# ADULT PARENTERAL NUTRITION CURRICULUM

Nassau University Medical Center

Revised 5-2019 by Lisa Musillo MS, RDN, CNSC
Formatting & Citations by Fariha Azad, MPH, MS, RDN

# Table of 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. This therapy has been in use for over 50 years, however its history dates back more than 350 years. 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. TPN is not a preferred acronym since total nutrition can be provided peripherally if a larger volume is prescribed. CPN has higher glucose content (usually greater than 12% final concentration) and, along with amino acids (AA) 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). [1]

Peripheral parenteral nutrition (PPN) can have similar nutrient composition as CPN but with a larger volume and lower osmolarity. It contains a lower concentration of dextrose (usually ≤10% final concentration) and amino acids (≤4.25% final concentration) so it may be delivered via the peripheral vein. PPN may be used for patients to provide partial or complete nutrition support when they are unable to receive it orally or enterally. PPN therapy is typically used in patients who can tolerate a higher fluid load.

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[2 3]

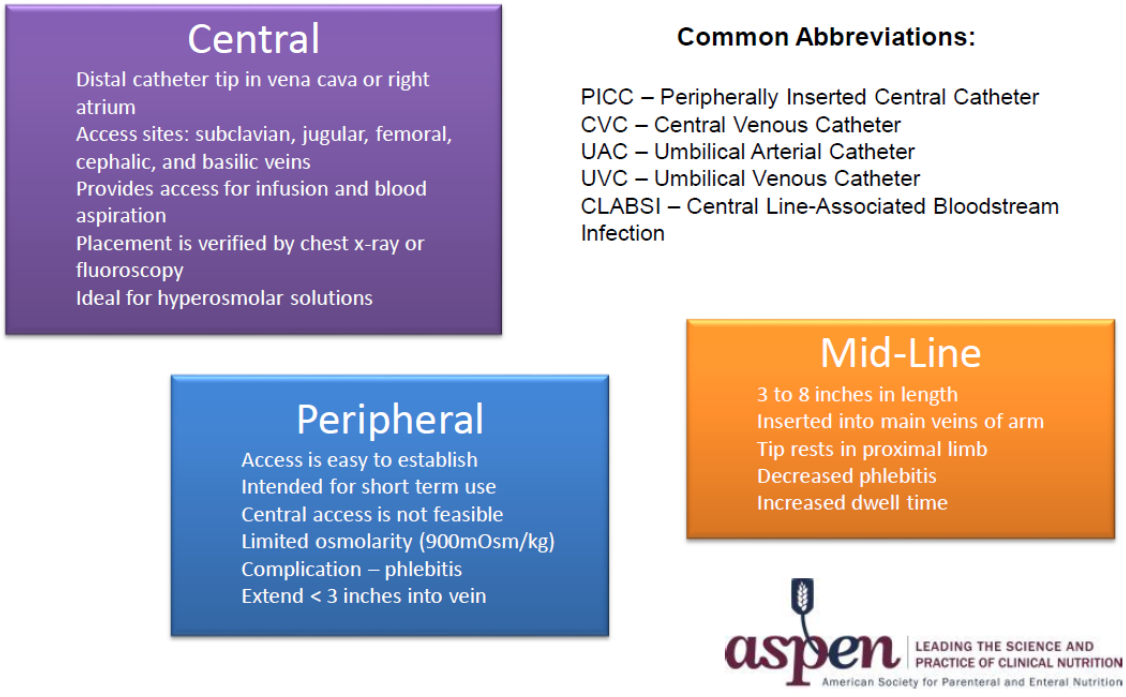
- Initiate PN after 7 days for well-nourished, *stable* adult patients who have been unable to receive significant (50% or more of estimated requirements) oral or enteral nutrients.
- Initiate PN within 3 to 5 days in those who are nutritionally-at-risk and unlikely to achieve desired oral intake or EN.
- Initiate PN as soon as is feasible for patients with baseline moderate or severe malnutrition in whom oral intake or EN is not possible or sufficient.
- Initiate PN in patients with a nonfunctioning gut or suspected nonfunctioning GI tract in a malnourished or hypermetabolic patient.
  [e.g. paralytic ileus, mesenteric ischemia, motility disorders, small bowel obstruction, gastrointestinal (GI) fistula (except when enteral access may be placed distal to the fistula or volume of output is greater than 500 ml/day)]
- Initiate exclusive PN in severely malnourished critically ill patients, or those determined to be at high nutritional risk in which EN is not feasible as soon as possible after admission to the intensive care unit (ICU).

### Contraindications for Parenteral Nutrition

- Functioning GI tract capable of adequate absorption of nutrients
- Inability to obtain venous access
- Patients whose prognosis does not warrant aggressive nutritional support (e.g. comfort measures)
- When the risks of PN are judged to exceed the potential benefits.
- Delay the initiation of PN in a patient with *severe* metabolic instability until the patient's condition has improved

# Vascular Access

**Figure 1:** [4]



## Peripheral Venous Access

One of the easiest and safest ways to access the vascular system is to place a cannula into a peripheral vein. The adequacy of the vein limits the use of the peripheral system for infusion. It is thought that catheter tips located in a peripheral vein 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.[5] [6] At NUMC the PPN osmolarity is maintained less than 1100 mOsm/L. Low blood flow in combination with a 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 PN. PPN is typically used for short periods (up to two weeks) because of limited tolerance and few suitable peripheral veins. See figure 1. Midlines are considered a peripheral access since they do not minimize the risk of PVT when hyperosmolar solutions are infused.

## Central Venous Access

In general, central venous access is preferred for PN administration since the rate of blood flow rapidly dilutes the hypertonic parenteral nutrition formulation to that of body fluids.[7] 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 requires PN and cannot tolerate the larger fluid load necessary with PPN to meet macronutrient requirements.

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 (avoid in patients with advanced chronic kidney disease due to high risk of central venous stenosis), jugular and femoral (least preferred site) veins. A chest radiograph is done afterwards to confirm placement. Central venous infusions are not limited by pH of the formulation, osmolarity or volume. See figures 1 and 2.

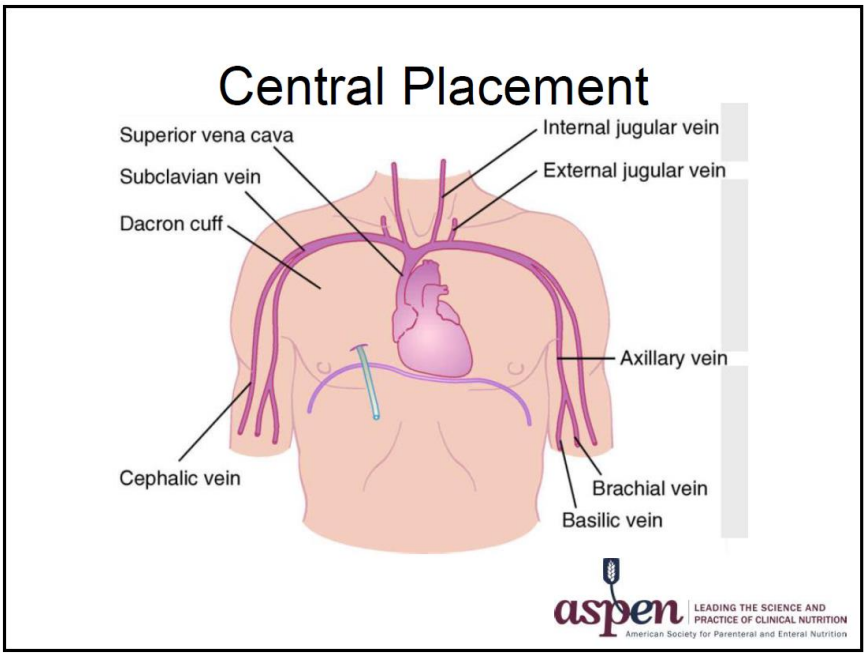
## Peripherally Inserted Central Catheter (PICC or PIC line)

PICC 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. A 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. PICCs do not restrict arm movement or normal activity. See figures 1 and 2.

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

**NEVER USE DIALYSIS ACCESS FOR PN ADMINISTRATION.**

**Figure 2:**[4]




# PN Formulation Components

PN is a finite solution, containing very specific ingredients. Components used in formulating PN typically include energy substrates such as carbohydrate, lipid and protein, as amino acids, as well as electrolytes, vitamins, and trace elements. Other essential or semi-essential nutrients are not found in the solution, and their absence may contribute to organ dysfunction or deficiency states over time (e.g., iron, glutamine, choline, carnitine, cysteine, taurine). Sterile water for injection is included to add volume to the PN formulation to meet prescription requirements. Sulfites are added as a preservative to many PN components and may cause an allergic reaction.

## Energy Substrates

Gluconeogenesis, from amino acids principally, is the major source of new glucose formation in malnourished or critically ill patients. 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. Providing an adequate energy source (as a mixture of dextrose and lipids) has protein-sparing effects. A minimum of ~ 1 mg/kg/min or 1.44 g/kg/d is necessary to minimize accelerated protein breakdown, loss of cations (especially sodium) and ketosis.[8]

## Carbohydrates

The most commonly used carbohydrate energy substrate is dextrose, which in its hydrated form provides **3.4 kcal/g**. The brain, renal medulla and red blood cells use glucose as their main energy source with an estimated daily requirement of 150 g.[9] 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. 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 PVT.

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 **7.2 g/kg/d** (5 mg/kg/min).[8] For critically ill patients, **4.3–5.8 g/kg/d** dextrose is recommended. PN should be initiated at a moderate dose (≥ 4.3 g/kg/d) to avoid potential complications. Provision of ~ 2.88 g/kg/d (2 mg/kg/min) provides maximal suppression of gluconeogenesis. Glucose production persisted at lower glucose infusion rate but was suppressed to nearly zero at the higher rate (1.7 +/- 0.5 mg/kg/min).[10] Be sure to take into account sources of dextrose provided by other therapies (e.g. CAPD, CRRT), medications given by intravenous piggy back (IVPB) (e.g. antibiotics) and drips (e.g. midazolam, fentanyl, cisatracurium).

**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%?

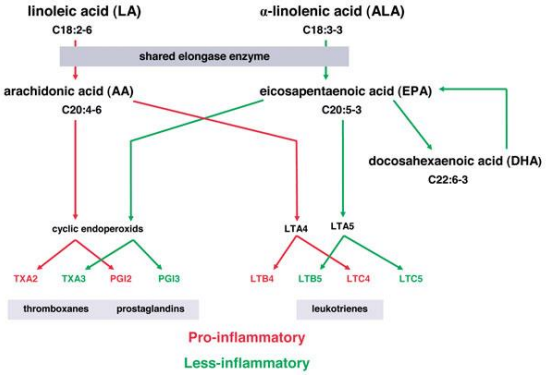
4. Is the solution in question #3 appropriate for a 50kg (110 lb) female?

Answers: 1. 680 kcal; 2. approximately 13.5%; 3. 432 g; 4. No, >7.2 g/kg/d

## Lipid Injectable Emulsion


Lipid injectable emulsion (ILE) is used to provide energy, is a source of essential fatty acids (EFA) and protein sparing calories, and is necessary for proper biologic function. Fatty acids are key structural components of cell membranes (phospholipids), assuring membrane integrity and fluidity. They serve as precursors of bioactive mediators such as eicosanoids (prostaglandins, leukotrienes, and thromboxanes) and steroid hormones (cholesterol), and regulate the expression of a variety of genes and modulate cell signaling pathways (apoptosis, inflammation, and cell-mediated immune responses.[11] Lipids can modulate metabolic processes at local, regional, and distant sites. Omega 3 and omega 6 fatty acids compete for the same enzyme systems, thereby exerting various effects on the body. See figure 3.

**Figure 3:** Omega 3 Fatty Acids compete with omega 6 fatty acids for production of less inflammatory eicosanoids[12]




The calories from ILE can decrease the dextrose load provided which may reduce the risk of hyperglycemia and liver dysfunction. Daily dosing is preferable to 3 times weekly. 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.[13] Current commercially available ILE in the United States (US) are derived from soybean oil (Intralipid, Nutrilipid) in 20% or 30% concentrations, and 2 newer emulsions.[11] SMOF lipid contains soybean oil, medium chain triglycerides, olive oil and fish oil, and is available in 20% concentration. Omegaven 10% contains fish oil and is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC) or direct bilirubin ≥2 mg/dl. Fish oil-based ILE improves clinical outcomes and decreases the overall costs of ICU stay compared with standard soy-based ILE.[11]

All ILEs contain long-chain triglycerides (LCT), egg yolk phospholipids as an emulsifier, glycerol to render the formulation isotonic, small source of phosphorus (15 mmol/L), selenium, vitamins E & K and cholesterol. The 30% ILE is approved for bulk mixing only. See table 1.

**Table 1:**[14]

**Commercially Available ILEs in the US**

| | Intralipid[1] | Nutrilipid[2] | Smoflipid[3] | Omegaven[4] |
|---|---|---|---|---|
| **Manufacturer** | Fresenius Kabi/ Baxter* | B. Braun Medical | Fresenius Kabi | Fresenius Kabi |
| **Pediatric Indication** | Yes | Yes | No | Yes† |
| **Oil Source** | Soybean Oil 100% | Soybean Oil 100% | Soybean Oil 30% MCT 30% Olive Oil 25% Fish Oil 15% | Fish Oil 100% |
| | Composition (Mean Values)[1-4] | | | |
| **Linoleic** | 53% | 53% | 19.5% | 1.5% |
| **α-Linolenic** | 7.5% | 7.5% | 2.5% | 1.1% |
| **Eicosapentaenoic (EPA)** | 0% | 0% | 2.3% | 19.5% |
| **Docosahexaenoic (DHA)** | 0% | 0% | 2.3% | 20.5% |
| **α-Tocopherol (mg/L)** | 38 | n/a | 163-225 | 150-300 |

ILE = Intravenous lipid emulsion; MCT = medium chain triglyceride
*Distributed
†Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)
1. Intralipid Prescribing Information, 2015; 2. Nutrilipid Prescribing Information 2014, B. Braun Medical, Inc.; 3. Smoflipid Prescribing Information, Fresenius Kabi USA, LLC. 2016 4. Omegaven prescribing information, Fresenius Kabi USA, LLC. 2018

Each gram of fat provides 9 kcal; however, the glycerol and phospholipids in ILE add calories so that 10% emulsion supplies 1.1 kcal/ml; 20% emulsion supplies **2 kcal/ml**; and 30% emulsion supplies 3 kcal/ml.[15] 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. (A shortcut method is to multiple the lipid grams by 10 for the 20% and 30% emulsion, by 11 for the 10 %.)[15] If patients are on the sedative 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% ILE has a relatively greater amount of phospholipids and can raise triglyceride levels to a greater extent as compared to 20% and 30% ILE. Fat intake should be limited to less than 30% of total kcal. A minimum of 2-4% of total kcal from linoleic acid in ILE is required daily to prevent essential fatty acid deficiency, 10% of total kcal from fat source.

