Chapter 165: Parenteral Nutrition

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 60, Nutrition Assessment and Support.

KEY CONCEPTS

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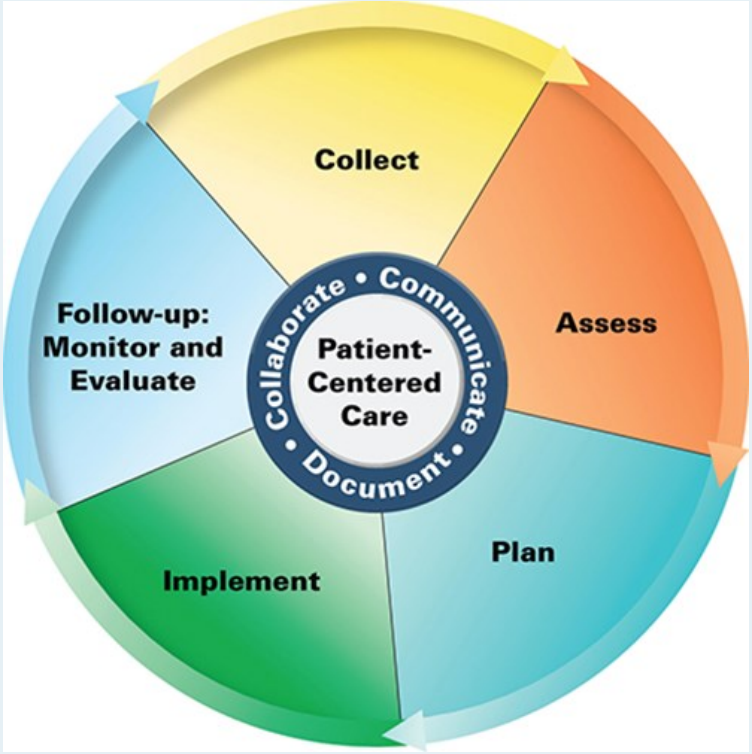
1. Development and implementation of an appropriate, individualized nutrition care plan requires definition of nutrition goals, determination of nutrition requirements and appropriate route of nutrient delivery, and design of a monitoring plan to evaluate suitability of the nutrition regimen as a patient's clinical condition changes.
2. The appropriate route of nutrition support depends on the functional condition of the patient's gastrointestinal (GI) tract, risk of aspiration, expected duration of nutrition therapy, and clinical condition.
3. Suitable candidates for parenteral nutrition (PN) therapy can be identified on the basis of their age, nutrition status, expected duration of GI dysfunction, and potential risks of PN therapy.
4. PN formulations include injectable amino acids, dextrose, water, electrolytes, vitamins, trace elements, and other additives. Some formulations may include lipid injectable emulsion (ILE).
5. PN solutions may be appropriately formulated for administration by peripheral or central venous access.
6. PN formulations are available as standardized commercial multichamber bag products or they may be compounded with an automated compounding device (ACD).
7. PN solutions may be infused continuously or intermittently.
8. Biochemical and clinical measurements for effective monitoring of patients receiving PN include serum chemistries, vital signs, body weight, total daily fluid intake and losses, and nutritional intake.
9. Non-catheter–related complications of PN therapy can be minimized by using age-appropriate nutrient dosing guidelines, frequent monitoring, and implementing rational adjustments to the PN regimen when metabolic abnormalities occur.
10. Individualized PN therapy should be based on nutrition therapy goals determined from a patient-specific nutrition assessment, type of available intravenous (IV) access, and macronutrient and micronutrient requirements.
11. A patient's nutrient requirements are affected by age, degree of metabolic demand, organ function, medication therapy, exogenous losses, acid-base status, and enteral intake in patients with recovering GI function.

