Systemic Approach to Parenteral Nutrition in the ICU

Sarah Peterson* and Yimin Chen

RUSH University Medical Center, Chicago, IL, USA

Abstract: The nutrition support clinician must understand and evaluate all components of parenteral nutrition (PN) to maximize benefits while avoiding unfavorable consequences for the patients in the intensive care unit. The various aspects in caring for the PN patient include appropriate patient selection, intravenous access choice and maintenance, and individualized PN prescription to meet each patient’s unique macronutrient and micronutrient requirements. Once the PN prescription has been determined, the clinician should also be familiar with the compounding process to ensure the final solution is safe for infusion. PN is one of the most complex solutions prepared in the pharmacy with numerous ingredients. Due to the number of components in the PN solution, physicochemical incompatibilities are a common and serious problem, thus specific compounding sequence and guidelines must be followed to avoid precipitation of mixed products. Once the PN solution is ready for infusion, protocols should be in place to assure safe administration. Close monitoring for tolerance of electrolytes and macronutrients, as well as glucose control is necessary initially; whereas monitoring of specific micronutrients is crucial in long-term PN usage. A standardized process for ordering, preparing, administering and monitoring PN is recommended to assure patient safety.

Keywords: Patient safety, nutrition, intensive care unit, parenteral, infusion.

INTRODUCTION

Malnutrition in critically ill patients is associated with increased nosocomial infections, prolonged hospital length of stay, higher mortality rates, and escalated hospital costs [1-4]. Using a definition of biochemical markers or changes in weight, 40% of patients admitted to the intensive care unit (ICU) are malnourished [5, 6]. Moreover, regardless of an admitting diagnosis of malnutrition, nutritional status may worsen during hospitalization due to hypermetabolism and inadequate nutrition support delivery [7-9].

The main goal of nutrition therapy in the ICU is to attenuate the decline in nutritional status. The benefits of nutrition support in the critically ill include improved wound healing, enhanced gastrointestinal (GI) tract structure and function, and a reduction in complications and length of stay [10]. Enteral nutrition (EN) is the preferred route of nutrition support in the ICU, as parenteral nutrition (PN) has been associated with gut mucosal atrophy, hyperglycemia and increased infectious complications [11]. However, EN cannot be prescribed to every patient in the ICU: ileus, obstruction, ischemic bowel and GI bleed are common complications in the ICU that preclude EN delivery [12]. Therefore, PN is utilized by nutrition support clinicians to feed critically ill patients in the ICU who cannot tolerate EN. With a potential for significant benefits in the ICU, its intricacy requires a standardized process for ordering, preparation, administration, and monitoring to assure a quality outcome for patients [13]. The goal of this review is to provide recommendations for the safe delivery of PN in the ICU.

APPROPRIATE CANDIDATE FOR PN IN THE ICU

EN should be utilized whenever the GI tract is intact and functional, as the provision of enteral stimulation results in less pneumonia, fewer line infections, a reduction in overall infections, and shorter ICU and hospital length of stay compared to PN [11]. One of the most well known theories for the increased risk of infection associated with PN has been bacterial translocation. The proposed sequence of events include villus atrophy, epithelial cell apoptosis, and altered mucosal permeability, which lead to loss of mucosal barrier function and ultimately result in bacterial translocation [11]. In addition to bacterial translocation, PN has been found to be associated with dysfunction of B and T lymphocytes, macrophages, and neutrophils. It is also associated with increased production of pro-inflammatory cytokines including tumor necrosis factor, interleukin (IL)-1, and IL-6 [11]. All of these negative outcomes consequently lead to increased complications often observed in patients receiving PN when compared with their enteral counterparts.

There are no prospective, randomized, clinical trials addressing when to initiate PN. Nutrition support is not indicated in every patient who is unable to eat unless the potential benefits outweigh the risks involved with the therapy. Choosing an appropriate candidate for PN is a complex process that should include evaluating the patient’s medical and surgical history, current clinical status, GI tract function and nutritional status [13]. The American Society for Parenteral and Enteral Nutrition’s practice guidelines indicate that PN should be started in patients who have a nonfunctional or inaccessible GI tract, or those patients requiring bowel rest for at least 5 to 7 days, including: short-bowel syndrome, bowel perforation, obstruction, ileus, GI bleeding, radiation enteritis, bowel ischemia, and high output fistula [12]. Patients with signs and symptoms of malabsorption or intractable vomiting or diarrhea, which may result from chronic pancreatitis or past pancreatic surgery chronic pancreatitis or past pancreatic surgery, should also be considered for PN. PN may be contraindicated despite a nonfunctional gastrointestinal tract in patients with a poor prognosis that does not warrant aggressive nutrition support [12].