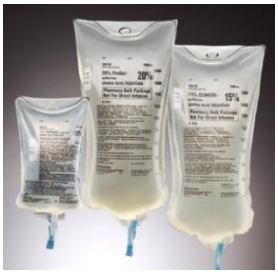

The CDC recommendation is to hang ILE for no longer than 12 hours because of enhanced microbial growth potential with ILE when infused separately from dextrose and amino acids formulations.[7] However, if volume considerations require more time, the infusion should be completed within 24 hours. The usual practice of our institution is to infuse ILE over 24 hours to minimize complications. The solution can be safely administered over 24 hours if ILE is infused as part of an admixture with dextrose and amino acids in the same container. The 24 hour hang time and infusion of this formulation is extended compared with the recommended 12 hour infusion of ILE alone because bacterial growth is inhibited at reduced pH.

ILE infusion rate should not exceed 0.11 g/kg/h (**2.5 g/kg/d**) whether infused separately from dextrose and amino acids or as an admixture.[7] Greater infusion rates are associated with an increased risk of side effects such as hypertriglyceridemia, infections, thrombocyte adhesiveness, reduced pulmonary diffusion capacity, reticuloendothelial system (RES) dysfunction and fat overload syndrome.[7,8] Fat overload syndrome symptomology includes headaches, seizure, fever jaundice, hepatosplenomegaly, abdominal pain, respiratory distress, pancytopenia and shock.[7] During critical illness ≤ **1 g/kg/d** should be provided to minimize potential complications when using a primarily soy-based ILE[7]**, 1.5 g/kg** when using SMOF.


Adverse events related to ILE are infrequent and may occur within minutes or hours after infusion, or be delayed for weeks to years with ongoing exposure.[1,16] Reactions may vary depending upon the specific ILE and rate of infusion, and may include dyspnea, cyanosis, nausea, vomiting, flushing, dizziness, pain in the back and chest, sweating, headache, priapism, ARDS, pancreatitis, cholestasis, fat overload syndrome, and fat emboli..[8,16] ILE should be withheld if the triglyceride level exceeds 400 mg/dl (and sample drawn with good technique from the IV access) or if an allergy exists to one or more of the ILE's components. Be aware of specific allergies to egg, soy, fish or peanuts. Lipid emulsion should be used cautiously in patients with severe liver disease or dysfunction, or history of hyperlipidemia as these patients have a decreased capacity to clear the infused fat.

**Amino Acids**

Crystalline AA are used in PN formulations to provide a source of protein and yield **3.4 kcal/g** if oxidized for energy. This is less than the 4 kcal/g derived from protein. Free AA contain less protein substrate, and less energy than the proteins they created due to a dehydration reaction. Therefore 100g of hydrated mixed AA provides only 340 kcal and 83 g of protein substrate.[17]. It is recommended to use total calories when calculating the PN prescription. Non-protein calories had been used historically but this practice is no longer recommended due to the risk of overfeeding.[18] The AA products can be categorized as standard or specialty. Standard or balanced AA products are mixtures of essential and nonessential AA. The stock solutions available range from concentrations of 3% to 20%, however, the most commonly used compounding preparations are 10% and 15%. Modified or specialty AA products have a modified AA profile to meet age or certain disease specific requirements.



*Disease specific modifications (more expensive):*[7,19]

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 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 AA 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 and may cause harm; therefore has very limited indications. Use may result in hyperammonemia.
   - Recommended not to exceed 0.5 g/kg/d.

4. Fluid restricted:
   - Most concentrated base solution available is 20% (often used in intradialytic PN)

Some commercially available AA formulations can also contain various concentrations and combinations of electrolytes and/or buffers (like P and acetate), in addition to inherent or endogenous electrolyte content of the individual AA.

**Calculations:** **calculating AA from % solution**

% x volume (ml) = grams

**Example 1.** Two liters of parenteral solution containing a final concentration of 6%

AA (or 60 g/L)

0.06 x 2000 ml = 120 grams

**Sample calculations:**

1. What is the final concentration of a solution containing 120 grams AA in 1500 ml?
2. How many AA are supplied in 1200 ml with a final concentration of 6.5%?
3. How many grams of **protein** are supplied?
4. How many kcal do the AA provide?

Answers: 1. 8%; 2. 78 g; 3. 64 g; 4. 265 kcal

## 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 2. Electrolytes are also available in various salt forms, Table 3.

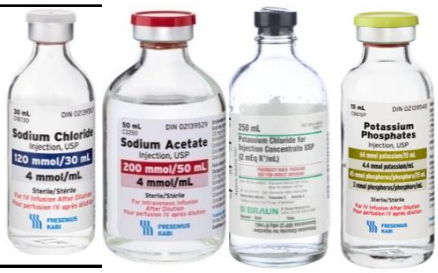
**Table 2. Daily Electrolyte Requirements**[7,20]

| Electrolyte | Parenteral Range | Average adult Dose |
|---|---|---|
| Sodium | 45 – 145 mEq/1-2 mEq/kg | 77 mEq/L (1/2 NS) |
| Potassium | 60 – 120 mEq/1-2 mEq/kg | 90 mEq |
| Calcium | 10 – 15 mEq | 13 mEq |
| Magnesium | 10 – 30 mEq | 20 mEq |
| Phosphate | 30 – 60 mEq/20-40 mmol | 45 mEq/30 mmol |
| Chloride | As needed to maintain acid-base balance | |
| Acetate | As needed to maintain acid base balance | |

*mEq – milliequivalents

**Table 3. Commercially Available Parenteral Electrolyte Salts Commonly Used in PN Formulations[7]**

| Electrolyte | Salt Form |
|---|---|
| Sodium | Chloride, acetate, phosphate |
| Potassium | Chloride, acetate, phosphate |
| Chloride | Sodium, potassium |
| Acetate | Sodium, potassium |
| Calcium | Gluconate*, gluceptate |
| Magnesium | Sulfate*, chloride |




* Preferred salt form for use in PN formulations

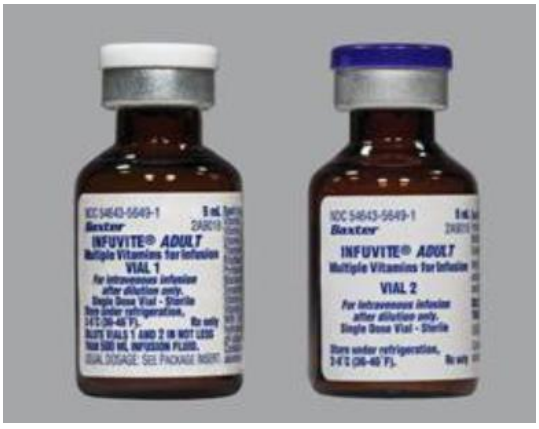
Chloride and acetate are used to adjust acid-base balance and therefore have no specific ranges. Acetate gets directly converted to bicarbonate in the body and is helpful in correcting acidosis when added. As a result, acetate should be avoided in alkalosis as it worsens the acid-base problem. In alkalosis, 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 the PN 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. There are multiple preparations available for use in PN solutions [Infuvite (table 4)], Multi Vitamin Infusion 12 (M.V.I. 12) and Cernevit-12]. The only difference between them is that Infuvite contains a source of vitamin K. NUMC uses the Infuvite preparation. The daily dose is 10 ml.

**Table 4. Composition of Adult Parenteral Multivitamin Product (in 10 ml dose) (Infuvite®)**

| 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 $K_1$ | 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 |




USP- United States Pharmacopeia

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. In a recent meta-analysis vitamin C in doses of 1–3 g daily reduced the length of ICU stay by 8.6%.[21] Additional vitamin K, folic acid and thiamin can also be added directly to PN solutions based on patient-specific needs. (e.g. refeeding syndrome, alcohol withdrawal).

## Trace Elements

Trace elements are metabolic cofactors essential for the proper functioning of numerous enzyme systems. Nearly 20 trace elements are thought to be essential for humans but only 4 or 5 are commonly added to PN solutions.[22] The recommended daily requirements can be found in table 5. Commonly used mixtures in PN formulations include zinc (Zn), copper (Cu), chromium (Cr), manganese (Mn) and selenium (Se), referred to as the MTE-5 (multitrace element) (Table 6). The MTE-4 does not contain selenium. All of these 5 can be purchased as single-element additives. 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 ILE 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 Zn and Cu deficiencies. To avoid Zn deficiency, 12 mg of Zn 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.[8,22,23] An additional 2 mg can be added for acute catabolism. Provision of additional Cu and Zn may be needed in patients with burns to compensate for losses of these elements in burn wound exudate.[23,24] Patients can lose 20 – 40% of body Cu content within the first week of injury with 20% or greater of total body surface area burn.

**Table 5. Trace Elements Daily Requirement for Adults –ASPEN 2004 Recommendations***[22]

| 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

**Table 6. MULTITRACE®5 Concentrate- 1 ml dose**

| Trace Element | Amount |
|---|---|
| Zinc | 5 mg |
| Copper | 1 mg |
| Manganese | 500 mcg |
| Chromium | 10 mcg |
| Selenium | 60 mcg |

# Parenteral Nutrient Preparations

PN formulations can be of 3 types: commercially available premixed solutions using dual-chambered bags [dextrose – AA products (e.g. Clinimix), dextrose – AA – lipid products (e.g. Kabiven / Perikabiven)] 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, lipid emulsion, and AA) 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 ILE, which can be infused separately. Specific advantages and disadvantages are associated with the use of each PN formulation system. See table 6.

**Table 7. Advantages and Disadvantages of the Total Nutrient Admixture System (TNA)** [7]

***Advantages***

- All components aseptically compounded by the pharmacy
- Preparation is more efficient for pharmacy personnel, especially if automated
- Fewer manipulations decrease the risk of touch contamination during administration
- Decreased nursing time needed in IV set-up and tubing changes, and no piggyback ILE
- Less supply and equipment expense for only one pump and IV tubing
- Can apply in fluid restricted patients because ILE 30% is restricted to use in TNA
- Inhibited or slower bacterial growth if contaminated compared to separate ILE
- 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 ILE 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
- Formulas are more sensitive to destabilization with certain electrolytes and low concentrations of dextrose and amino acids
- Difficult to visualize precipitate or particulate material in the opaque admixture
- Certain medications are incompatible with ILE portion of admixture
- Catheter occlusion more common with daily ILE

Our institution uses a premixed "2 in 1" solutions and ILE are infused separately as IV piggyback or a custom made '3 in 1' or TNA.


# Stability and Compatibility of PN

The stability of PN formulations refers to the degradation of nutritional components that changes their original characteristics. [7] It may also refer to the ability of the added medications to maintain their chemical integrity and pharmacological activity and resist degradation.[7] Compatibility, in contrast, refers to issues with PN formulations generally involving the formation of precipitates.[7]

The major concerns about the stability and compatibility of 3-in-1 PN solutions include: [15]

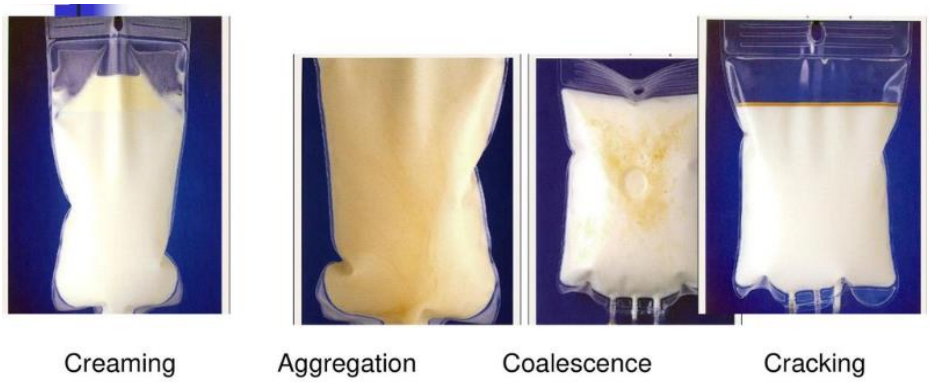
- The stability of the lipid emulsion,
- The potential for Ca P precipitation,
- The stability of vitamins and trace elements
- The stability implications of adding drugs to PN or giving drugs concurrently via the same tubing as the PN.

Formulations that appear stable when refrigerated could form precipitates at room temperature. Another important factor is pH; Ca P solubility increases as pH decreases. For maximal stability, TNA should maintain final concentrations of amino acid ≥4%, dextrose, ≥10%, and ILE ≥2% to more likely remain stable for up to 30 hours at room temperature (25°C) or for 9 days refrigerated (5°C) followed by 24 hours at room temperature.[6]

## Lipid Emulsion

ILE 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 the TNA. [7] 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.[6,7] The TNA is unsafe for administration beyond the creaming stage. Excess of any cation amounts, especially divalent cations such as calcium or magnesium can destabilize the ILE in TNA. Trivalent cations such as iron have even greater destabilizing effects and should not be added to the ILE-containing TNA.[15] See figure 4.

**Figure 4**: Stages of TNA/'3 in 1' Destabilization




Solution above can be used if lipid can be redispersed with gentle inversion.

Separated lipid does not redisperse with gentle inversion and must not be administered. Return to pharmacy.

## Calcium and Phosphate

The combination of Ca and P salts in excessive amounts in PN formulations may result in crystalline precipitates and possible pulmonary emboli and catheter occlusion. Ca P 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:[6,15,25]

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 Ca P solubility at low pH.