PATIENT CARE PROCESS

Patient Care Process for Use of Parenteral Nutrition



Collect

- Patient characteristics (eg, age, race, sex)
- Patient history (past medical, surgical, family, social, alcohol use)
- Nutrition history (dietary history, weight history)
- Current medications (including nutritional supplements)
- Age appropriate objective data (Fig. 165-3)
  - Height/length, weight, body mass index (BMI), head circumference
  - Fluid balance (intake and output)
  - Labs (eg, serum electrolytes, SCr, BUN, glucose, albumin, AST, ALT, alkaline phosphatase)
  - Vital signs (eg, temperature, pulse rate, respiration rate, blood pressure)

Assess

- Current nutrition status and time period of insufficient nutrient intake
- Clinical condition(s) preventing adequate oral nutrient intake
- Clinical condition(s) preventing use of enteral tube feeding to determine if an indication for PN therapy exists (Tables 165-1 and 165-2)

- Vascular access
- Current degree of metabolic instability (eg, hemodynamics, organ function, fluid/electrolyte status)
- Appropriate route of PN (central or peripheral)

Plan*

- Design an age-appropriate PN regimen that provides estimated nutrient requirements and minimizes risk of adverse medication reactions or worsening current metabolic conditions (see Designing a PN Regimen; Figs. 165-1 and 165-2)
- Monitoring parameters for efficacy (Fig. 165-3)

Implement*

- Provide education regarding all elements of treatment plan to patient/caregivers and other members of the healthcare team
- Use a standardized PN order form for ordering PN prescription to minimize risk of errors
- Verify the order to ensure that it is clear, complete, and correctly transcribed
- Confirm stability of formulation and compatibility of ordered nutrients and any non-nutrient medications
- Determine if PN solution will be provided as compounded sterile preparation according to United States Pharmacopoeia Chapter 797 standards or provided as a standardized, commercially available PN product
- Determine appropriate plan for patient-specific monitoring based on the patient's clinical condition to anticipate, prevent or treat mechanical/technical, metabolic/nutritional or infectious complications (Fig. 165-3)

Follow-up: Monitor and Evaluate

- Evaluate patient for mechanical, metabolic, and infectious complications (Fig. 165-3)
- Re-evaluate clinical condition(s) preventing adequate oral intake or precluding use of enteral tube feeding to anticipate either transition off of PN support or need for continuing PN therapy (Fig. 165-3)

* ***Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

These audiovisual materials are useful to enhance student understanding regarding the COLLECT and ASSESS steps (video) as well as the PLAN, IMPLEMENT, and FOLLOW-UP: MONITOR AND EVALUATE steps (podcast) in the patient care process.

Video: Watch the video entitled "PN Appropriateness: The General Approach" at the American Society for Parenteral and Enteral Nutrition (ASPEN) Website <http://www.nutritioncare.org/smartpn/>. This 13.5-minute video provides a brief overview regarding selection of appropriate PN candidates.

Podcast: Listen to the podcast entitled "When Times are Short: Managing Drug Shortages in PN" < https://soundcloud.com/user-67457490/when-times-are-short-managing-drug-shortages-mixdown?in=user-67457490/sets/parenteral-nutrition>. This podcast is just 14 minutes in length and discusses the approach to manage product shortages in PN support.

INTRODUCTION

Maintenance of adequate nutrition status during illness has been recognized for more than 50 years as an integral part of the treatment plan for patients who are unable to attain and sustain oral nourishment. Successful techniques for providing IV nutrition support were introduced to clinical practice in adults and subsequently, infants in the late 1960s.[1] Use of central venous access was investigated to reduce risk of metabolic complications associated with IV fluid overload and electrolyte imbalances. The use of large central vessels permitted infusion of concentrated formulas, which decreased the fluid volume required and avoided the phlebitis that commonly occurred when hypertonic infusions were given peripherally.

