 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	pH	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 ⅓NS	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 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 for sample order form)

1. Determine calorie and protein requirements.
   - Individual patients may require greater or less than the estimated requirements due to acute illness, therapies or underlying medical conditions.

   Estimated calorie requirements 20 – 30 kcal/kg

   Estimated protein requirements 0.8 – 2 g/kg

   Table 7. Estimating Protein Requirements

Clinical status	**Protein Requirements** (g/kg/day)*
Maintenance	0.8 – 1.0
Mild to moderate stress level	1.0 – 1.5
Severe stress level	1.5 – 2.0
Post-operative	1.2 – 2.0
Renal failure on chronic dialysis	1.2 – 1.3
Hepatic failure	
with encephalopathy	0.8 – 1.0
without encephalopathy	1.0 – 1.5

   *Note: based on usual body weight except in obese patients.

2. Determine volume of parenteral solution to be provided.

Daily estimated fluid requirements 30 – 40 ml/kg

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: 60 kg women with the following daily requirements: 1800 kcal, 100 g protein, and 2000 ml fluid total.

Calories provided by protein: 100 g protein x 4 kcal/g = 400 kcal

Calories provided by lipid at 1 g/kg/d: 60 g at 2 kcal/ml of 20% lipid emulsion
60 g x 2 kcal/ml x (1000 ml / 200 g) = 600 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
   - Important to calculate in order to assure that the final solution *can be* compounded using the available concentration of solutions
     - 70% dextrose
     - 20% Prosol (standard protein)

Example: 100 g protein x 20% standard protein solution
100 g x (1000 ml / 200 g) = 500 ml

235 g dextrose x 70% dextrose
235 g x (1000 ml / 700 g) = 340 ml

Total volume = dextrose (340 ml) + protein (500 ml) + ~ 150–200 ml for the average adult electrolytes and additives = 990 – 1040 ml

If the desired volume of the 2–in-1 solution is 1700 ml (2000 ml total – 300 ml from lipid emulsion), the addition of ~ 690 ml of sterile water will be needed to achieve the final requested volume.
Note: ~1010 ml is the minimal volume that can be compounded given the above component requirements.

5. Dose the individual electrolytes.

   See table 8 for daily electrolyte requirements.

   Table 8. Daily Electrolyte Dosing

Electrolytes	Average Dosing	Range
Sodium	77 mEq/L	45 – 145 mEq
Potassium	90 mEq	60 – 120 mEq
Calcium	15 mEq	10 – 20 mEq
Magnesium	20 mEq	10 – 30 mEq
Phosphate	45 mEq	30 – 60 mEq
Chloride	As needed to maintain acid-base balance	
Acetate	As needed to maintain 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 77 mEq/L (equivalent to ½NS Na concentration) or 155 mEq of NaCl in a 2L bag. Na concentration can be varied.

   - For K, Mg, Ca and P
     - Provide the average adult dose if the lab results are within normal limits.
     - Provide high adult dose range if the lab results are low or low normal.
     - Provide low adult dose range if the lab results are high or high normal.
     - Omit any electrolyte if the lab result is high.
     - Add a small amount back to the solution if or when level returns to normal
     - *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
     - If mild metabolic acidosis is present, can start with providing ⅓ – ½ of total Na dose as the acetate salt. With more severe metabolic acidosis can provide all of Na dose as the acetate salt.
     - If further bicarbonate buffering is needed, all of the K (excluding K given as KPhos) can be provided as the acetate salt.

6. Provide standard multivitamin and trace element preparations.
   - See tables 4 and 5
   - Provide 10 ml of adult multivitamin preparation and 1 ml of adult trace element preparation per day
   - Additional separate vitamins and trace elements can be added depending upon disease state

7. Complete the order form.

Alternatively, a premixed solution that is available in our institution (table 9) can be used. 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 9. 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
pH	6.0
Osmolarity	1070

Initiation of PN

Generally should begin dextrose, protein and fat at goal unless patient is at 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 and total calories should be limited to 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 10.