2. Ca and P concentrations
   - The concentration or the amounts of Ca and P 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 Ca and P should <u>not</u> exceed **33 mEq/L in a '3 in 1' or TNA and 45 mEq per liter in a "2 in 1"**.

3. Ca salt form
   - The risk of precipitation can be reduced by using Ca gluconate rather than Ca Cl, and by using the more acidic monobasic rather than dibasic P salts.

4. Temperature of solution
   - Ca and P are *less* soluble at higher temperatures (e.g. if temperature of solution is increased from room temperature, 25°C / 77° F to body temperature, 37°C/98.6°F)

5. Mixing procedures
   - Provided that compounding guidelines are adhered to, the amounts of Ca and P 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 Ca. AA decrease free Ca available to precipitate with P.

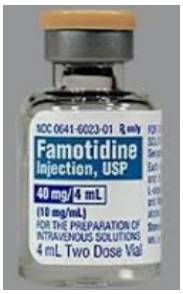
There are Ca P solubility curves available for specific AA solutions to aid in predicting the risk of precipitate formation.

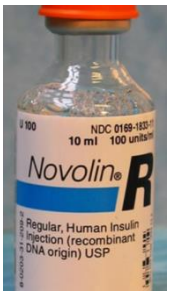
**<u>'2 in 1' Ca-P Precipitates</u>**
**Do not use if crystals or white flakes are observed.**

### 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**.[15] 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 and a light-protective covering applied.

### Drugs and PN

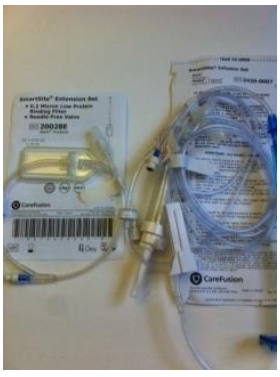




Certain drugs can be compatible in dextrose – amino acids solutions but not in TNA formulation. Other medications, usually fat soluble, can be compatible with TNA but not dextrose – amino acids formulations. Usually drugs are not added to 3-in-1 / TNA but can be added to "2 in 1" PN solution. Certain drugs that are compatible with the PN can be given via Y-site administration (piggyback drug delivery system).[26] Medications that can be safely added to PN solutions include H-2 antagonists and insulin.

## Filters

The need for filtration of PN at bedside is great. Filters can remove precipitates (e.g. Ca P), and particulate matter (e.g. plastic fragments from the bag) from a PN formulation. [7] 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. [7] However, because fat particles are larger than 0.22 microns, the use of this filter with ILE 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. Filters should be used to reduce infusion of particulates, microprecipitates and microorganisms. A 2016 Institute for Safe Medication Practices (ISMP) Medication Safety Alert highlighted a prescribing information change for ILE in the US. The manufacturers now recommend using a 1.2 micron filter when administering ILE in both a TNA and when infused separately.

**For '2 in 1' solutions: 0.22 micron (white) filter with Clear infusion set**



**For '3 in 1' solutions or TNA 1.2 micron (blue) filter with Low Sorbing (blue) infusion set**

# 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 reassessment of macronutrient and micronutrient requirements. The electrolyte composition of PN may be varied based on the serum electrolyte profile, changes in clinical status, organ function, drains, RRT 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 formulations are hypertonic to body fluids. The osmolarity is dependent primarily on the dextrose, AA, and electrolyte content. The maximum osmolarity tolerated by a peripheral vein is unknown but conservatively documented in the literature to be 900 mOsm/L. Higher osmolarity of up to 1700 mOsm/L as a TNA has been shown to be tolerated.[5,6] The solution osmolarity and the infusion rate will both contribute to the risk of phlebitis. 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 PPN osmolarity can be maintained at an acceptable value is more likely to be tolerated by the peripheral vein. Dextrose solutions greater than 10% final concentration may not be infused into peripheral veins (unless other components are reduced) and should be administered via a central venous catheter.

**Table 8:**

| Nutrient | Osmolarity |
|---|---|
| Amino Acid | 100 mOsm/% |
| Dextrose | 50 mOsm/% |
| Lipid injectable emulsion (20%) | 1.3-1.5 mOsm/g |
| Sodium (acetate, chloride) | 2 mOsm/mEq |
| Sodium phosphate | 3 mOsm/mEq sodium |
| Potassium (acetate, chloride) | 2 mOsm/mEq |
| Potassium phosphate** | 1.7-2.7 mOsm/mEq potassium |
| Magnesium sulfate | 1 mOsm/mEq |
| Calcium gluconate | 1.4 mOsm/mEq |

Mattox TW, Crill CM. Mattox T.W. Chapter 119. Parenteral Nutrition. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. DiPiro JT, et al. eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e*. New York, NY: McGraw-Hill 2014.

Usually for compounding purposes, it is assumed that the osmolarity of individual electrolytes are approximately equal (for simplicity) at 2 mOsm/mEq. Electrolytes usually are expressed in mEq per bag. Osmolarity is ***always*** based on a liter. See table 8.[4]

## Osmolarity calculations are based on a liter!

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

**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) ÷ 2 L volume x 2 mOsm/mEq = 280 mOsm in 1L

**Total osmolarity** = 450 mOsm/L + 500 mOsm/L + 280 mOsm/L
= 1230 mOsm/L

ILE 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 = 30.5 g/L

30.5 g x 1.4 mOsm/g = ~43 mOsm/L (or ILE % x 14)

**Total osmolarity** = 380 mOsm/L + 425 mOsm/L + 237 mOsm/L + 43 mOsm/L
= **1085 mOsm/L**

mOsm- milliosmole
IVPB- intravenous piggy back

**Table 9. 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. D5 LR, D10 ½NS).

## Parenteral Nutrition Order Writing

1. **Determine calorie and AA / protein requirements.**

- Individual patients may require greater or less than the estimated requirements due to acute illness, therapies or underlying medical conditions. Below is a quick method to start the process.

| | |
|---|---|
| Estimated calorie requirements | 25 – 30 kcal/kg |
| Estimated protein requirements | 1.5 – 2 g/kg |

*Note: based on usual or dry body weight except in obese patients
*Need to convert g protein to AA (g protein ÷ 0.83= g AA)

2. **Determine volume of parenteral solution volume to be provided.** [4]

**Table 10:**

| Methods to Calculate Fluids | | |
|---|---|---|
| **mL per kcal** | 1-1.5 mL/kcal | |
| **mL per kg** | >65 years old<br>55-65 y/o<br>30-55 y/o<br>15-30 y/o | 25mL/kg fluid<br>30mL/kg fluid<br>35mL/kg fluid<br>40mL/kg fluid |
| **Holliday-Segar** | <10 kg<br>10-20 kg<br>20 kg | 100 mL/kg<br>1000 mL + 50 mL/kg for every kg between 10-20 kg<br>1500 mL + 20 mL/kg for every kg >20 kg |
| **4-2-1 rule** | <10 kg<br>10-20 kg<br>kg<br>20 kg | 4 mL/kg/hr<br>40 mL/hr + 2 mL/kg/hr for every kg between 10-20<br><br>60 mL/hr + 1 mL/kg/hr for every kg >20 kg |

3. **Determine *moderate* amounts of dextrose, lipid and amino acids** to provide the amount of calories and protein desired. (Keep in mind that the protein in grams is 83% of the AA grams.)

- 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 / 120 g amino acids and 2000 ml volume.

Determine the number of g and kcal to be provided by ILE and dextrose.

Calories provided by AA: 120 g x 3.4 kcal/g = 408 kcal
Calories provided by lipid: 1 g/kg/d: 60 g, equivalent to 300 ml 20% ILE
60 g ÷ 20% ILE = 300 ml
2 kcal/ml x 300 ml = 600 kcal
Calories remaining to be provided by dextrose:
1800 kcal – 408 AA kcal – 600 lipid kcal = 792 kcal
Dextrose 792 kcal ÷ 3.4 kcal/g = ~233 g dextrose

4. **Determine amount (ml) of fluid required to provide the dextrose, AA and lipid** 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
    - 15% AA solution
    - 20% ILE

**Example:** 120 g AA ÷ 15% concentrated AA base solution
120 g x (1000 ml / 150 g) = 800 ml

235 g dextrose ÷ 70% dextrose solution
235 g x (1000 ml / 700 g) = ~336 ml

**Total volume** 2000 ml = **dextrose** (336 ml) + AA (800 ml) + ILE (300 ml) + ~ 150–200 ml for the average adult electrolytes + additives = 1586-1636 ml

**If the desired volume of the 3–in-1 solution is 2000 ml, the addition of ~ 364-415 ml of sterile water will be needed to achieve the final requested volume.**

***Note*:** ~1586-1636 ml is the minimum volume that can be compounded given the above component requirements.

5. **Guidelines for Macronutrient Dosing/TNA Stability**
   - Maintain TNA final concentrations of at ~AA ≥4%, dextrose ≥ 10% and ILE ≥2% for increased likelihood of remaining stable for up to 30 hr at room temperature (25°C) or for 9 d refrigerated (5°C) followed by 24 hr at room temperature.[6] There is leeway based on the content/percentage of each macronutrient.


6. **Dose the individual electrolytes.**

**Table 11. Daily Electrolyte Requirements**[7,20]

| Electrolytes | Average Dosing | Range |
|---|---|---|
| Sodium | 77 mEq/L (1/2 NS) | 45 – 145 mEq (1 mEq/kg) |
| Potassium | 90 mEq | 60 – 120 mEq (1 mEq/kg) |
| Calcium | 13 mEq | 10 – 15 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 P as a K salt.

- For Na
  - Dose according to the desired concentration. For maintenance begin with 77 mEq/L (equivalent to ½ NS concentration) or 155 mEq of NaCl in a 2L bag. The Na concentration can be varied based on the individual patient.

- 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 in low normal range.
  - Provide low adult dose range if the lab results are in upper normal range.
  - 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 **33 mEq/L** or 66 mEq in a 2L bag (due to risk of precipitation) for a TNA, **45 mEq/L** in a '2 in 1'.
- Always use clinical judgement!

- 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 buffering is needed, all of the K (excluding K given as KPhos) can be provided as the acetate salt.

7. **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 dependent upon disease state.

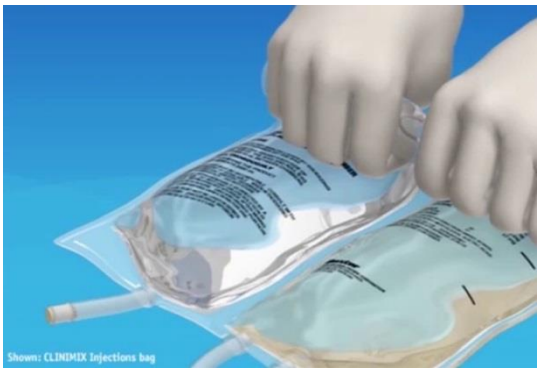
8. **Complete the order form in the electronic medical record. Custom PN orders MUST be received by 11am. All custom PN begin infusing at 6 pm. Discard any remaining PN solution from the previous day.**


## Premixed PN – Clinimix

Alternatively, a premixed solution is available in our institution (table 12) that can be used. It is available from pharmacy at any time of day. However, caution should be exercised with this solution as it can worsen alkalosis due to its high acetate content and can result in hyponatremia due to its low Na content (< ¼ NS) over time. Given the above problems and a lower dextrose and AA content, Clinimix is not an appropriate substitute for a customized PN in many situations.

**Table 12. 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

PN generally should begin with dextrose, AA and lipid at goal unless the patient is at high risk of refeeding syndrome or suboptimal tolerance is anticipated (e.g. brittle diabetic). If intolerance is expected, initiate PN on the first day with fewer 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 13.

**Table 13. Suggested Monitoring for PN**

| Parameter | Baseline | Critically Ill Patients | Stable Patients |
|---|---|---|---|
| Basic Metabolic Panel | Yes | Daily | Twice weekly |
| Calcium | Yes | Daily | Twice weekly |
| Ionized Calcium | Yes | 2-3x weekly | As needed |
| Phosphorus | Yes | Daily | Twice weekly |
| Magnesium | Yes | Daily | Twice weekly |
| Liver Function Tests | Yes | 3x weekly | Weekly |
| CBC with differential | Yes | Daily | Weekly |
| PT, PTT | Yes | Weekly | Weekly |
| Serum triglycerides | Yes | Weekly | Weekly |
| Albumin | Yes | Daily | 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 |

The monitoring should be tailored to the patient's medical condition and level of care.

**BE AWARE OF REFEEDING SYNDROME!**

## Storage and Handling

The PN solution should remain refrigerated until delivered to the patient care area. The light-protective brown covering ***should NOT*** be removed from the PN solution and remain in place during administration to the patient. The solution should be discarded after the 24 hr. infusion time has elapsed despite volume remaining in the bag. All PN solutions are prepared using a strict aseptic technique and have a beyond-use date and time clearly marked on the label. All custom solutions begin at 6 pm and run to completion over the next 24 hr. Solutions are frequently cycled over a shorter time frame (e.g. 12-20 hr. daily) for reasons including prevention of liver dysfunction, allowing a period of freedom from the infusion for the patient, and to compensate for periods of time the solution may not be infusing due to access issues, tests or other IV therapies.

## Discontinuation of PN

Rebound hypoglycemia upon discontinuation of PN is rare.[27] PN solutions prescribed today have significantly lower dextrose concentrations as compared to those used historically, minimizing the incidence of occurrence. To reduce the risk of rebound hypoglycemia in high risk patients, a 1 to 2 hour taper down of the infusion may be necessary. If a PN solution must be discontinued suddenly or unexpectedly in patients sensitive to abrupt discontinuation, 5-10% dextrose-containing IV fluid should be infused for 1 or 2 hours to avoid a possible rebound hypoglycemia.

To wean PN in a patient receiving and tolerating EN therapy or an oral diet:

1. In a patient receiving tube feedings (TF)
   - Once the patient is receiving TF at 50% of goal rate/dose with good tolerance, the PN may be reduced and then weaned off as TF rate/dose advances to goal and tolerance is demonstrated.
2. In a patient receiving an oral diet
   - Once the patient is orally consuming 50% of estimated energy and protein requirements, the PN may be reduced and subsequently weaned off per clinician judgment when intake is demonstrated to be $\geq$ 80% of estimated requirement.