PARENTERAL ACCESS

The infusion of central versus peripheral PN depends upon nutrient requirements and duration of therapy, as the osmolality of the PN can easily exceed 2000 mOsm/L while serum osmolality is only 278-305 mOsm/kg. Due to the high osmotic concentration of the solution the preferred mode of delivery is central PN via a central venous catheter (CVC) with its tip placed in the superior vena cava adjacent to the right atrium [13]. The selection of the most appropriate parenteral access device is based on the patient’s vascular anatomy and access history, duration of therapy, underlying disease state and care setting [14]. Temporary percutaneous non-tunneled CVC (placed in the subclavian or jugular vein) are most often used in the acute care setting for short duration of therapy. A femoral CVC should be avoided, as its use is associated with a higher risk of venous thrombosis and catheter
related sepsis. Femoral lines are only recommended for PN administration when no other venous access can be obtained [15].

Peripheral infusion of PN is indicated when central access is not available. However, the concentration of the peripheral PN solution should not exceed 900 mOsm/L [16]. The concentration of the PN solution is determined by calculating the osmolarity of each component (Table 1). The volume may be increased to provide more calories and protein, but providing excess fluid may not be practical in many ICU patients. Administration of PN via a peripheral vein requires close monitoring, as rapid onset of pain, thrombosis and thrombophlebitis are serious complications associated with PN infusion. Peripheral infusion of PN demands frequent changing of venous access sites to maintain patency and avoid phlebitis or infiltration of the infusion site [17].

**PN PRESCRIPTION**

PN formulations are extremely complex solutions containing amino acids, dextrose, fat emulsions, electrolytes, trace elements, vitamins and/or medications. Electrolyte abnormalities, concurrent drug therapy, and insulin administration are the most common errors associated with PN infusion [13]. Common factors associated with most PN errors include inadequate knowledge of PN therapy, miscalculation of PN dosages, and failure to recognize changes in clinical condition and organ function [13]. In an effort to avoid PN-associated errors, each PN prescription should be individualized to meet the unique needs of patients. Calculation of a patient’s nutrient requirements will vary based on organ function, disease state, metabolic condition, body composition, and medication usage. The nutrition support clinician should be familiar with the standard dosages for each nutrient and when to manipulate additives outside of standard ranges. Additionally, an accurate dosing weight is necessary to determine nutrient requirements and identifying dosing errors [13].

**Energy**

Assessment of energy expenditure in the critical care setting is important to avoid under or overfeeding, both of which are common errors in the PN prescription process [13]. However, energy assessment can be problematic. During stress, there is an increase in the production of counter-regulatory hormones and cytokines, which lead to overall hypermetabolism [18]. Indirect calorimetry is recommended to improve the accuracy of energy requirement determination [19]. In the absence of indirect calorimetry, a predictive equation can be utilized to determine energy requirements. Numerous predictive equations have been developed to calculate energy expenditure [19]. The American College of Chest Physicians published a consensus statement addressing nutrition in the ICU, which indicated that 25 kilocalories per kilogram of body weight is adequate for most ICU patients, and an additional 10% to 20% should be added for patients with systemic inflammatory response syndrome [20]. The lipid and dextrose components of the PN solution are primarily provided to meet energy requirements.

<table>
<thead>
<tr>
<th>Step</th>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Total grams of amino acids per liter of solution</td>
<td>grams x 10</td>
<td>mOsm</td>
</tr>
<tr>
<td>2. Total grams of dextrose per liter of solution</td>
<td>grams x 5</td>
<td>mOsm</td>
</tr>
<tr>
<td>3. Total mEq of sodium and potassium per liter of solution</td>
<td>mEq x 2</td>
<td>mOsm</td>
</tr>
<tr>
<td>4. Total mEq of calcium per liter of solution</td>
<td>mEq x 1.4</td>
<td>mOsm</td>
</tr>
<tr>
<td>5. Total mEq of magnesium per liter of solution</td>
<td>mEq x 1</td>
<td>mOsm</td>
</tr>
</tbody>
</table>