Table 10. Suggested Monitoring for PN

Parameter	Baseline	Critically Ill 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
CBC with differential	Yes	Daily	Weekly
PT, PTT	Yes	Weekly	Weekly
Serum triglycerides	Yes	Weekly	Weekly
Albumin	Yes	Daily	Weekly
Prealbumin	Yes	Weekly	Weekly
C-reactive protein	Yes	Weekly	Weekly
Glucose	Yes	Q6 hours (until controlled)	Daily (if controlled)
Weight	Yes	Daily	3 x weekly
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:

1. In a patient receiving tube feedings
   - Once patient is receiving tube feedings (TFs) at 50% of goal rate with good tolerance, the PN may be reduced and then weaned off as TFs rate advances to goal.
2. In a patient receiving a 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 $\geq$ 85% of estimated requirements.

Example:	50 year old woman is receiving 2L CPN containing 4.5% AA and 15% dextrose infusing at 84 ml/hr with IVFE 20% infusing as piggyback at 10 ml/hr providing a total of 1860 kcal. **To taper PN:** Start Jevity 1.5 tube feeds via NGT at 200 ml q6 hrs. Decrease CPN rate to 50 ml/hr, continue 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 Complications

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. Nonthrombotic catheter occlusion can be caused by external clamps, kinking of the catheter, occluded port needles and constricting sutures.

Metabolic Complications

Macronutrient –Related Complications

Hyperglycemia – is the most common complication associated with PN administration. Risk

factors for hyperglycemia include metabolic stress, medications, obesity, diabetes, and excess calorie (dextrose) administration.

Suggested prevention of hyperglycemia with PN includes:

- Glucose monitoring every 6 hours with initiation of PN. Maintaining levels between 80 and 110 mg/dl is associated with decreased morbidity and mortality in intensive care patients.
- Administration of decreased amounts of dextrose initially in at-risk patients (100 to 150 g/d or 2 to 3 mg/kg/min or 2.8 – 4.3 g/kg/d)
- A base level of insulin may be added to the PN formulation for glycemic control. An initial regimen of 0.05 – 0.1 units of regular insulin per gram of dextrose is common or 0.15 – 0.2 units/g dextrose in patients who are already hyperglycemic. Two thirds of the total amount of sliding scale insulin coverage received over the past 24 hours can be added to the next day's PN formulation to aid in optimizing glycemic control. Consider use of an insulin drip if a patient has high insulin requirements.
  Note: 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 (e.g. multivitamins and trace elements may enhance availability to 95%)
- Rarely, hyperglycemia can be caused by chromium deficiency. Insulin is ineffective in these patients.

Hypoglycemia – 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) – can occur within 1 to 3 weeks in adults receiving IVFE-free PN formulations. Two polyunsaturated fatty acids, linoleic and alpha-linolenic, can not be synthesized by the body and are considered essential. Clinical manifestations of EFAD include scaly dermatitis, alopecia, diarrhea, hepatomegaly, thrombocytopenia, fatty liver, anemia, and diminished wound healing. 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. Approximately 500 ml of 10% IVFE or 250 ml of 20% IVFE given twice weekly or 500 ml of 20% IVFE given once a week will prevent EFAD. 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.

Hypertriglyceridemia – 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 (greater than 110 mg/kg/h). Reducing the dose to **≤ 1 g/kg/d** and/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 (½ – 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.

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 in adults for IVFE administration should not exceed **2.5 g/kg/d**. Acceptable serum triglyceride concentration is ≤ 400 mg/dl.

Although rare, allergic reactions to IVFE can occur, especially in patients with history of egg allergy. Carnitine deficiency can result in high triglyceride levels. Carnitine is necessary for the optimum oxidation of fatty acids. Carnitine is not present in any component of PN formulations, however it can be added for selected patients (at 2 – 5 mg/kg/d) who have documented deficiency or are susceptible to a deficiency such as patients on a carnitine free diet or who have heart and liver disease or are on hemodialysis.

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, 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.

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.

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.

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, table 11.