***DO NOT*** abruptly discontinue PN therapy upon initiation of EN or an oral diet. Providing duel therapies is most appropriate to assure ongoing adequate nutrition provision until oral diet / EN is advanced and tolerance demonstrated! It is a costly, labor-intensive therapy so allow the last bag ordered to run to completion (unless true contraindication exists).

**Example:** 50 year old woman is receiving 2.25 L CPN containing 20% ILE 300 ml, 6% AA (135 g AA/112 g protein) and 10% dextrose (225 g dextrose) infusing at 115 ml/hr providing a total of 1824 kcal (or ~0.8 kcal/ml).

**To taper PN:**
Start Vital AF (1.2 kcal/ml) TF at 750 ml daily (900 kcal).
Decrease CPN dose to ~ 1150 ml/d while maintaining current % final concentrations of ILE, dextrose and AA.

**If tolerance of EN is demonstrated:**
Allow CPN to run to completion and
Increase TF dose to goal of ~1550 ml daily.

The patient will likely require additional water for hydration purposes.

# Parenteral Nutrition Safety

The ISMP recognizes PN as a complex, high alert medication due to its multiple components, requiring ongoing competency assessment for those involved. Numerous factors are involved with assuring PN safety for patients. The process involves multiple steps including the prescription, order review and verification, compounding and administration phases. Strategies must be in place to prevent errors in each phase.

The American Society for Parenteral and Enteral Nutrition (ASPEN) published *Clinical Guidelines: Parenteral Nutrition Ordering, Order Review, Compounding, Labeling and Dispensing, as well as the Parenteral Nutrition Safety Consensus Recommendations* in 2014 to assist organizations in providing PN in the safest manner possible. [6,28] A summary is provided in table 14. Technology can aid in decreasing the risk of error as see in table 15.

**Table 14. ASPEN Recommendations For Safe PN Prescribing and Administration**

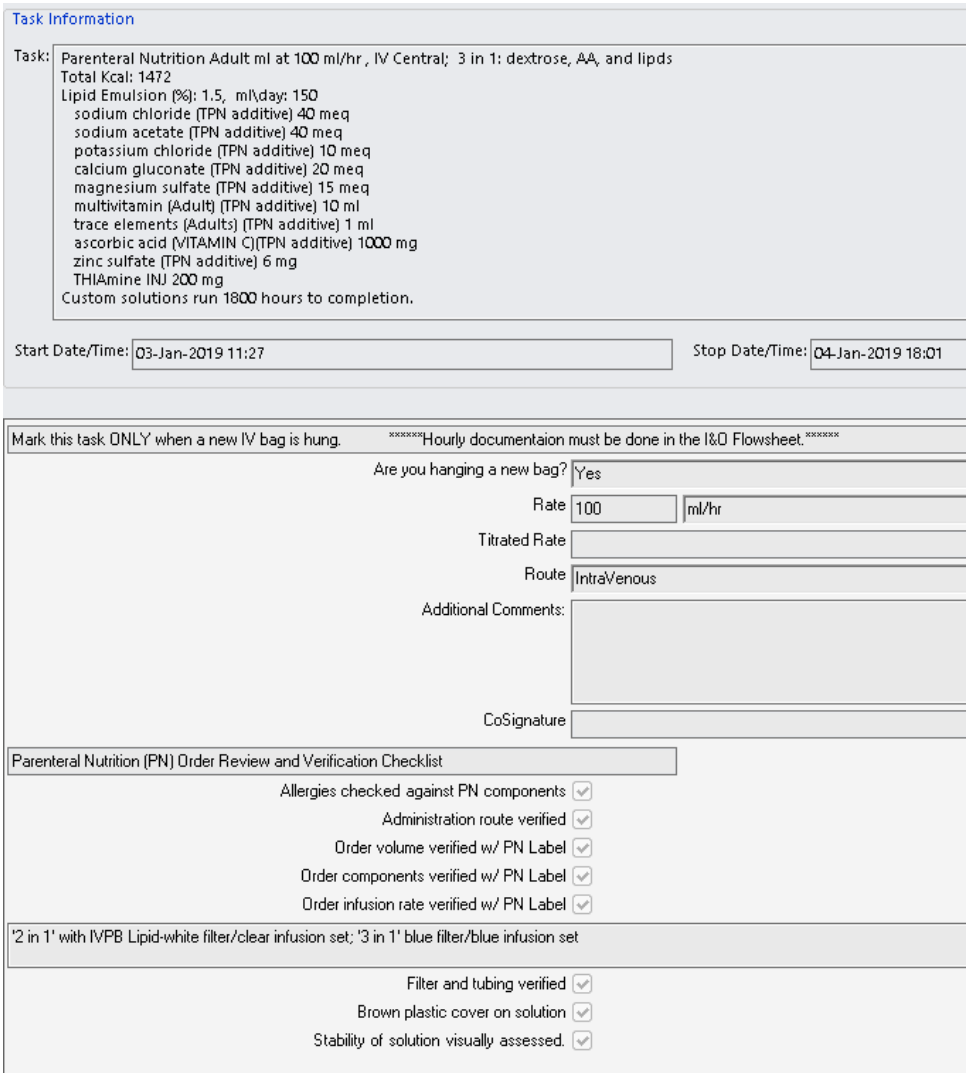
| **Prescribing** |
|---|
| • Standardized process for PN management<br>• Comprehensive PN education and competency assessment<br>• Appropriate indication and access<br>• Goals for protein and energy documented<br>• Standardized PN order form, electronic preferred<br>• Clinical decision support within electronic order<br>• PN ingredients ordered as amounts /day in adults and amounts/kg/d in pediatric + neonatal patients<br>• PN ingredients listed in the same order on the order form for all patients |
| **Order Review/Verification** |
| • Prescribe PN using a computer prescriber order entry system fully integrated with an automated compounding device.<br>• Verbal and telephone orders should be avoided.<br>• Transcribed data should be double-checked by an independent process.<br>• Pharmacist should be skilled and knowledgeable in PN.<br>• Compare PN formulation with previous day's order.<br>• Review for compatibility and stability.<br>• Outsourced PN should undergo the same standardized pharmacy review and verification.<br>• Quality improvement programs should be in place to report, track, and analyze errors. |
| **Compounding** |
| • Compliance with U.S. Pharmacopeia chapter <797><br>• Provision of in-depth training focusing on compounded sterile preparations<br>• Certification of pharmacy technicians<br>• Annual competency assessments of pharmacists and pharmacy technicians<br>• Maximizing automation and technology<br>• Soft and hard limits for parenteral nutrition ingredients<br>• Restricting automated compounding device change privileges to well-trained personnel<br>• Use of checklists or sign-off sheets |
| **Administration** |
| • Education and competency assessment for nurses, caregivers<br>• Interdisciplinary quality improvement programs for analysis of PN errors<br>• Policies addressing extravasation<br>• Polices prohibiting the use of PN prepared for home or in subacute or long-term facilities<br>• Protocols for safe operation of infusion pumps<br>• Verifying PN label against PN order and independent double-check of infusion pump settings<br>• Polices for selection, insertion, care, and maintenance of vascular access device<br>• Policies for tubing change and appropriate filters for administration |

**Table 15. Benefits of Technology in Parenteral Nutrition Compounding**[29]

| |
|---|
| • Reduces the need for order transcription with computer-prescriber order entry and electronic health record-to-compounder interfaces |
| • Introduces a "photo-finish" check for hand-added ingredients with barcode-assisted medication preparation |
| • Introduces quality-assurance checks with refractometry and laboratory measures |
| • Introduces new techniques to detect micro-organisms and endotoxin |
| • Alerts prescribers to medication interactions as well as to medication dose adjustments needed because of changes in weight or renal function |

Providers placing PN orders must be fully competent in all aspects of PN therapy. All providers are expected to read the PN curriculum and pass a competency test to obtain ordering privileges. Attention to details (changes in lab values, access availability, urine output) is of the utmost importance during the prescribing process. 'Inattentive' reordering of solutions can result in electrolyte abnormalities, under/over hydration, excessive cost and suboptimal outcomes for patients. The electronic health record contributes to safety by allowing only credentialed providers at NUMC to order PN, provides ordering guidelines within the form, performs calculations and automatically transmits the completed order to the pharmacy. Alerts are sent simultaneously via page and email to the dietitians for PN review. Upon PN delivery to the patient care area, the nurse is required to complete an electronic checklist prior to administering the solution. See figure 5.

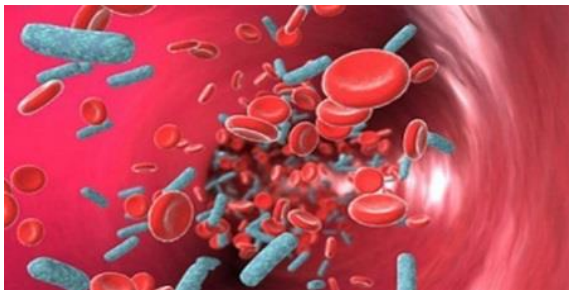
**Figure 5:**



# 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.

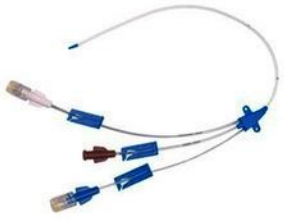
## Infections



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. As is evident in the literature, infection risks associated with PN use are controversial. Infection rates associated with PN were clearly much higher during the days of overfeeding (historically referred to as hyperalimentation) and poor glucose control. More recent data, with hypocaloric to eucaloric feeding, tight glucose control and improved CVC care, have failed to consistently show increased infection risk with PN verses EN.[30,31]

Steps can be taken to mitigate infection risk. These include appropriate catheter care and manipulation of the device, glycemic control between 140 and 180 mg/dl, and using a ω-3 containing ILE. SMOF lipids are now available in the US, and are available for use at NUMC in the custom PN solutions. PN should no longer be considered contraindicated in patients at high risk for infection since malnutrition can be a confounding variable. Risk mitigation strategies should be used to provide appropriate nutrition, as inappropriately withholding such nutrition may lead to malnutrition or worsening of existing malnutrition, immunosuppression, and infection. [31]

## Mechanical Complications



Mechanical complications are usually related to vascular access devices or catheters 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. Factors that may influence the incidence of PVT include the solution osmolarity, infusion rate, addition of heparin or corticosteroid and the presence of fat emulsion (when PPN is prepared as a TNA).[6] The coinfusion of intravenous fat emulsion (IVFE) has not been shown to reduce phlebitis.[6] It is not recommended to include heparin to a TNA because it may destabilize the solution. Nonthrombotic catheter occlusion can be caused by external clamps, kinking of the catheter, malpositioning, occluded port needles and constricting sutures.[7]

## 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, insulin resistance and excess calorie (dextrose) administration. Suggested prevention of hyperglycemia with PN includes:

- Glucose monitoring every 6 hours with initiation of PN. Maintaining levels ≤ 180 mg/dl is associated with decreased morbidity and mortality.[3] Avoid of overfeeding and excessive dextrose administration

- A base level of insulin may be added to the PN formulation for glycemic control for the diabetic patient. 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 or glucose levels are erratic.
  *Note*: Insulin is not 100% available (may range from 50-95%) due to adhesion to the bag and tubing and depends upon other components of the solution (e.g. multivitamins and trace elements may enhance availability to 95%).[32,33]

- 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 but is a rare phenomenon. Obtaining blood glucose 30 minutes to 1 hour after the PN solution is discontinued will help identify rebound hypoglycemia in high risk patients.

**Essential Fatty Acid Deficiency (EFAD)** – can occur within 1 to 3 weeks in adults receiving ILE-free PN formulations. Two polyunsaturated fatty acids, linoleic and alpha- linolenic, cannot 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.[7] To biochemically diagnose EFAD, the Holman Index should be used. A triene**:**tetraene ratio of > 0.2 (previously > 0.4) is diagnostic of EFA deficiency (demonstrates that more mead acid than arachidonic acid is being produced), where a ratio of 0.2 is the upper limit of normal. Approximately 250 ml of 20% ILE given at a minimum twice weekly or 500 ml of 20% ILE given once a week will prevent EFAD.[7] 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.[7,34]

**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 ILE or propofol infusion) or can occur with dextrose overfeeding or with rapid administration rate or an excessive dose of ILE (greater than 110 mg/kg/h). Reducing the dose to **≤ 1 g/kg/d** or <30% of total kcal and/or lengthening the ILE infusion time will help minimize these side effects. An acceptable triglyceride level is ≤ 400 mg/dl.[7]

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. Insulin promotes the synthesis of lipoprotein lipase (LPL) by adipocytes and myocytes , aiding in triglyceride clearance. Heparin promotes the release and translocation of tissue bound

LPL in the capillary endothelium also aiding in triglyceride clearance.[35] The addition of heparin to PN can be tried in certain situations in a '2 in 1' PN solution. LPL resides in the capillary bed. Malnourished patients have less capillary mass and therefore slower rates of lipid clearance.

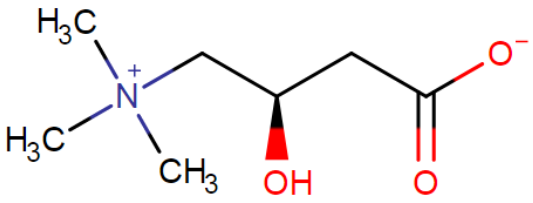
Fat overload syndrome is a rare complication of ILE therapy and is potentially lethal. It is characterized by lipemic serum, headaches, fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous hemorrhage. Other symptoms include immune suppression, anemia, leukopenia, thrombocytopenia, low fibrinogen levels, and coagulopathy.[36] To avoid the fat overload syndrome, the dose in adults for ILE administration should not exceed **2.5 g/kg/d or 0.11 g/kg/hr**.