Total Osmolarity = _____mOsm

**Lipid**

Intravenous lipid emulsions in the United States contain soybean oil, egg yolk phospholipid, glycerol, and water. Two concentrations of lipids are available, 10% and 20%. The 10% emulsion provides 1.1 kilocalories per milliliter (mL) and 25 grams of fat in the 250 mL solution or 50 grams of fat in the 500 mL solution. The 20% emulsion provides 2 kilocalories per mL and 50 grams of fat in the 250 mL solution or 100 grams of fat in the 500 mL solution. To minimize adverse metabolic consequences, lipid administration is limited to 1 gram/kilogram/day or less than 30% of total calories, especially in critically ill patients [21-23]. Acceptable serum triglyceride levels should be less than 250 milligram (mg)/deciliter (dL) four hours after lipid emulsion is discontinued and less than 400 mg/dL for continuous lipid infusions [24]. Lipid emulsion should be held when triglyceride levels exceed these recommendations, and restarted only when the serum triglyceride level is below 250 mg/dL [24]. Additionally, contraindications for lipid usage include soybean or egg allergies.

Essential fatty acid (EFA) deficiency can develop in patients who receive lipid-free PN for more than 20 days. EFA deficiency can be prevented by providing at least four percent of total calories as lipid. This can be achieved by providing lipid two to three times per week [13]. Symptoms of EFA deficiency include alterations in platelet function, hair loss, decreased wound healing, and dry, scaly skin unresponsive to water miscible creams [13].

Lipids are either administered as part of the PN solution, referred to as a total nutrient admixture (TNA) or 3-in-1, or as a separate infusion, referred to as a 2-in-1. Typically, 2-in-1 solutions are utilized in the acute care setting to enhance compatibility of the multiple components. TNA or 3-in-1 solutions are used more often for long-term PN administration [13].

**Carbohydrate**

The primary function of parenteral carbohydrate is to serve as an energy source. Carbohydrate is provided as dextrose monohydrate and provides 3.4 kilocalories per gram. Complications associated with excessive carbohydrate administration can be avoided by limiting the glucose infusion rate to 4 mg/kilogram/minute in the critically ill patient [25]. To achieve blood glucose control, patients should receive a limited amount of dextrose upon starting PN [26]. This can be achieved by starting with either 150-200 grams or half of the patient’s final goal amount of dextrose. Dextrose content should not be increased to goal until blood glucose concentrations are consistently <200 mg/dL [13].

**Protein**

The protein requirements for patients in the ICU are based on metabolic demand and underlying disease; daily protein requirements for the critically ill are outlined in Table 2. Various synthetic crystalline amino acids are used in parenteral formulations and provide 4 kilocalories per gram when oxidized for energy. The brand of amino acid solutions used to compound PN formulations should be visible on the PN order and label, as amino acid concentrations differ between manufacturers. Chloride and acetate are added to amino acid formulations for long-term PN administration [13].

**Table 1. Steps for Calculating the Osmolarity of Parenteral Nutrition Solutions**

<table>
<thead>
<tr>
<th>Step</th>
<th>Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Total grams of amino acids per liter of solution</td>
<td>grams x 10</td>
</tr>
<tr>
<td>2.</td>
<td>Total grams of dextrose per liter of solution</td>
<td>grams x 5</td>
</tr>
<tr>
<td>3.</td>
<td>Total mEq of sodium and potassium per liter of solution</td>
<td>mEq x 2</td>
</tr>
<tr>
<td>4.</td>
<td>Total mEq of calcium per liter of solution</td>
<td>mEq x 1.4</td>
</tr>
<tr>
<td>5.</td>
<td>Total mEq of magnesium per liter of solution</td>
<td>mEq x 1</td>
</tr>
</tbody>
</table>

Total Osmolarity = _____mOsm
solutions as buffering agents [27]. The concentration of chloride and acetate per liter should also be available on the PN order and label for acid-base balance [13]. Many synthetic amino acid solutions also contain additional electrolytes, thus it is necessary to state the amount on the PN order to avoid electrolyte abnormalities.

Electrolytes

The standard dosing range for parenteral electrolytes assumes normal organ function, without abnormal losses. Daily electrolyte requirements for adults with normal and impaired renal function can be seen in Table 3; however these levels should be customized to meet individual requirements [13]. Restrictions of potassium, phosphate, and magnesium may be required in patients with renal disease due to impaired excretion. Conversely, requirements of these electrolytes may be increased due to excessive losses, intracellular shifts, increased metabolic demands or in those at risk for refeeding syndrome [13]. Typically, sodium and potassium concentrations in PN solution are not limited by compatibility restraints; but large quantities of the cations may destabilize intravenous fat emulsion in TNA or 3-in-1 solutions [13]. Calcium and phosphorus compatibility should be reviewed whenever changes are made to the solution because individual patient requirements may exceed PN solubility limits, which can result in calcium phosphate precipitates [13]. As mentioned previously, some amino acid solutions contain electrolytes, the content of which should be considered during the prescription process.