Table 11. Lipid-soluble Vitamins Deficiency and Toxicity Symptoms

Vitamin	Deficiency	Toxicity
A (Retinol, β-carotene)	Night blindness, xerophthalmia, keratinization of skin and eyes, impaired immune function.	Dry skin, anorexia, irritability, fatigue, insomnia, blurred vision, alopecia, bone and joint pains, birth defects.
D (Calciferol)	Rickets in children = poor mineralization of bone; osteomalacia in adults = bone demineralization.	Nausea, vomiting, anorexia, muscular weakness, soft tissue calcifications, growth retardation, bone disease, confusion.
E (Tocopherols, tocotrienols)	Extremely rare – neuromuscular dysfunction, hemolysis.	Nontoxic under normal conditions. In severe overdose – nausea.
K (Phylloquinone, menaquinones)	Impaired blood clotting, hemorrhagic disease.	No known toxicity. Interference with oral anticoagulant therapy.

Also, inadequate thiamin might be provided in the multivitamin preparations in certain disease states (e.g. refeeding syndrome, alcoholism) resulting in vitamin deficiency.

Trace Elements

Parenteral nutrition provides a limited range of nutrients and bypasses GI homeostatic mechanisms leaving patients at risk for deficiencies and toxicities, including 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 may result in cerebral Mn deposition. Excessive GI losses via drains and stool can result in zinc, copper and chromium deficiencies. 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.

Symptoms of certain trace elements deficiencies and toxicities are listed in table 12.

Table 12. Trace Element Deficiency and Toxicity Symptoms in Adults[b]

Trace Element	Deficiency	Toxicity
Manganese (Mn)	Impaired metabolism of carbohydrate and lipid, dermatitis, impaired protein synthesis, weight loss. (Has not been reported in PN patients).	Extrapyramidal neurologic symptoms: headache, tremor, facial nerve deficit, gait disturbance. Hyperintensity of signals on brain MRI in basal ganglia.
Selenium (Se)	Cardiomyopathy, skeletal myopathy, myalgias, myositis, impaired cellular immunity, discoloration of nails.	Alopecia, brittle hair and nails, skin rash, GI disturbance, "garlic" breath odor, nervous system abnormalities.
Zinc (Zn)	Dermatitis, alopecia, anorexia, reduced taste sensitivity, impaired immune function, impaired wound healing, glucose intolerance.	Anemia, hyperamylasemia, fever, central nervous system dysfunction in renal patients; deficiency of Cu (enteral Zn interferes with Cu absorption).
Chromium (Cr)	Glucose intolerance, hyperlipidemia, peripheral neuropathy, encephalopathy	No known toxicity of Cr^{3+} (trivalent form). Has not been reported in PN patients.
Copper (Cu)	Hypochromic, microcytic anemia, leucopenia, neutropenia, skeletal abnormalities, and rarely, thrombocytopenia.	Accumulation in liver, hepatocellular damage.
Iron (Fe)	Hypochromic microcytic anemia, pallor, fatigue, decreased work performance.	Hemosiderosis, hemochromatosis, accumulation in liver and heart, some endocrine tissues; iron toxicity can be fatal.
Molybdenum (Mo)	Tachycardia, tachypnea, headache, night blindness, lethargy.	Limited toxicity data for humans. Possible gout (high incidence in areas where soil is high in Mo), and possible excessive urinary copper excretion.
Iodine (I)	Hypothyroidism – weakness, cold intolerance, weight gain, thinning hair, goiter (thyroid enlargement).	Thyroiditis, goiter, hypo- or hyperthyroidism, thyroid papillary cancer, dermatoses (iodermia).

[b]From Fessler TA. Trace Element Monitoring and Therapy for Adult Patients Receiving Long-term Total Parenteral Nutrition. Practical Gastroenterology 2005; March: 44-65

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 hypomagnesmia.
- 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 carbohydrate provided to 150 – 200 g/d.
- Including adequate amounts of potassium, magnesium, phosphorus, and vitamins in initial PN. Provide adequate thiamin (additional 100 mg/d for 3 to 7 consecutive days).
- 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 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 since they are not a part of the standard PN solution.

Management of PN-induced hepatobiliary abnormalities usually includes decreasing dextrose and lipid calories to about 1/3 of total calories (limiting the lipid dose to 1 g/kg/d), 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.

Metabolic Bone Disease

Osteoporosis and osteomalacia are associated with long-term PN use. 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. Number of factors has been associated with increased urinary calcium excretion: higher protein doses (2 g/kg/d as compared to 1 g/kg/d) 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 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; 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.