Clinical experience and research fostered development of protocols that promoted better patient care and resulted in a decline in complications and costs associated with parenteral nutrition (PN) therapy.[2] The scope of practice for nutrition support clinicians has broadened as a result of increasing knowledge regarding the metabolic consequences associated with acute injury and chronic disease states. The pharmacist's role in providing safe and effective nutrition-support care requires knowledge of the principles of patient selection, initial therapy design, outcome monitoring, and strategies for providing therapy during PN product shortages.[3-5] In addition, the pharmacist is uniquely prepared to take on the responsibility for PN order verification as well as compounding and dispensing of the PN admixture. The PN order must be verified by a pharmacist to ensure the order is clear, complete, and correctly transcribed. A clinical review should be performed to confirm appropriate indication, nutrient dosing, and non-nutrient medication dosing. A pharmaceutical review should be performed to confirm compatibility of ordered nutrients and any non-nutrient medications in addition to the expected stability of the formulation.[4,5] Other responsibilities of the nutrition support pharmacist may include development of policy and procedures as well as quality improvement activities for patient care and operational processes associated with providing PN and enteral nutrition (EN).[4,5] The clinical role of other healthcare professionals may be similar because of the evolving interprofessional approach to nutritional support.[6-10] This chapter reviews indications for PN, components of PN formulations, routes of IV administration, practical aspects of regimen design, solution admixture, outcome monitoring, and management of complications for both adult and pediatric (neonates, infants, and children) patients.

DESIRED OUTCOMES

1 The primary objective of nutrition support therapy is to promote positive clinical outcomes of an illness and improve a patient's quality of life. Four fundamental steps are key to providing optimal care for patients who require nutrition support. They are establishing patient-specific nutrition goals, determining nutrient requirements to achieve the nutrition goals, assuring delivery of the required nutrients, and subsequently assessing the nutrition regimen.[5-7]

A patient's nutrition goals can be established after a thorough nutritional assessment (see Chapter 164). Nutrient requirements and an appropriate route for delivery of the required nutrients can then be determined. Nutrition support goals include correction of the patient's caloric and nitrogen imbalances and any fluid, electrolyte, vitamin, or trace element abnormalities. An additional goal is to lessen the metabolic response to injury by minimizing oxidant stress and favorably modulating immune response. These interventions should not cause or worsen other metabolic complications.

2 The gastrointestinal (GI) tract is the optimal route for providing nutrients unless obstruction or other GI complications are present (see Chapter 166).[11] Two other considerations that may impact selection of the optimal route for delivery of nutrition support include expected duration of nutrition therapy and risk of aspiration. Patients who have nonfunctional GI tracts or are otherwise not candidates for EN may benefit from PN.

INDICATIONS FOR PARENTERAL NUTRITION SUPPORT

The association between malnutrition and development of complications and mortality is well documented for adult and pediatric patients.[7,11-13] Although various clinical nutrition markers are improved for patients who receive PN, the impact on clinical outcomes has been difficult to demonstrate in many adult populations. The effect of PN on complications and mortality is unclear.[11] Consensus guidelines for PN use for adults and pediatric patients are based on clinical experience and investigations in specific patient populations.[11-18] Unfortunately, a lack of consistency in published guidelines from different sources complicates identification of the patient who is most likely to benefit from PN.

3 PN use should not be determined by medical diagnosis or disease state.[11] However, there are more detailed considerations for specific disease

states.[11-18] The decision to initiate PN is based on the findings of an assessment performed after a patient demonstrates an inability to meet nutritional needs enterally for an extended time period (Tables 165-1 and 165-2). This assessment must include an evaluation of the patient's nutrition status, clinical status, age, and potential risks of initiating therapy (eg, infection, metabolic abnormalities). The appropriate length of time to wait before starting PN therapy depends on patient's age and clinical status.[11-18] PN therapy is not an emergent intervention and should not be initiated until the patient is hemodynamically and metabolically stable.[11]