Vitamins and Trace Elements

Vitamin and trace element preparations are included in the PN solution daily. Parenteral vitamin recommendations were intended to meet the needs of patients with increased requirements (Table 4). Available commercial products for adults contain 12, without

Table 2. Daily Protein Requirements for Adults in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Indication</th>
<th>Grams of Protein/Kilogram (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>1.2-1.5 g/kg [20]</td>
</tr>
<tr>
<td>Trauma</td>
<td>2.5-3 g/kg [54]</td>
</tr>
<tr>
<td>Burn</td>
<td>3 g/kg [55]</td>
</tr>
<tr>
<td>Obese (BMI ≥25)</td>
<td>1.5-2.1 g/kg of ideal body weight [57-58]</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>1.2-2.0 g/kg [59]</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>1.5 g/kg [60]</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1.0-1.2 g/kg [61]</td>
</tr>
<tr>
<td>Acute renal failure and renal replacement therapy</td>
<td>1.5-1.8 g/kg [62]</td>
</tr>
<tr>
<td>Chronic renal failure on hemodialysis</td>
<td>1.2 g/kg [63]</td>
</tr>
<tr>
<td>Chronic renal failure on peritoneal dialysis</td>
<td>1.2-1.3 g/kg [63]</td>
</tr>
<tr>
<td>Renal failure with no renal replacement therapy</td>
<td>0.8 g/kg [63]</td>
</tr>
</tbody>
</table>

Table 3. Daily Parenteral Electrolyte Requirements for Adults

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Initial Dosing</th>
<th>Renal Dosing</th>
<th>Daily Adjustment</th>
<th>Compounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium [13]</td>
<td>1-2 mEq/kg</td>
<td>1-2 mEq/kg</td>
<td>If serum sodium increases to &gt;147 mEq/L the sodium is removed from the PN solution. If serum sodium decreases below &lt;137 mEq/L additional sodium may be required</td>
<td>Sodium is added as a salt of chloride (1:1 ratio), acetate (1:1), or phosphate (4:3)</td>
</tr>
<tr>
<td>Potassium [13]</td>
<td>1-2 mEq/kg</td>
<td>0.5-1 mEq/kg</td>
<td>For patients who have not received IV supplementation of potassium, the level is increased by 10 mEq increments in an attempt to increase the serum potassium by 0.1 mEq/L, except in patients with renal failure or those requiring &gt;240 mEq/day.</td>
<td>Potassium is added as a salt of chloride (1:1 ratio), acetate (1:1), or phosphate (4:4:3)</td>
</tr>
<tr>
<td>Chloride [27]</td>
<td></td>
<td></td>
<td>As needed to maintain acid-base balance</td>
<td>See Sodium and Potassium</td>
</tr>
<tr>
<td>Acetate [27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium [13]</td>
<td>10-15 mEq</td>
<td>10-15 mEq</td>
<td>Calcium is increased to 20 mEq for patients with an ionized calcium below 0.95 and taken out of the PN if patients have a ionized calcium greater than 1.1</td>
<td>Calcium is added as calcium gluconate.</td>
</tr>
<tr>
<td>Magnesium [13]</td>
<td>8-20 mEq</td>
<td>4-12 mEq</td>
<td>For patients who have not received IV supplementation of magnesium, the level is increased by increments of 8-16 mEq/L in attempt to increase the serum magnesium by 0.1</td>
<td>Magnesium is added as magnesium sulfate.</td>
</tr>
<tr>
<td>Phosphorus [13]</td>
<td>20-40 mmol</td>
<td>20-30 mmol</td>
<td>Phosphorus levels below 2.5 should be corrected with supplemental intravenous phosphorus to avoid complications associated with refeeding syndrome</td>
<td>See Sodium and Potassium</td>
</tr>
</tbody>
</table>
vitamin K, or 13, with vitamin K, known vitamins [28]. Additional individual vitamins can be added to the PN solution to supplement excessive losses or in the event of deficiency.

Guidelines for parenteral trace element requirements in adults are provided in Table 5. Additional individual trace elements can be added to the PN solution to limit manganese and copper infusion, whereas zinc, chromium, and selenium can be individually added back to the PN solution. If the patient requires prolonged PN administration without manganese and copper due to impaired bilirubin excretion, levels should be measured routinely to ensure the patient does not eventually become depletes of these two trace elements. When patients require long-term PN, vitamin and trace element levels should be measured routinely to ensure deficiencies do not develop [31]. If low levels are detected, additional supplementation of individual micronutrients should be included and re-checked routinely to avoid over supplementation.