References

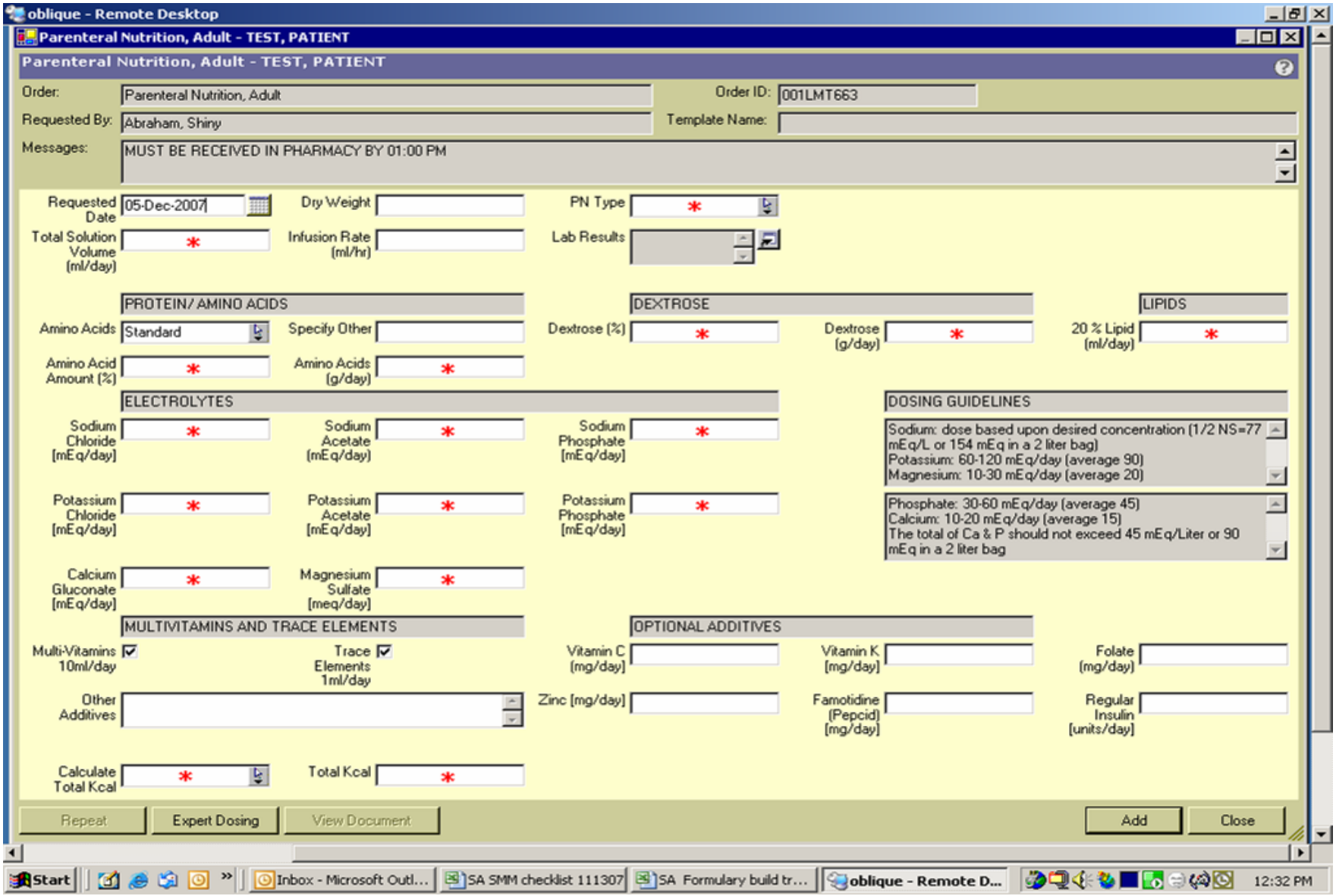
1. American Gastroenterological Association Medical Position Statement: Parenteral Nutrition. Gastroenterology 2001; 121:966-969
2. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors and The Clinical Guidelines Task Force: Specific guidelines for diseases- adult. JPEN 2002; 26(1)suppl:61S-96S. http://www.nutritioncare.org
3. Baumgartner TG (ed). Clinical Guide to Parenteral Micronutrition, 3rd edition. Fujisawa USA Inc;1997:27-51.
4. Berger MM. Antioxidant Micronutrients in Major Trauma and Burns: Evidence and Practice. NCP 2006;21(5):438-449.
5. Buchman A. Total parenteral nutrition-associated liver disease. JPEN 2002;26(5)suppl:S43-S48.
6. Christianson MA, Schwartz MW, Suzuki N. Determinants of insulin availability in parenteral nutrition solutions. JPEN 2006;30(1):6-9.
7. Fessler TA. Trace Element Monitoring and Therapy for Adult Patients Receiving Long-term Total Parenteral Nutrition. Practical Gastroenterology. 2005; March: 44-65.
8. Gottschlich M.(ed). The ASPEN Nutrition Support Core Curriculum: A Case-Based Approach- The Adult Patient: ASPEN, Silver Springs MD;2007:264-338, 540-557.
9. Hamilton C, Austin T, Seidner DL. Essential fatty acid deficiency in human adults during parenteral nutrition. NCP 2006;21(4):387-394.
10. Kane KF, Cologiovanni L, McKiernan J, Panos MZ, Ayres RCS,Langman MJS et al. High osmolarity feedings do not increase the incidence of thrombophlebitis during peripheral IV nutrition. JPEN 1996;20(3):194-197.
11. Kearns LR, Phillips MC, Ness-Abramof R, Apovian CM. Update on parenteral amino acids. NCP 2001;16(4):219-225.
12. Kelly DG. Guidelines and available products for parenteral vitamins and trace elements. JPEN 2002;26(5):S34-S36.
13. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. NCP 2005;20(6):625-633.
14. Lee, V. Liver dysfunction associated with parenteral nutrition: What are the options? Practical Gastroenterology 2006;Dec:49-68.