TABLE 165-1

Time Frame for Initiating Parenteral Nutrition

1. Adults
   a. Previously well-nourished patients: Initiate PN after 7 days of oral intake or EN less than 50% of estimated requirements
   b. Nutritionally at-risk patients (ie, involuntary loss of 10% or more of usual body weight within 6 months; involuntary loss of greater than or 5% or more of usual body weight in 1 month; involuntary loss or gain of 10 pounds within 6 months; BMI less than 18.5 kg/m^2; inadequate nutrition intake, including inadequate food or nutrition products for greater than 7 days): Initiate PN after 3 to 5 days of oral intake or EN less than 50% of estimated requirements.
   c. Moderate or severely malnourished patients: Initiate PN as soon as feasible for those in whom oral intake or EN is not possible or sufficient.
   d. Delay PN in metabolically unstable patients until improvement in clinical condition.
2. Neonates
   a. Very low birth weight infant (birth weight less than 1,500 g): Begin PN promptly.
   b. Critically ill: Initiate PN when EN is unable to meet energy requirements for energy expenditure and growth.
3. Pediatrics
   a. Infant, child, or adolescent with self-limited illness: Delay PN for up to 7 days.
   b. Infants: Initiate PN within 1 to 3 days when EN is unable to provide sufficient nutrients to support growth for an extended period.
   c. Older children and adolescents: Initiate PN within 4 to 5 days when EN is unable to provide sufficient nutrients to support growth for an extended period.

BMI, body mass index; EN, enteral nutrition; PN, parenteral nutrition.

Data from Reference 11.

TABLE 165-2

Indications for Parenteral Nutrition

1. Impaired absorption or loss of nutrients via the GI tract because of one or more of the following:
   a. Massive small bowel resection: Adult patients with less than 120 cm of small bowel distal to the ligament of Treitz without a colon or less than 60 cm of small bowel with an intact colon; neonates, infants, and pediatric patients who are unable to meet nutrient, electrolyte, and fluid requirements regardless of intestinal length
   b. High output GI fistulae: Greater than 500 mL/day; location precludes enteral access
   c. High volume fistula output with EN
   d. Neutropenic colitis: Typhlitis or opportunistic infection in an immunocompromised patient
   e. Small bowel mucosal disease: Radiation or chemotherapy-related enteritis, autoimmune enteropathy, intractable diarrhea of infancy
   f. Intestinal atresia
   g. Gastroschisis
   h. Volvulus
   i. Meconium ileus
   j. Necrotizing enterocolitis
   k. Mesenteric thrombosis

2. Mechanical bowel obstruction: Intrinsic or extrinsic blockage of intestinal lumen
    a. Stenosis or stricture
    b. Inflammatory disease
    c. Peritoneal carcinomatosis
    d. Severe adhesive disease
    e. Severe superior mesenteric artery syndrome
3. Restricted oral intake or EN necessary for bowel rest
    a. Ischemic bowel
        - Mesenteric artery stenosis
        - Abdominal compartment syndrome
        - Low flow states
    b. Severe pancreatitis
        - EN exacerbated pain
        - Worsening serum lipase levels
        - Infected pancreatic phlegmon/pseudocyst
        - Complex pancreatic fistula
        - Abdominal compartment syndrome
    c. Chylous fistula: High output with low-fat diet or elemental formula
    d. Preoperative status: Severely malnourished patient with non-functional GI tract for 7 to 10 days prior to surgery
4. Motility disorders
    a. Prolonged ileus
        - Diffuse peritonitis
        - Medical treatment-induced
        - Other disease states
    b. Pseudo-obstruction
    c. Scleroderma
    d. Visceral organ myopathy
    e. Very long segment Hirschsprung's disease
    f. Severe adhesive disease
5. Inability to achieve or maintain enteral access or EN
    a. Hemodynamic instability
    b. Active GI bleeding
    c. Severe neutropenic fever
    d. Low birth weight infant

EN, enteral nutrition; GI, gastrointestinal.

Data from Reference 11.

COMPONENTS OF PARENTERAL NUTRITION

PN formulations include IV sources of protein, dextrose, fat or lipid, water, electrolytes, vitamins, trace elements, and other additives. PN solutions should provide the optimal combination of macro- and micronutrients to provide a patient's specific nutritional requirements. Macronutrients include water, protein, dextrose, and lipid (Table 165-3). Micronutrients include vitamins, trace elements, and electrolytes. Both macronutrients and micronutrients are necessary for maintenance of normal metabolism. In general, macronutrients are used for energy (dextrose and lipid) and as structural substrates (protein and lipid). Micronutrients on the other hand support a variety of metabolic activities necessary for cellular homeostasis such as enzymatic reactions, fluid balance, and regulation of electrophysiologic processes.