Medications

The addition of medications to the PN formulation is not recommended because of the potential for physicochemical interactions [13]. If no other administration route is available, the stability and compatibility of the medication and PN solution are known [13]. If an incompatible or unstable condition exists or if there is no information available, the medication should be administered separate from the PN.

Insulin is commonly administered with PN as a method of blood glucose control but can be associated with frequent harmful events [13]. The following guidelines should be followed to avoid insulin related complications. Patients should not receive more than 150 to 200 grams of dextrose on the first day of PN infusion to avoid hyperglycemia [26]. A common initial regimen of insulin is 0.05 to 0.1 units per gram of dextrose in the PN formulation [26]. If the patient remains hyperglycemic the following day, the dextrose concentration is not changed and the insulin is increased by 0.05 to 0.1 units per gram of dextrose, until blood glucose control is achieved [26]. The dextrose content of the PN solution should not be increased until normal glucose levels are attained. The nutrition support clinician should monitor all factors including steroid dosage, signs of infection, or changes in clinical status that may influence the patient’s glycemic control and adjust insulin to avoid both hyperglycemic and hypoglycemic events. The amount of insulin in the PN solution should be clearly labeled on both the order and PN bag [13]. Administration of additional insulin, given outside the PN solution, should also be clearly documented to avoid a hypoglycemic event. A protocol should be instituted for the management of blood glucose upon abrupt discontinuation of PN. Before compounding, the pharmacist should assess the PN formulation to assure the insulin dosage is within a safe range based on the specific patient population. Adding additional insulin in the PN solution to cover hyperglycemia from oral intake or EN should be avoided to prevent hypoglycemia in the event the patient’s oral

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dietary Reference Intake (DRI) [64-67]</th>
<th>Recommend Parenteral Intake [28]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B1 (Thiamin)</td>
<td>1.1-1.2 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>Vitamin B2 (Riboflavin)</td>
<td>1.1-1.3 mg</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>Niacin (Nicotinamide)</td>
<td>14-16 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 mcg</td>
<td>640 mcg</td>
</tr>
<tr>
<td>Pantothenic acid (Dexpanthenol)</td>
<td>5 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin B6 (Pyridoxine)</td>
<td>1.3-1.7 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>Vitamin B12 (Cyanocobalamin)</td>
<td>2.4 mcg</td>
<td>5 mcg</td>
</tr>
<tr>
<td>Biotin</td>
<td>30 mcg</td>
<td>60 mcg</td>
</tr>
<tr>
<td>Ascorbic acid (Vitamin C)</td>
<td>75-90 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>700-900 mcg (Retinol)</td>
<td>3300 IU (900 retinol equivalents)</td>
</tr>
<tr>
<td>Vitamin D (Cholecalciferol)</td>
<td>5-15 mcg</td>
<td>200 IU (5 mg cholecalciferol)</td>
</tr>
<tr>
<td>Vitamin E (Alpha-tocopherol)</td>
<td>15 mg</td>
<td>10 IU (6.7 mg dl-alpha tocopherol)</td>
</tr>
<tr>
<td>Vitamin K (Phylloquinone)</td>
<td>90-120 mcg</td>
<td>150 mcg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trace Element</th>
<th>Dietary Reference Intake (DRI) [65, 66]</th>
<th>Recommend Parenteral Intake [29]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>20-35 mcg</td>
<td>10-15 mcg</td>
</tr>
<tr>
<td>Copper</td>
<td>0.9 mg</td>
<td>0.3-0.5 mg</td>
</tr>
<tr>
<td>Manganese</td>
<td>1.8-2.3 mg</td>
<td>60-100 mcg</td>
</tr>
<tr>
<td>Selenium</td>
<td>55 mcg</td>
<td>20-60 mcg</td>
</tr>
<tr>
<td>Zinc</td>
<td>8-11 mg</td>
<td>2.5-5.0 mg</td>
</tr>
</tbody>
</table>
intake or EN stops.

Compounding, Stability and Compatibility

The most important step in the compounding process is to assure that the PN is prepared and labeled properly [13]. To assure a safe solution is produced, the calorie, protein, fluid, electrolyte, vitamin, trace element and medication content of the PN formulation should be reviewed for every PN prescription prior to compounding [13]. The compounding pharmacist should review each PN order to ensure an appropriate indication, route of administration, nutrient dosage and potential for drug-drug and drug-nutrient interactions. To facilitate this assessment the patient’s height, dosing weight, laboratory values, hepatic, renal and GI function should be accessible to the compounding pharmacist [13]. Any nutrient or medication dose outside of the standard range that is not explained by the patient’s condition or history should be clarified before the PN is prepared.