Although rare, allergic reactions to ILE can occur, especially in patients with history of egg, soy, peanut or fish allergies. Carnitine deficiency can result in high triglyceride levels. Carnitine is derived from methionine and lysine, and is necessary for the oxidation of fatty acids. It transports fatty acids from the cytoplasm to the site of oxidation in the mitochondria.[37] 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.[38]

Patients at risk of deficiency include:[37–41]

- those on a carnitine free diet (PN)
- with decreased endogenous production (e.g. preterm infants)
- with malabsorption (e.g. short bowel syndrome, gastric bypass)
- on certain medications (e.g. antiretroviral agents, anticonvulsants [valproic acid, phenobarbital, phenytoin, or carbamazepine])
- with heart and liver disease
- on hemodialysis

Carnitine homeostasis is impaired in renal disease due to factors including decreased synthesis, increased loss (by the kidney/ hemodialysis) and reduced intake. A deficiency may cause muscle necrosis, myoglobinuria, lipid-storage myopathy, hypoglycemia, fatty liver, and hyperammonemia with muscle aches, fatigue, confusion, and cardiomyopathy.[37]




*L-Carnitine*

## Micronutrient Related Complications

### *Electrolytes*[8,20]

**Hyponatremia** –The most common cause of hyponatremia is administration of excessive hypotonic fluid. Based on the etiology, hyponatremia is usually treated with fluid restriction or an increase in the sodium concentration in the PN solution.

**Hypernatremia** –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 reducing the Na content of the PN solution and/or increasing solution volume.

**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. 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 eliminated.

**Hypocalcemia** – may be attributed to decreased vitamin D intake, 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. Obtain ionized calcium levels periodically for more accurate assessment.

**Hypercalcemia** – may be attributed to administration of excess vitamin D, prolonged immobilization and metastatic disease. 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, and the content increased in the PN solution.

**Hypermagnesemia** – may be seen with excessive magnesium intake associated with renal dysfunction. Hypermagnesemia is usually treated by decreasing or discontinuing magnesium in the PN formulation.

**Hypophosphatemia**- may be seen with refeeding syndrome, and with inadequate phosphorus intake. Hypophosphatemia may be treated with phosphate supplementation and/or an increase in the PN formulation.

**Hyperphosphatemia** – may be seen with administration of excess phosphate especially in patients with renal dysfunction. Hyperphosphatemia may be treated by decreasing or eliminating phosphorus in the PN solution.

### *Vitamins*

Excessive intake of lipid-soluble vitamins A, D, E, and K has the potential for accumulation and therefore, the potential for toxicity. See table 16.

**Table 16. Lipid-soluble Vitamins Deficiency and Toxicity Symptoms**[42–46]

| Vitamin | Deficiency | Toxicity |
|---|---|---|
| **A (retinol)** | Xerophthalmia -stages include night blindness, conjunctival xerosis, Bitot's spot, corneal xerosis and ulceration and scarring. low iron status (due to effect on hematopoiesis), increases severity and risk of infections (particularly diarrhea and measles) | Chronic excessive vitamin A intake can lead to increased intracranial pressure (pseudotumor cerebri), dizziness, nausea, headaches, skin irritation, pain in joints and bones, coma, and even death |
| **D (Calciferol)** | Rickets, osteomalacia, osteoporosis, hypocalcemia, hypophosphatemia, generalized symptoms may include bone pain, myalgia, and generalized weakness, immune incompetence | hypervitaminosis D, hypercalcemia, hyperphosphatemia, hypercalciuria clinical symptoms/signs of hypercalcemia (e.g., nausea, dehydration, and constipation), hypercalciuria (e.g., polyuria and kidney stones), anorexia, weight loss, heart arrhythmias, drowsiness, continuous headaches |
| **E (tocopherols, tocotrienols)** | Deficiency rare, may include peripheral neuropathy, ataxia, skeletal myopathy, retinopathy, and impairment of the immune response, hemolytic anemia | Hemorrhage, coagulopathy, muscle weakness, fatigue, nausea, and diarrhea |
| **K (phylloquinone (vitamin K1), menaquinones (vitamin K2)** | prothrombin time, bleeding, hemorrhage, reduce bone mineralization, osteoporosis | No adverse effects associated with vitamin K consumption from food or supplements have been reported, interference with oral anticoagulation therapy |

Thiamin may be provided in suboptimal amounts in the multivitamin preparation in certain disease states in comparison to increased requirements (e.g. refeeding syndrome, alcoholism, Lasix use) resulting in deficiency. Provision of adequate Mg (in combination with thiamin) is necessary since it is a cofactor in the conversion of thiamin to its active form in the liver.[47] Other vitamins that are commonly added include vitamin C (for enhanced immune response and wound healing), vitamin K and folic acid.

### *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.

Mn and 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. This initially occurs asymptomatically. The patient later develops a parkinsonian-like syndrome consisting of tremor, hypertonia, bradykinesia, and gait disturbance, but nonspecific symptoms have been reported, including visual disturbance, headache, anxiety, memory loss, and seizures.[23,48] Cu and Mn are sometimes withheld in long term PN patients even if labs are normal for 'hepatic relief'. Excessive GI losses via drains and stool can result in Zn and Cu deficiencies.[8,22] Burn victims can develop Cu and Zn deficiencies from losses in burn wound

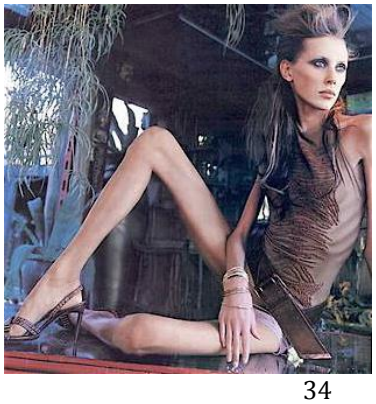
exudate.[23,24] The trace element mixture does not contain iron, and as a result a patient on prolonged PN may develop iron deficiency.
Symptoms of certain trace elements deficiencies and toxicities are listed in table 17.

**Table 17. Trace Element Deficiency and Toxicity Symptoms in Adults**[22]

| *Trace Element* | *Deficiency* | *Toxicity* |
|---|---|---|
| Manganese | 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 magnetic resonance images in basal ganglia. |
| Selenium | 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 | 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 | Glucose intolerance, hyperlipidemia, peripheral neuropathy, encephalopathy | No known toxicity of $Cr^{3+}$ (trivalent form). Has not been reported in PN patients. |
| Copper | Hypochromic, microcytic anemia, leukopenia, neutropenia, skeletal abnormalities, and rarely, thrombocytopenia. | Accumulation in liver, hepatocellular damage. |
| Iron | Hypochromic microcytic anemia, pallor, fatigue, decreased work performance. | Hemosiderosis, hemochromatosis, accumulation in liver and heart, some endocrine tissues; iron toxicity can be fatal. |
| Molybdenum | 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 | Hypothyroidism – weakness, cold intolerance, weight gain, thinning hair, goiter (thyroid enlargement). | Thyroiditis, goiter, hypo- or hyperthyroidism, thyroid papillary cancer, dermatoses (iodermia). |

## Refeeding Syndrome

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 during the first 2-5 days after initiation of nutrition support.[7] It encompasses a constellation of fluid and electrolyte abnormalities affecting multiple organ systems, including neurologic, cardiac, hematologic, neuromuscular, and pulmonary function.[49]



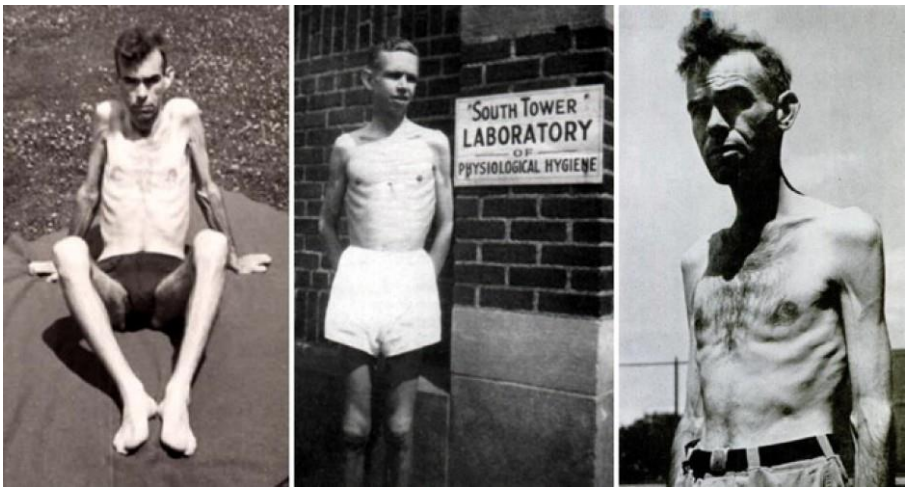
Risk factors for refeeding syndrome are anorexia nervosa, classic kwashiorkor and marasmus, chronic alcoholism, chronic malnutrition-underfeeding, prolonged IV hydration, morbid obesity with massive weight loss (e.g. after bariatric surgery) and prolonged fasting. This syndrome may involve hemolytic anemia, respiratory distress, paresthesia, tetany, and cardiac arrhythmias.

The physiological basis of the "refeeding syndrome" is believed to stem from the following: [49]

- 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 arrhythmias 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.
- Deficiencies of B-vitamins, especially thiamin, are speculated to have a role in the refeeding syndrome since these vitamins are required in carbohydrate metabolism.

The following measures will help prevent the development of refeeding syndrome in patients deemed at risk:

- Repletion of serum K, Mg and P concentrations via intravenous fluids before initiating PN.
- Limiting initial carbohydrate to 2.88 g/kg/d (amount needed to produce maximal suppression of gluconeogenesis)[10]
- Including adequate amounts of K, Mg, P and vitamins in initial PN. Provide adequate thiamin (additional 100 mg/d for 3 to 7 consecutive days).
- Increasing carbohydrate-dependent minerals (K, Mg, P) 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. Other terms commonly used to describe the condition are PNAC and intestinal failure-associated liver disease (IFALD). The development of liver injury associated with PN is multifactorial and may include: [50]

- Non-specific intestine inflammation
- Compromised intestinal permeability and barrier function associated with increased bacterial translocation
- Primary and secondary cholangitis
- Cholelithiasis
- Short bowel syndrome
- Disturbance of hepatobiliary circulation
- Lack of enteral nutrition
- Shortage of some nutrients (proteins, essential fatty acids, choline, glycine, taurine, carnitine, etc.)
- Toxicity of components within the nutrition mixture itself (glucose, phytosterols, manganese, aluminum, etc.)

PNALD can present clinically as steatosis, cholestasis, gallbladder sludge/stones, fibrosis, and cirrhosis. These disorders may coexist or occur separately. Steatosis, or hepatic fat accumulation, is predominant in adults and is generally benign and reversible. Mild elevations in transaminase concentrations (alkaline phosphatase, gamma-glutamyl transferase, and conjugated bilirubin) 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.

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. Gallbladder stasis during PN therapy may lead to the development of gallstones or gallbladder sludge with subsequent development of cholecystitis. Note that cholestasis is common in patients with sepsis and other infections, regardless of the use of PN. Activation of the negative acute-phase response (by cytokines) leads to cholestasis by decreasing bile salt synthesis, reducing canalicular bile salt export, and suppressing bile salt import.[51]

Another factor that may contribute to the risk of liver complications is the phytosterol content of ILE. 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. Soybean-based lipid emulsions have been reported to interfere with hepatocyte, macrophage, and platelet cholesterol uptake due to its pytosterol content.[51] The 10% emulsion contains greater amounts than the 20%, with the 30% emulsion containing the least.

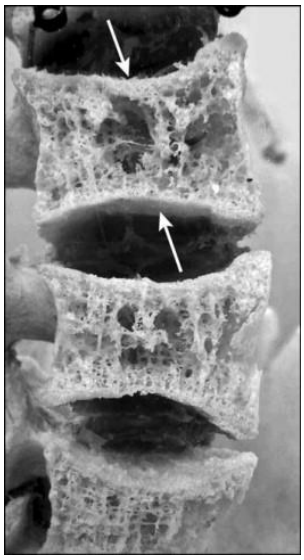
Other potential contributing factors to PNALD include nutrient deficiencies, infusion regimen and microbiome dysbiosis. Deficiencies in taurine, cysteine, choline, lecithin, carnitine, glutathione and glutamine have all been implicated since they are not a part of the standard PN solution. Also the provision of lipid-free PN solutions can result in negative effects on effect on hepatic microsomal enzyme

function, with lipid clearly appearing to have a direct positive effect on cytochrome P450 enzyme complex activity.[13] Lipid-free PN results in greater hepatic lipid synthesis as compared to a lipid-containing solution with similar total calories. Cycling the PN solution down to 12 hr per day can minimize liver dysfunction. Continuous PN may be a predisposing factor for excess circulating insulin, which stimulates the deposition of fat in the liver.[52] Lastly, the result of providing exclusive PN support is the radical alteration of gut microbiome composition and function, leading to detrimental effects on the intestine.[50]

Management of PN-induced hepatobiliary abnormalities usually includes:

- Include a source of lipid emulsion to the PN regimen
- Decrease dextrose and lipid calories to about 1/3 of total calories
- Limit especially soy-based ILE dose to 1 g/kg/d
- Avoid 10% ILE due to its high phytosterol content (as compared to the 20% and 30% emulsions)
- Changing to a fish oil containing ILE
- Cycling the PN
- Initiating EN to stimulate bile flow and to avoid gut mucosal atrophy and bacterial translocation

**Metabolic Bone Disease**

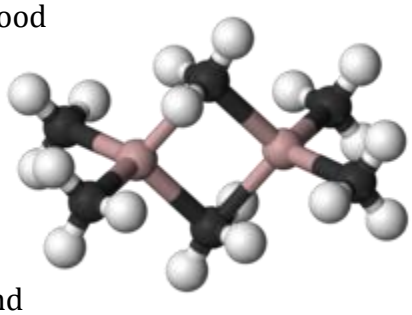


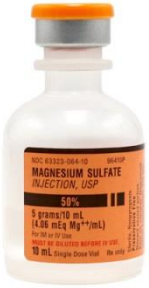
Osteoporosis and osteomalacia are associated with long-term PN use. It is important to provide adequate amounts of Ca and P. Calcium contributes to the maintenance of bone integrity by slowing bone loss and decreasing bone turnover.[53] Phosphorus also enhances calcium reabsorption, supporting a positive calcium balance.[53] Patients on PN are particularly vulnerable to negative Ca balance because of limited intake, increased urinary Ca loss and limitations related to compounding (due to the physical compatibility of calcium and phosphorus in solution). A number of factors have been associated with metabolic bone disease:[15,53,54]

- Inadequate Ca and P intake
- Higher AA doses (2 g/kg/d as compared to 1 g/kg/d) in PN formulations
- Chronic metabolic acidosis
- Cyclic PN
- Vitamin d deficiency
- Vitamin d toxicity
- Aluminum toxicity
- Mg deficiency
- Copper deficiency
- Vitamin K deficiency

Osteomalacia had been associated with PN formulations that in the past had significant aluminum contamination, attributed to the use of casein hydrolysates. The aluminum content is significant less now with the use of crystalline amino acids as the source of nitrogen. There is still a significant amount of aluminum from other parenteral nutrient additives including calcium gluconate, inorganic phosphates injection (sodium or potassium), vitamins, trace elements and cysteine hydrochloride.[55]

Aluminum contamination can also be found in products such as albumin and blood products, and certain medications (e.g. heparin). The aluminum content of parenterals increases over time due to leaching from glass and elastomeric closures. Aluminum deposition on the bone surface inhibits Ca retention and likely interferes with the ionic exchanges at the level of the bone plasma surface, thus causing hypercalciuria and osteomalacia.[54] It also interferes with PTH secretion and decreases vitamin d activation by inhibiting the 1 α hydroxylase enzyme. 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 can also result in progressive dementia and iron/erythropoietin resistant microcytic anemia. Patients at risk for aluminum toxicity are those with significant renal dysfunction, high intake of parenteral products and iron deficiency.