TABLE 165-3

Macronutrient Components of PN Solutions

Nutritional Substrate	IV Source	Description
Fluid	Sterile water for injection USP	
Nitrogen	Crystalline amino acids	
	Standard solutions	Contain a balanced profile of essential, semi-essential, and nonessential L-amino acids
	Pediatrics	Amino acid profile includes standard essential, semi-essential, and nonessential amino acids with lower methionine, phenylalanine, and glycine concentrations; these solutions also contain taurine, glutamate, and aspartate
Energy		
Carbohydrate	Dextrose	
Fat	Lipid injectable emulsion • LCT emulsions • Fish oil emulsions • Mixed lipid emulsions	Fatty acid source • Soybean • Fish oil • Soybean-olive oil • SMOF (soybean oil, MCT, olive, and fish oils)

LCT, long-chain triglycerides; MCT, medium-chain triglycerides; PN, parenteral nutrition; SMOF, soybean oil, MCT, olive, and fish oils; USP, United States Pharmacopeia.

Over the past 5 to 10 years, there have been shortages of all PN components.[3] The unavailability of these products has resulted in delays in PN therapy initiation, restricted or limited nutrient dosing, and negative effects on all steps of the PN process that have compromised patient health and safety. Providing safe therapy during PN product shortages can be challenging for PN patients and practitioners.[3,5] Conservation recommendations and alternative therapy measures may need to be employed to optimize quality of care and avoid patient harm.[3,5] In addition, the Food and Drug Administration (FDA) may permit the temporary importation of PN products from foreign manufacturers that have been used safely and successfully in the foreign market. However, the products may have not received official FDA approval for routine use and distribution in the United States because the manufacturer has not sought FDA approval. Imported products have included PN components such as sodium glycerophosphate, multitrace element products, and amino acids.[3] If such products are imported and used in the United States, practitioners should thoroughly familiarize themselves with the prescribing information located in the product's package insert because of potential differences in product ingredients and concentration that may affect dosing. In addition, potential interactions resulting in stability or compatibility problems should be considered.

Amino Acids

Protein in PN solutions is provided in the form of crystalline amino acids (CAAs), which when oxidized for energy yield 4 cal or approximately 17 J/g of protein. However, including the caloric contribution from protein when calculating calories provided by the PN regimen is controversial.[19] While sufficient energy substrate should be provided to allow utilization of amino acids for protein synthesis rather than an energy source, oxidation of amino acids for energy has been demonstrated in critically ill patients and is thought to occur because of metabolic derangements seen during severe metabolic stress. Hence, some practice settings may differ in expressing calories provided by a PN regimen as total calories (protein, carbohydrate, and lipid calories) or non-protein calories (carbohydrate and lipid calories).

Commercially available CAA solutions may be categorized as standard amino acid solutions or modified amino acid solutions. Standard CAA solutions are designed for patients with "normal" organ function and nutritional requirements (see Table 165-3). Although standard CAA solutions differ in the proportion of specific amino acids, they contain a balanced profile of essential, semi-essential, and nonessential L-amino acids. Despite these differences, there are similar effects on markers of protein metabolism.[20] The protein concentration, total nitrogen, and electrolyte content may also differ among products. Because the nitrogen concentration of dietary protein is approximately 16%, 6.25 (100 g protein/16 g nitrogen) is commonly accepted as the conversion figure for calculating the nitrogen amount provided by CAA protein. Differences in nitrogen content per gram of amino acids among CAA products may affect calculation of nitrogen amounts infused when determining nitrogen balance.[20,21] The clinical significance of these differences in determining nitrogen balance for routine clinical use is unknown.[21]