Due to the complexity of preparation and large number of components, PN solutions are categorized as medium-risk sterile preparations [13]. There are two critical factors in establishing stability of the PN solution: microbial sterility and chemical stability. Microbial sterility is defined as the inhibition or prevention of microorganism growth within the PN solution. Chemical stability refers to a PN solution preserving its labeled strength within 10% variance until its beyond-use date [13]. Chemical stability can be impaired by exposure to extreme temperatures during storage and hydrolysis or oxidation of ingredients over time. In general, amino acids, vitamins, trace elements, and intravenous fat emulsions are most vulnerable to degradation [13]. The principal concern is the deterioration of vitamins and trace elements from light exposure and oxidation, which can lead to micronutrient deficiencies [13]. Yet, micronutrient deficiencies are rare in the acute care setting, as PN solutions are typically compounded daily with minimal storage time in the acute care setting. If sterility or stability testing within an individual pharmacy is not performed for PN formulations, the beyond-use dating of the PN cannot exceed the published limits by the United States Pharmacopeia (USP): use within 30 hours if stored at controlled room temperature, use within 7 days if stored at 2-8 degrees Celsius, or use within 45 days if stored at less than -20° Celsius [32].

Physicochemical incompatibilities, including both solid and liquid precipitates, may develop within the PN solution [13]. An incompatible combination of salts within the PN solution leads to the development of solid precipitates; typically calcium, the most reactive compound, forms insoluble products. To avoid calcium precipitates, calcium gluconate should be used in PN solutions [13]. Additionally, during the compounding process additives that may react with calcium, namely phosphorus, should be added at the beginning and calcium should be added near the end of the sequence [13]. Precipitate formation can also occur with use of bicarbonate salts for base replacement; as a result, acetate should be utilized as an alkalizing agent [13]. In addition to precipitate formation, phase separation is another possible incompatibility of the PN solution. Particularly in TNA and 3-in-1 solutions, as high concentrations of cations, namely sodium and potassium, can destabilize lipid [13].

Examining the physical appearance of the final PN solution is an important step to assuring patient safety [13]. For translucent PN solutions, 2-in-1 solutions, clinicians should search for the presence of oil droplets or an opaque parenteral solution, TNA or 3-in-1 solutions [13]. For opaque solutions, the clinician should search for signs of phase separation, where the presence of free oil either as individual droplets or a continuous layer on the surface indicates an incompatible formulation. It is important to remember that the absence of an obvious physical sign of incompatibility does not equate with overall safety [13].

ADMINISTRATION

The first and most important step of PN administration is to verify that the correct PN solution was delivered to the appropriate patient [13]. A dangerous PN-associated error is due to the infusion of PN to the wrong patient. Therefore, the bedside nurse should be instructed to double-check the patient’s name and medical record number on the PN label to avoid infusing the solution on the wrong patient.

Tubing sets with a 0.22 micron filter should be utilized for PN administration to remove particulates, precipitates, and microorganisms, but this practice can only be used with 2-in-1 formulations [13]. The composition of the intravenous fat emulsion is disrupted when infused through filters less than 1.2 microns in size. Therefore, a 1.2 micron filter should be used for all TNA or 3-in-1 solutions and intravenous fat emulsion infusions [13]. TNA or 3-in-1 and lipid administration sets should be changed every 24 hours, while formulations containing only dextrose and protein can be changed every 72 hours. PN administration tubing sets should be replaced using aseptic technique while applying universal precautions [13].

In the hospital setting, PN solutions are usually provided over a 24-hour period since a continuous infusion requires less nursing effort, less manipulation of intravenous lines, and less metabolic complications such as hyperglycemia and electrolyte disturbances [13]. If PN solution infusion needs to be interrupted, the infusion rate should be tapered down to half of the main infusion rate for one hour to prevent rebound hypoglycemia [13]. If a taper is not possible, a dextrose containing intravenous solution should be started to prevent rebound hypoglycemia. Patients who are stabilized with continuous PN infusion or who will require long-term therapy benefit from shortening the infusion time over 12 to 16 hours to maximize mobility and allow hepatic rest. To prevent hyperglycemia, electrolyte abnormalities, and volume overload, the cycling of PN infusion time is gradually decreased by 4-hour increments over several days until the desired infusion time is reached and tolerated by the patient.