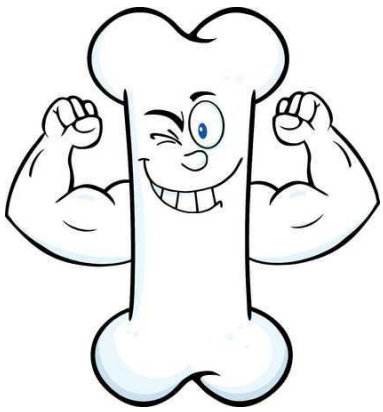





Mg deficiency can also contribute to the development of bone disease. Severe chronic hypomagnesemia inhibits the release of parathyroid hormone (PTH), resulting in excessively low PTH levels for the degree of hypocalcemia. Hypomagnesemic hypocalcemia should be treated by magnesium repletion as it is often refractory to only calcium repletion.[15]

Copper deficiency can cause osteoporosis as low serum copper levels impair bone formation.[53] Vitamin d deficiency may be present prior to initiating PN therapy. Appropriate treatment is necessary since it is associated with reduced bone turnover and a mineralization defect affecting the remodeling process. Excessive doses of vitamin D should be avoided as it can cause PTH suppression and directly promote bone resorption.[54] A vitamin K deficiency can result in changes in bone metabolism. Supplementation of vitamin K may reduce calciuria. It has been suggested to supplement 1 mg daily in PN patients to minimize calcium loss.[54]


Strategies are necessary for all patients who require long-term PN therapy to prevent or treat metabolic bone disease. PN formulation should be designed to minimize hypercalciuria, provide adequate vitamin K, Mg, Ca, and P, avoid metabolic acidosis, provide appropriate amino acid dose, vitamins and trace elements, and minimize aluminum contamination.



**Allergy/Hypersensitivity to components of PN**

Many allergenic foods are potential ingredients of PN however hypersensitivity reactions are rare events. Reactions can include cutaneous symptoms/signs (urticarial rash, swelling, erythema, hives, pruritus), back pain , diarrhea, hypoxia , nausea, vomiting, increased body temperature, cyanosis, edema, oral dryness, dyspnea, respiratory distress, stridor, bronchospasm, acute respiratory distress syndrome and anaphylaxis. The most common allergens of concern involve the ILE and multivitamin preparation. Other potential allergens include the AA solution, trace elements or other unknown components of the PN therapy.[56]

The allergen may also not be contained in the solution itself, but be chemicals or devices that the patient is exposed to during the process such as chlorhexidine gluconate (skin disinfectant), nickel (from an eyelet in an intravenous needle), latex (from the rubber stopper of the PN solution) and bisulphite additive (which is commonly added to medications and AA as an antioxidant and preservative).[56]

ILE is the most likely component of concern since it may contain or cause a cross reaction with 1 or more of the following allergens (depending on the specific ILE) including lecithin, soy, egg, fish, olive and peanut.[16] Patients on PN therapy with sensitivity reactions need to be evaluated by eliminating solution components one at a time in order to ascertain the potential allergen. This should be done with the assistance of Allergy and Immunology specialists. The PN solution should be discontinued if the reactions are severe in nature.

## PN Ordering on Sunrise

Sunrise EMR allows physicians to place two types of PN orders – custom order and premixed PN order; however a nutrition referral is required for either type of order to be placed. Please go through the Appendix for more detail about the PN ordering process. Custom PN orders are required to be submitted by 11AM to the pharmacy in order for the patient to begin PN later that day.

Glossary of terms can be found after the reference page.

# References


1. Mueller C, McClave S, Kuhn J, American Society for Parenteral and Enteral Nutrition. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2012.

2. Worthington P, Balint J, Bechtold M, et al. When Is Parenteral Nutrition Appropriate? *Journal of Parenteral and Enteral Nutrition*. 2017;41(3):324-377. doi:10.1177/0148607117695251

3. McClave S, Taylor B, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient. *JPEN-PARENTER ENTER*. 2016;40(2):159-211. doi:https://doi.org/10.1177/0148607115621863

4. A.S.P.E.N. A.S.P.E.N. Clinical Nutrition Webinar Series. Parenteral Nutrition: Back to Basics - Where Do I Start? Presented at the: October 10, 2017.

5. Kane KF, Cologiovanni L, Mckiernan J, et al. High Osmolality Feedings Do Not Increase the Incidence of Thrombophlebitis During Peripheral IV Nutrition. *Journal of Parenteral and Enteral Nutrition*. 1996;20(3):194-197. doi:10.1177/0148607196020003194

6. Boullata JI, Sacks G, Crill C, Kumpf V, Plogsted S, American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. Clinical Guidelines. *JPEN-PARENTER ENTER*. 2014;38(3):334-377.

7. Mueller C, Lord L, Marian M, McClave S, Miller S, American Society for Parenteral and Enteral Nutrition. *The A.S.P.E.N. Adult Nutrition Support Core Curriculum.* 3rd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2017.

8. Gottschlich MM, Matarese L, Shronts E, American Society for Parenteral and Enteral Nutrition. *The A.S.P.E.N. Nutrition Support Dietetics Core Curriculum*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 1993.

9. Mundi MS, Nystrom EM, Hurley DL, McMahon MM. Management of Parenteral Nutrition in Hospitalized Adult Patients. *Journal of Parenteral and Enteral Nutrition*. 2017;41(4):535-549. doi:10.1177/0148607116667060

10. Hertz DE, Karn CA, Liu YM, Liechty EA, Denne SC. Intravenous glucose suppresses glucose production but not proteolysis in extremely premature newborns. *J Clin Invest*. 1993;92(4):1752-1758.

11. Klek S. Omega-3 Fatty Acids in Modern Parenteral Nutrition: A Review of the Current Evidence. *Journal of Clinical Medicine*. 2016;5(3):34. doi:10.3390/jcm5030034

12. Polyunsatured Fatty Acids (PUFA) and Depression. http://flipper.diff.org/app/items/6050. Published March 27, 2019. Accessed March 26, 2019.

13. Burgess P, Hall RI, Bateman DN, Johnston IDA. The Effect of Total Parenteral Nutrition on Hepatic Drug Oxidation. *Journal of Parenteral and Enteral Nutrition*. 1987;11(6):540-543. doi:10.1177/0148607187011006540

14. Kuenstler H. Omegaven®(fish oil triglycerides) injectable emulsion. Presented at the: January 9, 2019; Nassau University Medical Center.

15. Gottschlich MM, DeLegge MH, Guenter P, American Society for Parenteral and Enteral Nutrition. *The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach: The Adult Patient*. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007.

16. Hayes BD, Gosselin S, Calello DP, et al. Systematic review of clinical adverse events reported after acute intravenous lipid emulsion administration. *Clinical Toxicology*. 2016;54(5):365-404. doi:10.3109/15563650.2016.1151528

17. Hoffer LJ. Parenteral Nutrition: Amino Acids. *Nutrients*. 2017;9(3). doi:10.3390/nu9030257

18. Skipper A, Tupesis N. Is There a Role for Nonprotein Calories in Developing and Evaluating the Nutrient Prescription? *Nutrition in Clinical Practice*. 2005;20(3):321-324. doi:10.1177/0115426505020003321

19. Nakasaki H, Katayama T, Yokoyama S, et al. Complication of Parenteral Nutrition Composed of Essential Amino Acids and Histidine in Adults With Renal Failure. *Journal of Parenteral and Enteral Nutrition*. 1993;17(1):86-90. doi:10.1177/014860719301700186

20. Baumgartner TG. *Clinical Guide to Parenteral Micronutrition*. 3rd ed. Fujisawa USA, Inc.; 1997.

21. Hemilä H, Chalker E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients*. 2019;11(4). doi:10.3390/nu11040708

22. Fessler T. Trace Element Monitoring and Therapy for Adult Patients Receiving Long-term Total Parenteral Nutrition. *PRACTICAL GASTROENTEROLOGY*. 2005:44-65.

23. Vanek VW, Borum P, Buchman A, et al. A.S.P.E.N. position paper: recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutr Clin Pract*. 2012;27(4):440-491. doi:10.1177/0884533612446706

24. Berger MM. Antioxidant Micronutrients in Major Trauma and Burns: Evidence and Practice. *Nutrition in Clinical Practice*. 2006;21(5):438-449. doi:10.1177/0115426506021005438

25. Maswoswe J, Okpara A, Hilliard M. An old nemesis: calcium and phosphate interaction in TPN admixtures. *Hosp Pharm*. 1995;30:579-586.

26. Robinson CA, Sawyer JE. Y-Site Compatibility of Medications with Parenteral Nutrition. *J Pediatr Pharmacol Ther*. 2009;14(1):48-56. doi:10.5863/1551-6776-14.1.48

27. Eisenberg PG, Gianino S, Clutter WE, Fleshman JW. Abrupt discontinuation of cycled parenteral nutrition is safe. *Dis Colon Rectum*. 1995;38(9):933-939. doi:10.1007/BF02049728

28. Ayers P, Adams S, Boullata J, et al. A.S.P.E.N. Parenteral Nutrition Safety Consensus Recommendations. *Journal of Parenteral and Enteral Nutrition*. 2014;38(3):296-333. doi:10.1177/0148607113511992

29. Curtis C. Technology in Parenteral Nutrition Compounding. *Nutrition in Clinical Practice*. 2018;33. doi:10.1002/ncp.10086

30. Wischmeyer PE, Hasselmann M, Kummerlen C, et al. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. *Critical Care*. 2017;21(1):142. doi:10.1186/s13054-017-1736-8

31. McCleary E, Tajchman S. Parenteral Nutrition and Infection Risk in the Intensive Care Unit. *Nutr Clin Pract*. 2016;31(4):476-489.

32. Marcuard SP, Dunham B, Hobbs A, Caro JF. Availability of Insulin from Total Parenteral Nutrition Solutions. *Journal of Parenteral and Enteral Nutrition*. 1990;14(3):262-264. doi:10.1177/0148607190014003262

33. Christianson MA, Schwartz MW, Suzuki N. Determinants of Insulin Availability in Parenteral Nutrition Solutions. *Journal of Parenteral and Enteral Nutrition*. 2006;30(1):6-9. doi:10.1177/014860710603000106

34. 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(3):419-423. doi:10.1093/ajcn/46.3.419

35. Poonuru S, Pathak SR, Vats HS, Pathak RD. Rapid reduction of severely elevated serum triglycerides with insulin infusion, gemfibrozil and niacin. *Clin Med Res*. 2011;9(1):38-41. doi:10.3121/cmr.2010.898

36. Moon HJ, Hwang IW, Lee JW, Hong SY. A case of fat overload syndrome after rapid infusion of SMOFlipid emulsion in an adult. *Am J Emerg Med*. 2017;35(4):660.e3-660.e4. doi:10.1016/j.ajem.2015.08.044

37. Morley J. Carnitine Deficiency - Nutritional Disorders. Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/nutritional-disorders/undernutrition/carnitine-deficiency. Published March 27, 2019. Accessed March 27, 2019.

38. Borum PR. Carnitine in Parenteral Nutrition. *Gastroenterology*. 2009;137(5):S129-S134. doi:10.1053/j.gastro.2009.08.016

39. Bhavsar H, Forster J. G185(P) Carnitine deficiency in long term parenteral nutrition (PN) dependent children. *Archives of Disease in Childhood*. 2017;102(Suppl 1):A74-A75. doi:10.1136/archdischild-2017-313087.184

40. Office of Dietary Supplements - Carnitine. https://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/. Accessed May 15, 2019.

41. Hamilton JW, Li BUK, Shug AL, Olsen WA. Carnitine transport in human intestinal biopsy specimens. *Gastroenterology*. 1986;91(1):10-16. doi:10.1016/0016-5085(86)90432-4

42. Office of Dietary Supplements - Vitamin K. https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/. Published March 27, 2019. Accessed March 26, 2019.

43. Kennel KA, Drake MT, Hurley DL. Vitamin D Deficiency in Adults: When to Test and How to Treat. *Mayo Clinic Proceedings*. 2010;85(8):752-758. doi:10.4065/mcp.2010.0138

44. Vitamin E - Nutritional Disorders. Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/nutritional-disorders/vitamin-deficiency,-dependency,-and-toxicity/vitamin-e. Published March 27, 2019. Accessed March 26, 2019.

45. Office of Dietary Supplements - Vitamin A. https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. Published March 27, 2019. Accessed March 26, 2019.

46. Office of Dietary Supplements - Vitamin D. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/. Published March 27, 2019. Accessed March 26, 2019.