Standard CAA solutions may also include obligatory electrolyte concentrations that may affect PN compounding as well as the total clinical dose provided to the patient.[22] CAAs are available in several different concentrations, which facilitate compounding of patient-specific PN regimens. Use of highly concentrated products (15%-20% amino acids) is attractive for critically ill patients who typically require fluid restriction but have large protein needs. Modified amino acid solutions are designed for patients who have altered protein requirements, such as neonates and pediatric patients (see Table 165-3). For example, several commercially available CAA solutions are designed to provide conditionally essential amino acids, which are considered nonessential during health because they are produced from other amino acids. However, under certain physiologic conditions, such as prematurity or sepsis, these amino acids cannot be synthesized in sufficient quantities.[20,22] CAA solutions specifically designed for neonates and pediatric patients contain increased amounts of taurine, aspartic acid, and glutamic acid. Other conditionally essential amino acids, such as cysteine, carnitine, and glutamine, are not available in commercial CAA solutions in pharmacologic amounts because they are relatively unstable or poorly soluble.[20,22]

Consequently, PN solutions may need to be modified to provide the desired amount of supplemental conditionally essential amino acids. For example, cysteine is a conditionally essential amino acid for preterm and term infants because of their enzymatic immaturity of the trans-sulfuration pathway. Cysteine may be added to PN solutions at the time of compounding as a supplement to CAA solutions and to enhance calcium and phosphate solubility by decreasing solution pH.[22] Carnitine is a quaternary amine required for long-chain fatty acid transport into the mitochondria for β-oxidation and energy production. Newborns are at risk for carnitine deficiency because of their immature biosynthetic capacity. Decreased plasma carnitine concentrations occur in infants and children receiving PN without carnitine.[16] Supplemental carnitine may be added to the PN solution at the time of compounding. Although the benefit of carnitine supplementation in PN has not been clearly identified, positive effects on nutritional markers, including improved fatty acid oxidation, weight gain, and nitrogen balance, have been documented. In general, carnitine supplementation is reserved for neonates expected to receive PN support for 7 days or longer.[16]

Glutamine is the most abundant free amino acid in the body and is an important intermediate for many metabolic processes. Glutamine has an important role in maintaining intestinal integrity, immune function, and protein synthesis during conditions of metabolic stress.[23] Positive effects on nutritional markers (eg, improved nitrogen balance) as well as outcome markers (eg, decreased length of hospitalization, incidence of infections, GI toxicities associated with chemotherapy or radiation) are associated with glutamine.[23] Unfortunately, the best candidate for response to glutamine therapy has not been clearly identified.[23,24] Use of both IV and enteral glutamine in combination with a variety of antioxidant supplements in critically ill adult patients has been associated with increased mortality.[24] Despite an association between increased brain volume and head circumference in school-aged children, who were premature at birth and received glutamine during the first year of life, the clinical usefulness of glutamine in neonates and infants is unclear.[23,25,26] Plasma glutamine concentrations increase with supplementation, but there is no beneficial effect on sepsis incidence or outcome, enteral feeding tolerance, necrotizing enterocolitis, growth, or mortality.[23,26,27] The clinical use of glutamine is further complicated because there is no parenteral glutamine formulation commercially available in the United States. Available CAA solutions do not contain glutamine because of

poor solubility and instability.[22] Use of parenteral glutamine requires special manufacturing techniques not readily available in many institutional pharmacies.[23] However, parenteral glutamine has been made available from several licensed pharmacies that extemporaneously compound glutamine crystalline powder under sterile conditions either as a separate parenteral solution or as a part of a CAA solution.

Dextrose

The primary energy source in PN solutions is carbohydrate, usually in the form of dextrose monohydrate, hereafter referred to as dextrose which is available in concentrations ranging from 5% to 70%. When oxidized, each gram of dextrose provides 3.4 kcal (14.2 kJ). The appropriate IV dextrose dose depends on the patient's age, estimated caloric requirements, and clinical condition. For example, minimum dextrose requirements for neonates are estimated to be approximately 6 to 8 mg/kg/min and infusion rates should not exceed 14 to 18 mg/kg/min for infants or 4 to 7 mg/kg/min for adults.[16,28,29] The recommended dextrose dose for routine clinical care rarely exceeds 5 mg/kg/min for adolescents and adults.[16,28,29] Maintaining an age-appropriate dextrose infusion rate is necessary to minimize risk of adverse medication reactions. If the dextrose infusion rate exceeds the glucose oxidation rate, metabolically expensive pathways, such as glycogen repletion and lipid synthesis, are favored, resulting in increased energy expenditure, increased oxygen consumption, and increased carbon dioxide production. Excessive dextrose infusion rates also may contribute to the development of hyperglycemia and an increase in the concentration of biochemical markers indicative of fatty infiltration of the liver.[29,30]