Bacteria can flourish in intravenous fat emulsions, as the solution is iso-osmotic with an osmolarity of 250-290 mOsm/L, has a neutral environment with a pH of 7.5 and contains glycerol for nutrients; all of which are favorable for the growth of microorganisms [13]. Due to the possibility of contamination the Center for Disease Control (CDC) and USP recommend that intravenous fat emulsion products be infused within 12 hours of opening the original container [13, 33]. For a slower infusion time, lipids should be given in two separate infusions to not exceed the 12 hour infusion time for any single container. The risk for microbial growth is decreased in TNA and 3-in-1 solutions, therefore these formulations can be infused over a 24-hour period [13].

MONITORING

Monitoring PN administration is necessary to determine the efficacy of the specialized nutrition therapy, detect and prevent complications, and evaluate changes in clinical condition [13]. Clinicians should examine vital signs, temperature, daily intake and output, weight, glucose levels and laboratory tests to monitor for complications related to PN infusion. Patients receiving their first PN formulation should be monitored closely for adverse reactions and refeeding syndrome [13].

Electrolytes

Fluid and electrolyte imbalance is a common complication of PN. To prevent complications, the nutrition support clinician should
look for changes in fluid status and closely monitor intake and output, as well as trends in hepatic and renal function [13]. Typically, laboratory monitoring of serum chemistries are more frequent when PN is initiated and can decrease in frequency as the patient’s clinical status stabilizes. A chemistry panel, including sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, phosphorus and magnesium should be monitored daily for at least the first week after initiating PN. After that time period, laboratory values can be monitored less frequently [13].

Refeeding syndrome is a serious complication often associated with the initiation of PN [34]. Risk factors for the development of refeeding syndrome include recent significant unintentional weight loss (usually defined as greater than 10% weight loss over the past two to three months), little to no oral intake over the past seven to ten days, and obvious stress or depletion [34]. The classic characterization of refeeding syndrome consists of hypophosphatemia, hypokalemia, hypomagnesemia, rapid fluid shifts, peripheral edema, and sometimes thiamine deficiency [34]. Of these characteristics, the most commonly seen abnormality is hypophosphatemia, which should be monitored very closely and replenished as needed to avoid complications associated with hypophosphatemia such as heart failure, arrhythmia, and respiratory failure. The most frequently observed and life-threatening complication is respiratory failure [35, 36]. This results from the initial phosphate depleted state which is further exacerbated by the introduction of nutrient administration, in particular the infusion of dextrose. When this occurs, insulin is secreted and there is an increase in cellular uptake of phosphate, as well as increased synthesis adenosine-5'-triphosphate (ATP), 2,3-diphosphoglycerate (2,3DPG), and creatine phosphokinase (CPK), all leading to decreased serum phosphorus levels. Refeeding syndrome is a serious complication that presents itself within the first few days of nutrition support initiation that is often under-appreciated. An astute nutrition support clinician must be proactive and closely monitor phosphate, potassium, and magnesium levels, as well as fluid status upon initiating nutrition support.

Blood Glucose

Hyperglycemia is one of the most common complications associated with PN, which can lead to increased infectious complications and increased mortality [37]. Much attention has been received in achieving optimal glycemic control in the acutely ill hospitalized patient population since the landmark study by Van den Berghe et al., which showed impressive improvements in morbidity and mortality [38]. Stress-induced hyperglycemia has been well described in the literature in the acutely ill patient population owing to insulin resistance and increased gluconeogenesis (McMahon 2004). In the face of stress-induced hyperglycemia, the provision of dextrose infusion in the form of PN can further exacerbate hyperglycemia, thus making the achievement of euglycemia more challenging [26]. To ensure PN dextrose is not provided in an amount that cannot be tolerated, in critically ill patients the glucose oxidation rate of 4 milligrams/kilogram/minute should not exceed [39]. Insulin can be added to the PN solution to provide blood glucose control; however in the ICU insulin requirements can change quickly. Utilization of a continuous insulin infusion allows for rapid adjustment of insulin administration to control glucose. Once a stable dose of insulin administration is determined, insulin can be added to the PN. However, strict blood glucose monitoring is still indicated to monitor for hypoglycemia.