47. Osiezagha K, Ali S, Freeman C, et al. Thiamine Deficiency and Delirium. *Innov Clin Neurosci*. 2013;10(4):26-32.

48. Livingstone C. Manganese Provision in Parenteral Nutrition: An Update. *Nutr Clin Pract*. 2018;33(3):404-418. doi:10.1177/0884533617702837

49. Kraft M, Bhatiche I, Sacks G. Review of the Refeeding Syndrome. *Nutr Clin Pract*. 2005;20:625-633.

50. Cahova M, Bratova M, Wohl P. Parenteral Nutrition-Associated Liver Disease: The Role of the Gut Microbiota. *Nutrients*. 2017;9(9):987. doi:10.3390/nu9090987

51. Zaloga GP. Phytosterols, Lipid Administration, and Liver Disease During Parenteral Nutrition. *Journal of Parenteral and Enteral Nutrition*. 2015;39(1S):39S-60S. doi:10.1177/0148607115595978

52. Arenas Villafranca JJ, Nieto Guindo M, Álvaro Sanz E, Moreno Santamaria M, Garrido Siles M, Abilés J. Effects of cyclic parenteral nutrition on parenteral-associated liver dysfunction parameters. *Nutr J*. 2017;16. doi:10.1186/s12937-017-0289-7

53. Davila J, Konrad D. Metabolic Complications of Home Parenteral Nutrition. *Nutr Clin Pract*. 2017;32(6):753-768. doi:https://doi.org/10.1177/0884533617735089

54. Acca M, Ragno A, Francucci C M, D'Erasmo E. Metabolic bone diseases during long-term total parenteral nutrition. *J Endocrinol Invest*. 2007;30(Supplement 6):54-59.

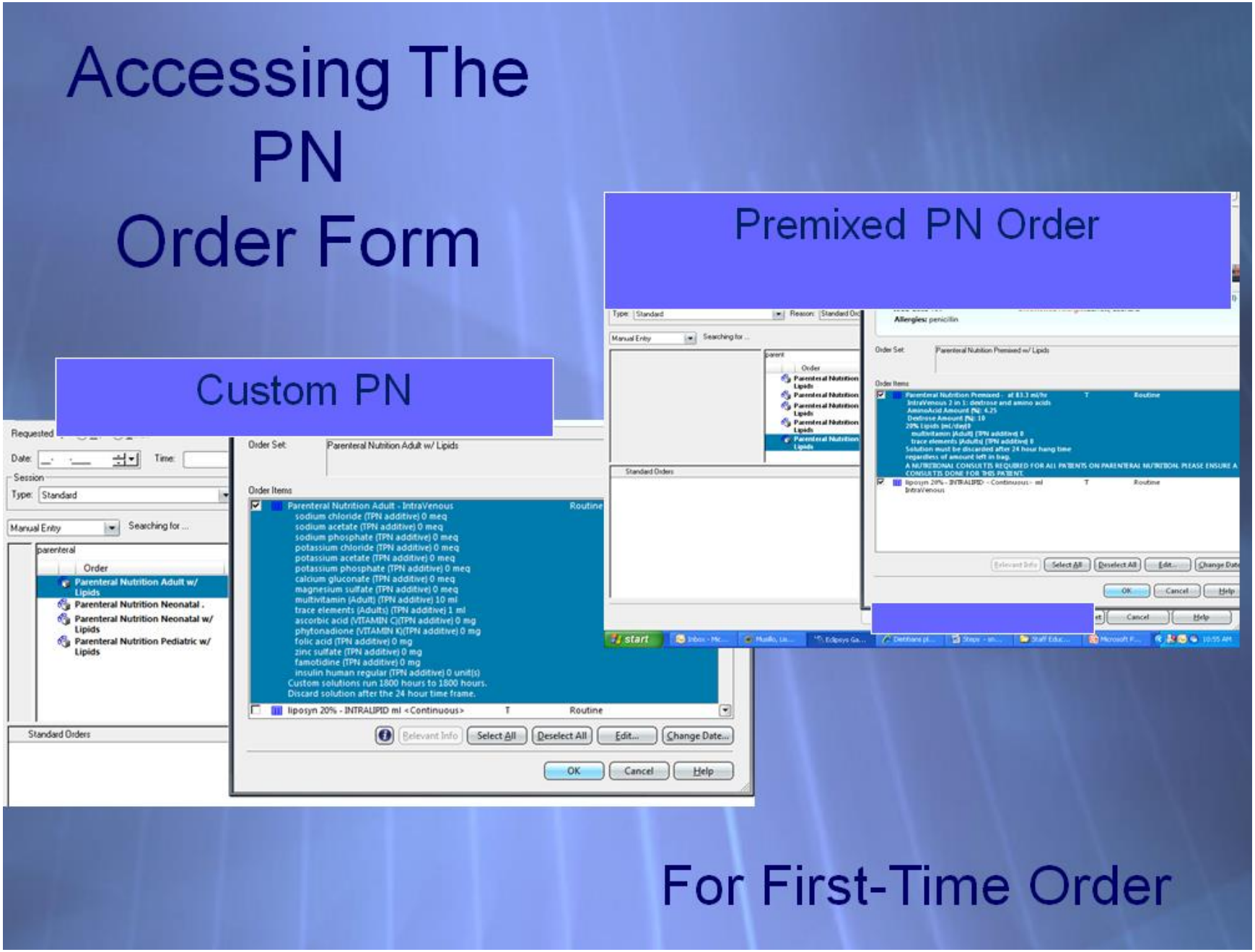
55. Canada TW. Aluminum exposure through parenteral nutrition formulations: Mathematical versus clinical relevance. *Am J Health Syst Pharm*. 2005;62(3):315-318. doi:10.1093/ajhp/62.3.315

56. Christian VJ, Tallar M, Walia CLS, Sieracki R, Goday PS. Systematic Review of Hypersensitivity to Parenteral Nutrition. *Journal of Parenteral and Enteral Nutrition*. 2018;42(8):1222-1229. doi:10.1002/jpen.1169

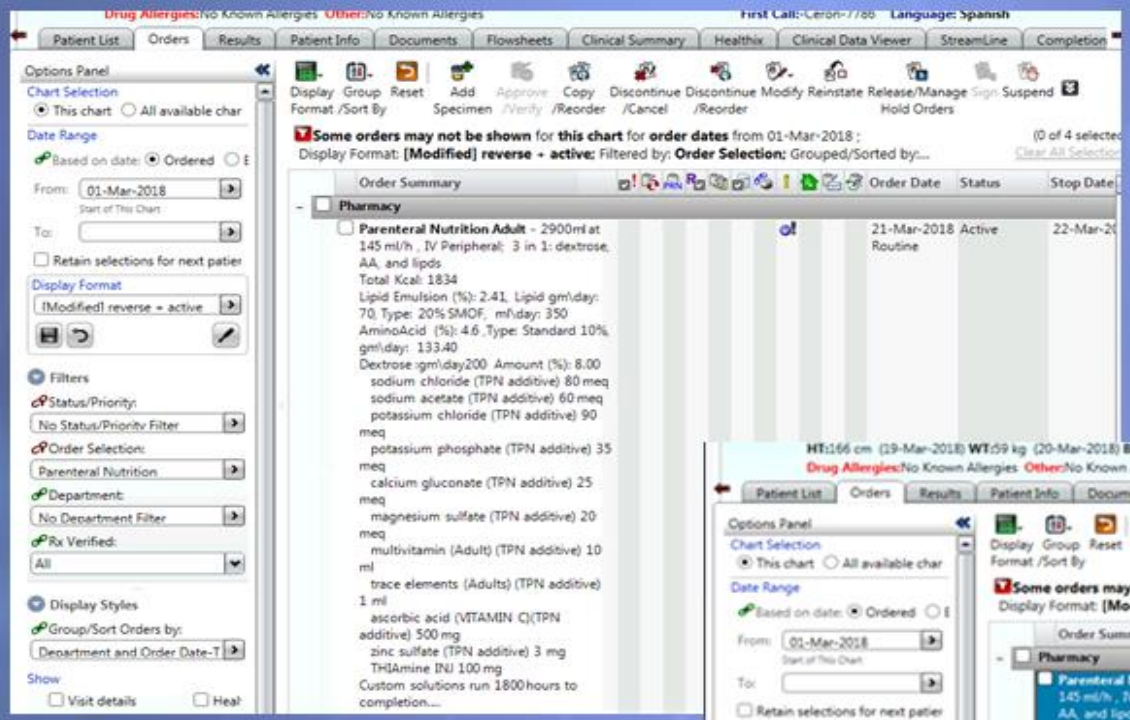
# Glossary of Terms/Abbreviations

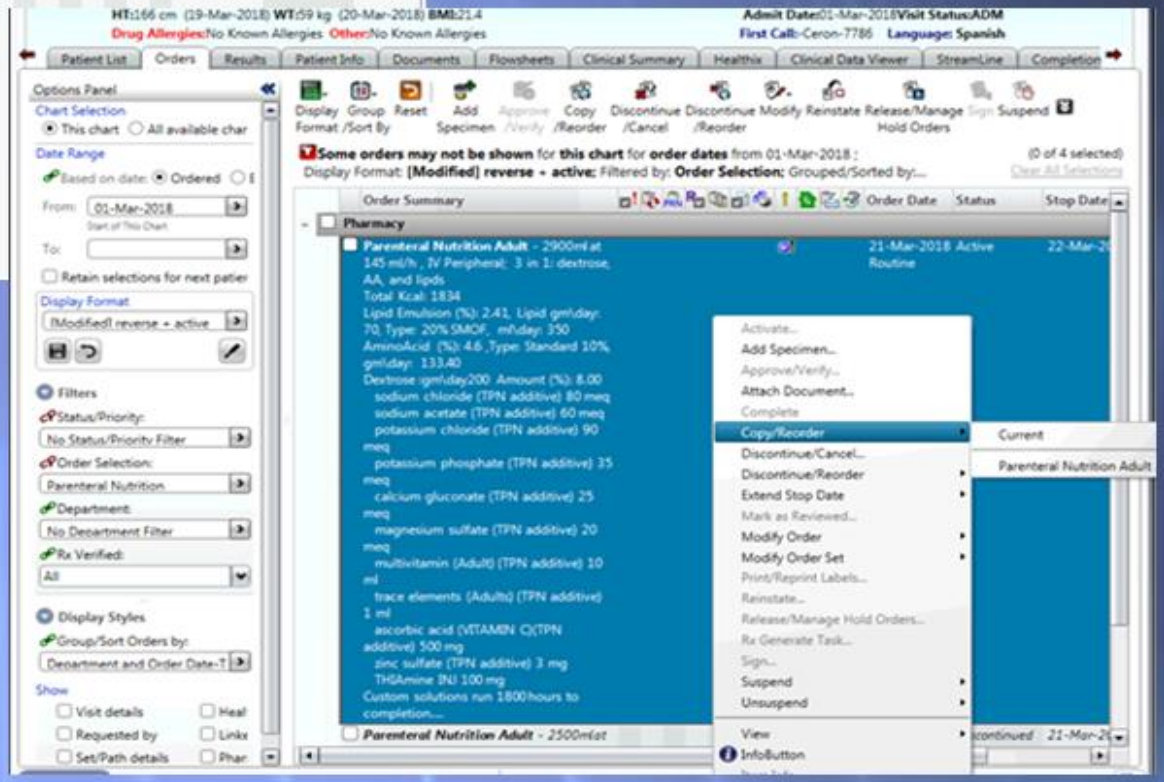
| | |
|---|---|
| AA | Amino acids |
| AAA | Aromatic amino acids |
| BCAA | Branch chain amino acid |
| CAPD | Continuous ambulatory peritoneal dialysis |
| CDC | Centers for Disease Control |
| CPN | Central parenteral nutrition |
| CPOE | Computer-prescriber order entry |
| CRRT | Continuous renal replacement therapy |
| EFA | Essential fatty acids |
| EFAD | Essential fatty acid deficiency |
| HER | Electronic Health Record |
| EN | Enteral nutrition |
| GI | Gastrointestinal |
| ICU | Intensive care unit |
| IFALD | Intestinal failure-associated liver disease |
| ILE | Lipid injectable emulsion |
| ISMP | Institute for Safe Medication Practices |
| IV | Intravenous |
| IVPB | Intravenous piggy back |
| Kcal | Kilocalorie |
| LCT | Long-chain triglycerides |
| LPL | Lipoprotein lipase |
| Mcg | Microgram |
| mEq | Milliequivalents |
| Mg | Milligram |
| MTE | Multitrace element |
| mOsm | Milliosmole |
| NUMC | Nassau University Medical Center |
| PICC | Peripherally inserted central catheter |
| PN | Parenteral nutrition |
| PNAC | PN-associated cholestasis |
| PNALD | PN associated liver disease |
| PPN | Peripheral parenteral nutrition |
| PVT | Peripheral vein thrombophlebitis |
| RES | Reticuloendothelial system |
| TF | Tube feeding |
| TNA | Total nutrient admixture |
| TPN | Total parenteral nutrition |
| USP | United States Pharmacopeia |