15. Marcuard SP, Dunham B, Hobbs A, Caro JF. Availability of insulin from total parenteral nutrition solutions. JPEN 1990;14(3):262-264.
16. Maswoswe JJ, Okpara AU, Hilliard MA. An old nemesis: Calcium and phosphate interaction in TPN admixtures. Hosp Pharm 1995;30(7):579-586.
17. Miller DG, Williams SK, Palombo JD, Griffin RE, Bistrian BR, Blackburn GL. Cutaneous application of safflower oil in preventing essential fatty acid deficiency in patients on home parenteral nutrition. Am J Clin Nutr. 1987;46:419–423.
18. Morbidity and Mortality Weekly Report (MMWR). Guidelines for the Prevention of Intravascular Catheter-Related Infections. Aug 9, 2002; 51(RR10);1-26
19. Nakasaki H, Katayama T, Yokoyama S, Tajima T, Mitomi T, Tsuda M et al. Complication of parenteral nutrition composed of essential amino acids and histidine in adults with renal failure. JPEN 1993;17(1):86-90.
20. Payne-James JJ, Khawaja HT. First Choice for total parenteral nutrition. The peripheral route. JPEN 1993;17(5):468-478.

21. Skipper A, Tupesis N. Is there a role for nonprotein calories in developing and evaluating the nutrient prescription? NCP 2005;20(3):321-324.
22. Task force for the revision of safe practices for parenteral nutrition. Safe practices for parenteral nutrition. JPEN 2004;28(6)Suppl:S39-S70.
23. Van Den Berghe, G,Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345(19):1359-1366.

Glossary Terms

AA	Amino acids
EN	Enteral nutrition
PN	Parenteral nutrition
AAA	Aromatic amino acids
CDC	Centers for Disease Control
CPN	Central parenteral nutrition
EFA	Essential fatty acids
LCT	Long-chain triglycerides
LPL	Lipoprotein lipase
PPN	Peripheral parenteral nutrition
PVT	Peripheral Vein Thrombophlebitis
TNA	Total nutrient admixture
TPN	Total parenteral nutrition
RES	Reticuloendothelial system
BCAA	Branch chain amino acid
EFAD	Essential Fatty Acid Deficiency
IVFE	Intravenous fat emulsion
PICC	Peripherally inserted central catheter
PNAC	PN-associated cholestasis
PNALD	PN associated liver disease

Appendix I. Sample order form.



* Required field