Acid-Base

The PN solution contains both preformed acids and nutrients that are metabolized into acids [27]. Patients with normal renal function receiving PN are generally able to maintain acid-base equilibrium through excretion of the excess acid. However, critically ill patients may have impaired ability to buffer and excrete the acid load of PN [27]. Patients in the ICU may experience excess bicarbonate losses from the GI tract, from diarrhea or fistula output, and kidneys, from type II renal tubular acidosis (RTA). Hydrogen excretion may also be diminished during acute renal failure, from type I RTA. Amino acid metabolism contributes to PN-associated metabolic acidosis through the generation of sulfuric, phosphoric and organic acids [27]. Chloride and acetate contents in the PN solution should be adjusted to maintain acid-base balance. In general, acid-base balance can be maintained by using approximately equal amounts of chloride and acetate, but may require adjustment based on the clinical situation, as well as the infusion of other intravenous fluids and medications [27]. Amino acid solutions contain various amounts of chloride and acetate, depending on the individual product and manufacturer, for buffering purposes. For this reason it is necessary to state the specific amino acid product name used in compounding on the PN label in order to account for the chloride and acetate content [13]. The nutrition support clinician should always remember to include the amounts of chloride and acetate from the amino acid solution during total chloride and acetate balance calculation in order to make verification process by the pharmacist less prone to error.

Under and Overfeeding

When caring for the critically ill patient receiving nutrition support, one must consider that both under and over feeding are serious risks associated with PN delivery. Errors can be made in the original estimation of nutrient needs or during the ordering process [13]. Infusion of PN may also be interrupted in the critical care setting, stopping PN for incompatible medication or therapeutic and diagnostic procedures may lead to under delivery of nutrients. Even a brief period of inappropriate calorie delivery can lead to numerous consequences, which can easily outweigh the potential benefits of PN.

Lean body mass is usually sacrificed during periods of underfeeding due to proteolysis, in an attempt to provide substrate for wound healing, tissue repair, and the production of positive acute phase reactants. Up to 10% of skeletal muscle mass can decrease in the underfed critically ill patient [40]. Underfeeding can also lead to decreased cardiac function by directly causing heart muscle wasting and worsening respiratory function by producing prolonged ventilatory dependence [41, 42]. Additionally, patients who are underfed have decreased immune function and increased risk of developing an infectious complication [43, 44]. Under delivery of nutrients can lead to worse clinical outcomes in the ICU population.

Overfeeding results in serious complications, including azotemia, fat overload syndrome, hepatic steatosis, hyperglycemia and hypercapnia. Azotemia occurs when the production of urea exceeds excretion of the waste product. Urea is synthesized in the liver using nitrogen from the metabolism of amino acids. The rate of synthesis depends on blood amino acid concentration, which is dependent on protein content of the PN solution and endogenous catabolism. Azotemia can result from overzealous protein infusion, and in some instances renal replacement therapy is necessary to decrease the urea load [45]. Fat-overload syndrome can result from either overall total calorie overfeeding, overfeeding of lipids, or both [45]. The most commonly observed complications include respiratory distress, coagulopathy, abnormal liver function tests (LFTs), and hypertriglyceridemia [46, 47]. Hepatic steatosis was commonly observed in the early days of hyperalimentation, when the practice of overfeeding was widespread. Hepatic steatosis is associated with elevated LFTs, coagulopathy, and hyperbilirubinemia and can ultimately lead to liver failure [45]. Hypercapnia can result as a complication of administration of excess nutrients. Carbon dioxide is produced when intracellular substrates are metabolized. As more nutrients are provided, lipogenesis occurs and carbon dioxide production increases [45, 38 Current Drug Safety, 2010, Vol. 5, No. 1 Peterson and Chen, 2010, Vol. 5, No. 1 Peterson and Chen.
Systemic Approach to Parenteral Nutrition in the ICU

Infection

Central venous catheter (CVC) related infection is a serious complication associated with PN that has been well documented in the literature [49, 50]. Furthermore, candidemia, which is associated with a mortality rate of 30% to 75%, has been the most widely recognized complication since the development of PN [51-53]. In a number of studies conducted both in the U.S. and internationally, PN, as well as duration of PN therapy, were the most common risk factors associated with CVC infections [52, 53]. In addition, PN was found to be the only risk factor independently associated with CVC infection in some of these studies [49, 51, 53].

CONCLUSION

PN solutions are a complex formulation of macronutrients, electrolytes, micronutrients and medications. The delivery of PN to critically ill patients increases the complexity of the treatment modality. Many errors and complications are associated with PN including, inappropriate macronutrient prescription, electrolyte abnormalities, micronutrient deficiencies, medication interaction, precipitate development, hyperglycemia, acid-base disorders and infections. An understanding of the etiology of errors and complications associated with PN is necessary to provide optimal nutrition support in the ICU setting. A standardized process for ordering, preparing, administering and monitoring PN is recommended to assure patient safety.

REFERENCES


Received: March 17, 2009 Revised: April 1, 2009 Accepted: April 24, 2009