## Appendix: Sample order forms and processes



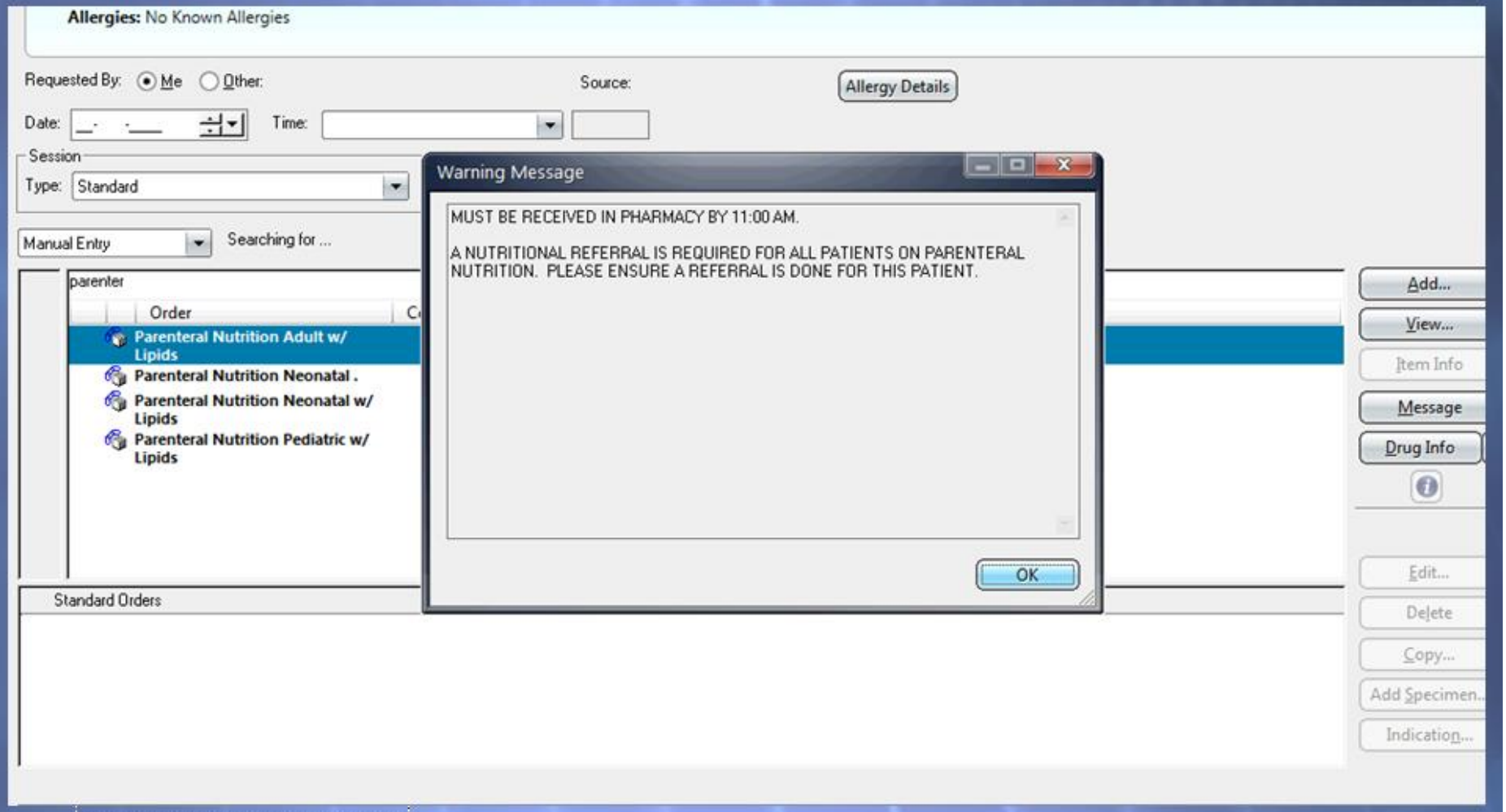
# Accessing The PN Order Form



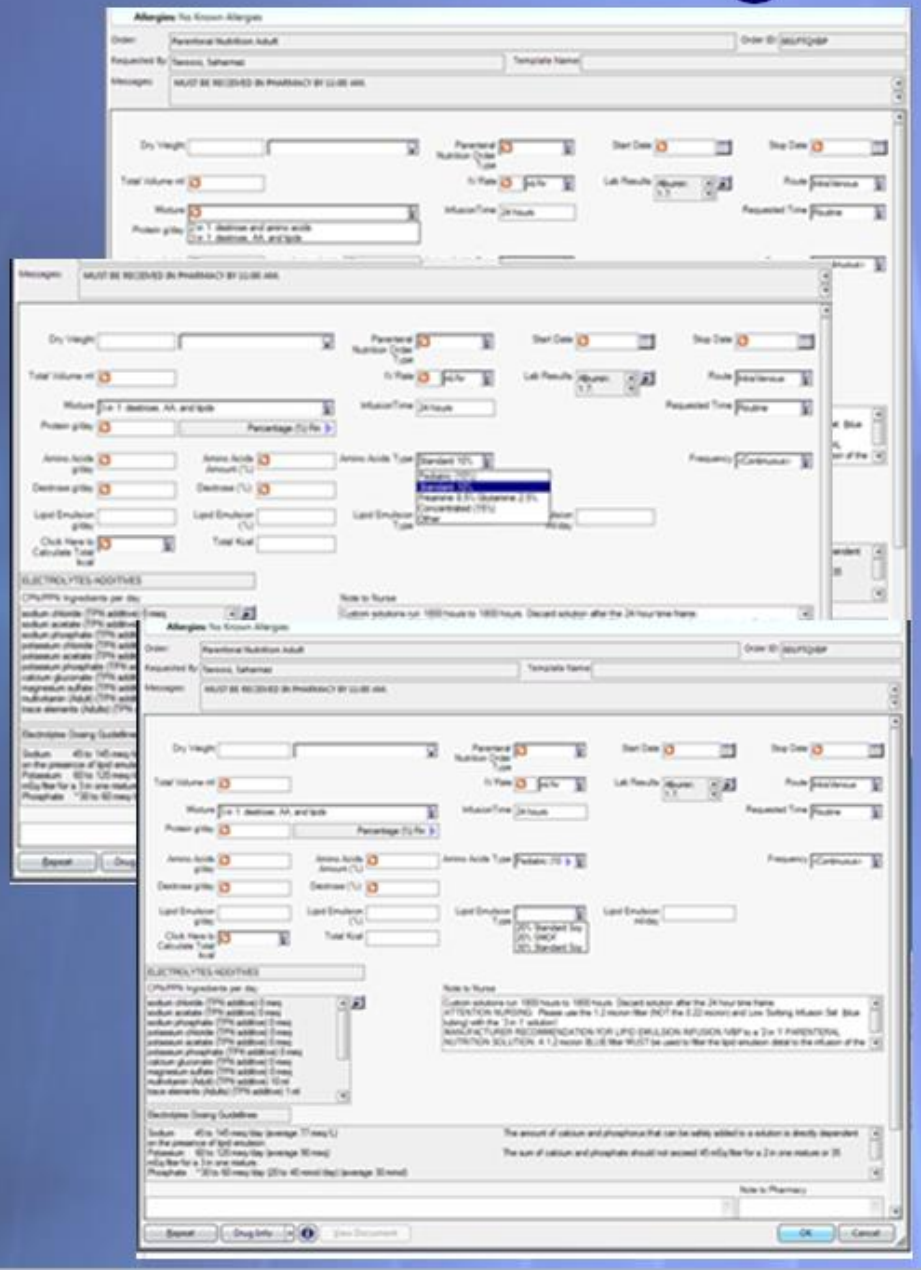




# For Renewals

# Take The Time To Read The Pop-Up Messages



# Ordering Custom PN

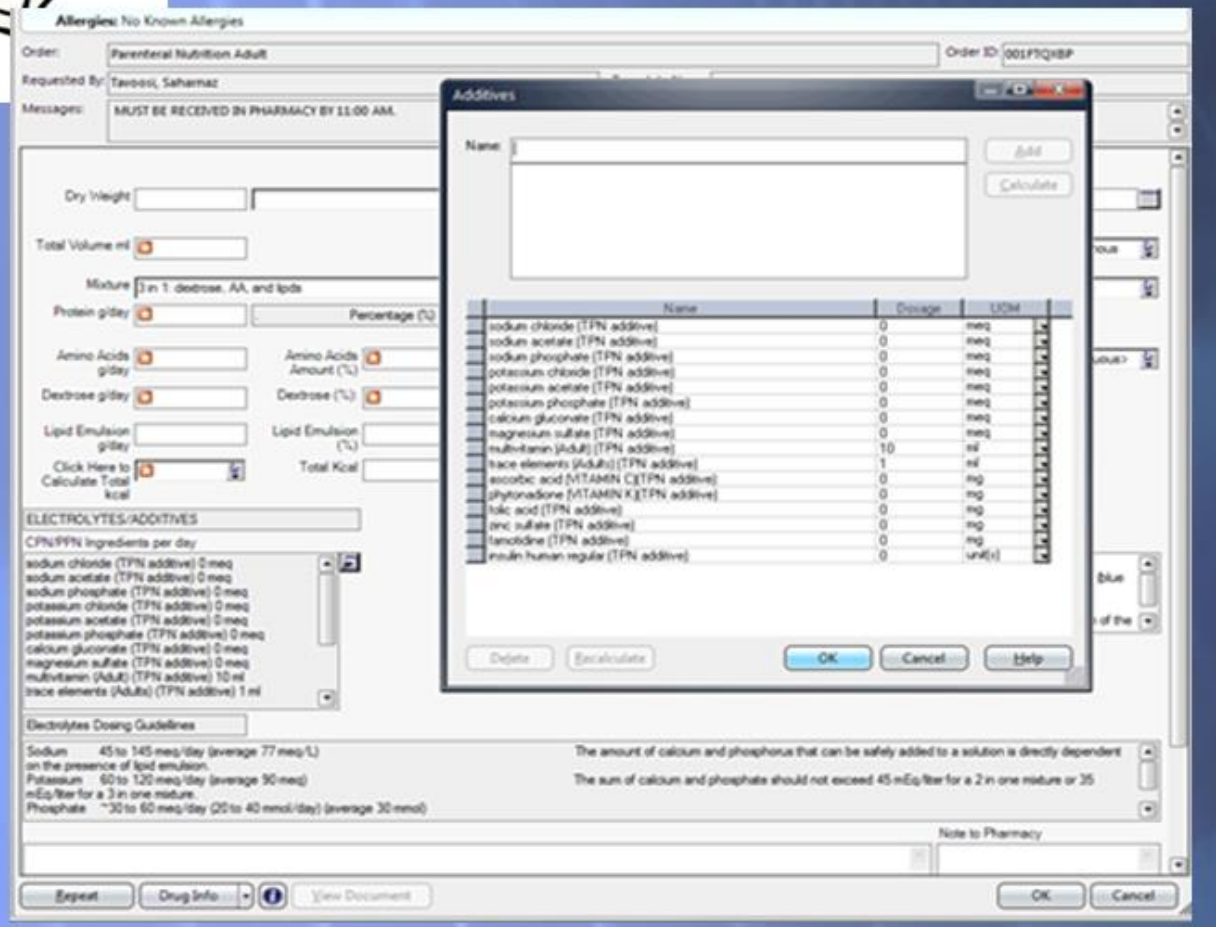


Submit orders by 11AM.
Compounding done by CAPS.

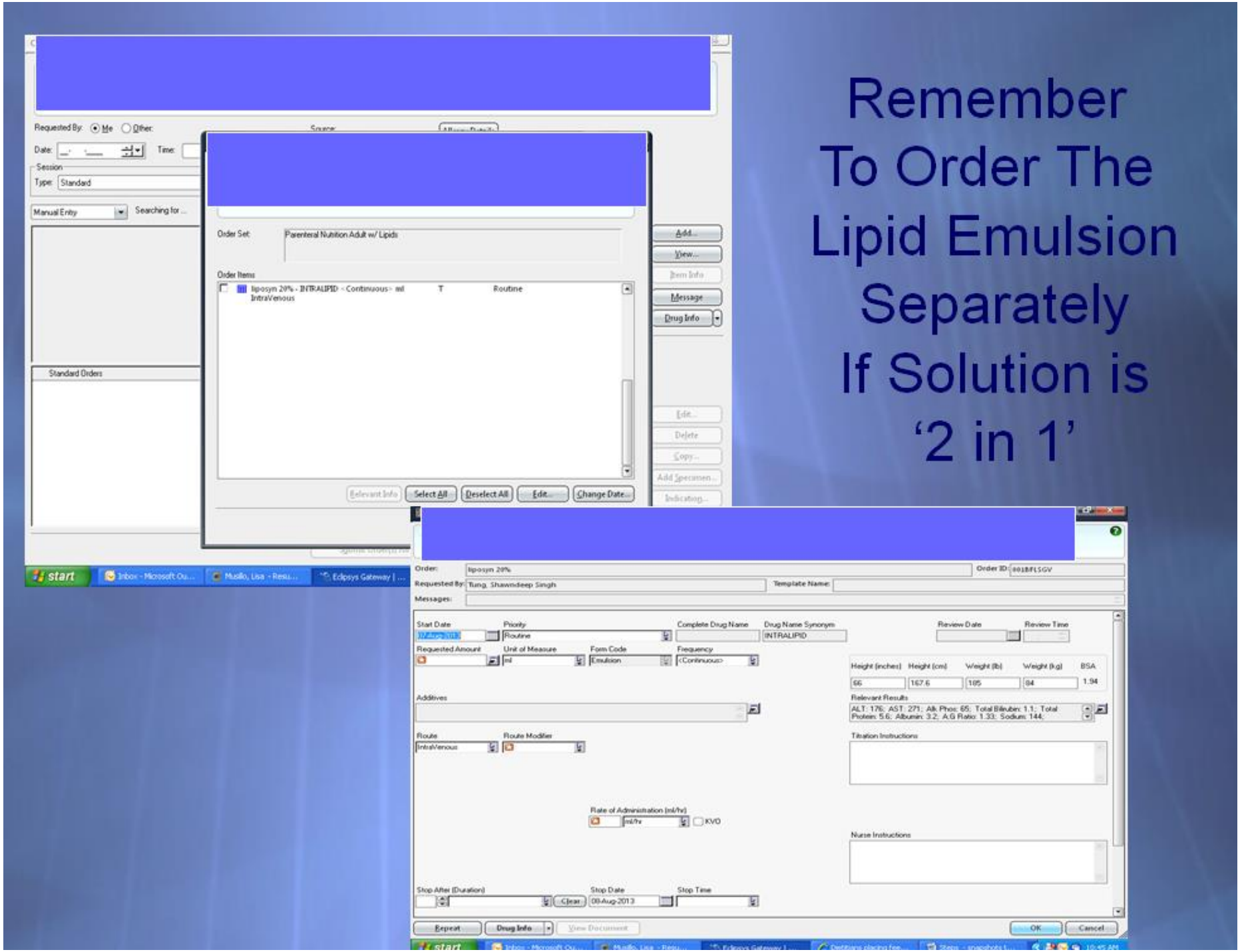
Dosing recommendations
and lab values
are available on the
order form.

Calculate the
Kcal only when all
necessary fields
are completed.

# Thoroughly Complete Form




**Use the Labs + Guidelines Provided To Dose the Electrolytes**




Remember
To Order The
Lipid Emulsion
Separately
If Solution is
'2 in 1'