Lipid Injectable Emulsion

Lipid injectable emulsion (ILE) is used as a concentrated source of calories and essential fatty acids.[31-35] Commercially available ILE products have traditionally contained soybean oil (SO) or a combination of SO and safflower oil. However, SO-based ILE may have negative effects on immune function and hepatic function, and this has led to approval of alternative mixed oil ILE for clinical use.[35,36] These products contain combinations of SO and olive oil, as well as SO, olive oil, medium chain triglyceride oil (MCT), and fish oil (FO), collectively known as SMOF.[32,33] An additional ILE alternative containing 100% FO is also approved for clinical use (Table 165-3).[34]

As a caloric source, ILE use may facilitate provision of adequate calories and minimize complications of nutrition therapy such as hyperglycemia, hepatotoxicity, or increased carbon dioxide production.[35] In the past, SO-based ILE has been used for treatment or prevention of essential fatty acid deficiency (EFAD) in both adult and pediatric patients because of the higher linoleic and linolenic FA composition.[35,36] EFAD is the result of a biochemical deficiency of linoleic acid and arachidonic acid, which are considered essential for humans.[28,35,36] Linoleic acid, an omega-3 FA, and linolenic acid, an omega-6 FA, are important for a variety of functions such as cellular integrity, platelet function, postnatal brain development, and wound healing.[36] Both are polyunsaturated long chain triglycerides (LCT). Normally, linoleic acid is converted to the tetraene arachidonic acid. When linoleic acid is not present in sufficient amounts, oleic acid is converted to the tetraene 5,8,11-eicosatrienoic acid, an FA of lesser physiologic integrity, and as a result, EFAD develops. EFAD may be prevented by providing 2% to 4% of total calories as linoleic acid and 0.25% to 0.5% of total calories as linolenic acid. This may be achieved for most adult patients by giving approximately 100 g SO ILE weekly and approximately 200 g mixed oil ILE weekly (based on approximately 2,000 calories/day [~8,400 J/day]).[35,36] Neonates and infants require a minimum of 0.5 to 1 g/kg SO ILE daily.[16] The SO-olive oil product is not approved for use in pediatric patients because of the lower linoleic and linolenic acid content and inadequate provision of essential fatty acids to prevent or treat EFAD when used in recommended doses.[32] In general, the 100% FO product is not indicated for treating EFAD because of the relatively lower essential FA content.[34,35] This product is indicated for use in pediatric patients with PN associated cholestasis.[34] However, EFAD may be prevented in PN-dependent infants who received FO ILE as the sole source of fat calories for at least 1 month.[37]

ILEs with SO as the lipid source may have negative effects on immune function as the result of omega-6 PUFA influence on proinflammatory eicosanoid production through arachidonic acid metabolic pathways.[35,36] Mixed oil ILE may promote lower production of proinflammatory cytokines by providing lower amounts of omega-6 FA. Olive oil–based ILEs provide essential fatty acids, are a rich source of vitamin E, and have a neutral effect on immune function because of the decreased amount of omega-6 PUFA linoleic acid.[35] MCTs may offer several advantages, especially for critically ill patients. MCTs are hydrolyzed and cleared more rapidly than LCTs, and they do not accumulate in the liver. In addition, MCTs do not require carnitine for entrance into mitochondria for oxidation. However, MCTs are not a source of essential fatty acids. IV MCT-LCT mixtures demonstrate safety and efficacy comparable with standard LCT emulsions.[35,36] FO–based ILE contain predominantly omega-3 PUFAs, which are metabolized to cytokine mediators that may be less inflammatory and immunosuppressive than those derived from omega-6 PUFAs. The clinical effect of FO-containing ILE administration on

immune function, as well as on patient morbidity and mortality, is not clear.[35,36,38]

Phytosterols are sterols that are a natural component of plant-based oils used in ILE formulations.[39] SO-based ILE and phytosterol intake are associated with cholestasis of PN-associated liver disease (PNALD). SO-based ILE have a higher phytosterol content relative to the other mixed oil ILE products.[39] Use of mixed oil or 100% FO ILE in PN-dependent patients who developed cholestasis while receiving SO-based ILE may improve in or reverse of PNALD.[39]

Commercially available products are reviewed in Table 165-3. All commercially available ILE formulations contain egg phospholipids as an emulsifying agent and glycerol to make the emulsion isotonic.[22] Although the caloric contribution of fat is 9 kcal/g (38 kJ/g), the caloric content of 10% ILE is 1.1 kcal/mL (4.6 kJ/mL), 2 kcal/mL (8.4 kJ/mL) for 20% ILE, and 3 kcal/mL (12.6 kJ/mL) for 30% ILE because of the caloric contribution of the egg phospholipid and glycerol.

Commercially available ILE products may be administered by either the central or the peripheral route. They may be added directly to the PN solution as a total nutrient admixture (TNA), also referred to as a three-in-one system (lipids, protein, glucose, and additives), or they may be co-infused with the CAA-dextrose solution, commonly referred to as a two-in-one admixture.[5,31-34,40] However, 30% ILEs are only approved for use in the preparation of TNA and are not intended for direct IV administration.

Plasma ILE clearance is directly related to gestational age of infants and is influenced by the infusion rate and the patient's clinical status.[16] Rapid SO-ILE infusions contribute to decreased oxygenation for neonates.[41] Adverse pulmonary effects are thought to be caused by polyunsaturated fatty acid (PUFA)–driven prostaglandin production, which results in altered vascular tone. Although the association between ILE and pulmonary dysfunction is not clear, a boxed warning appears in the FDA product labeling for both SO and SO-olive oil ILE that acknowledges deaths in preterm infants associated with pulmonary fat accumulation thought to be related to ILE infusions.[31,32] In addition, rapid infusion of long-chain fatty acid formulations may have a negative impact on immunocompetence by saturating the reticuloendothelial system.[28,35,42]

Although the frequency of acute adverse medication reactions is less than 1% with current formulations, patients receiving their first ILE dose should be monitored for dyspnea, chest tightness, palpitations, and chills. Headache, nausea, and fever may also occur, especially with a rapid infusion rate. In general, ILE use is contraindicated for patients with an impaired ability to clear fat emulsion, such as patients with pathologic hyperlipidemia, lipoid nephrosis, and hypertriglyceridemia associated with pancreatitis.[31-35] Patients should be evaluated for hypersensitivity to any of the product-dependent ingredients such as fish, egg, soybean, or peanut protein prior to initiating ILE.[31-34,43]

ILE products remain the most common source of parenteral fat, but a number of medications have been introduced that contain lipid either as a vehicle for delivery or as a portion of the medication formulation. Propofol, an IV anesthetic, is delivered in a soybean-oil-in-water emulsion that has essentially the same composition and caloric concentration as 10% SO-ILE. This agent is used commonly for continuous sedation of mechanically ventilated patients and should be considered a potential source of calories that may require adjustment of a patient's nutrition regimen.[35,44] Clevidipine is an injectable calcium channel blocker that contains 20% ILE as a vehicle that may also be a potential source of IV fat when used as a continuous infusion for multiple days of therapy.[45] The antifungal amphotericin B is available in several lipid-containing combinations such as liposomal and lipid complex formulations. The caloric contribution from amphotericin B is generally small and not clinically relevant when used in standard doses.

Vitamins

The Nutrition Advisory Group of the American Medical Association (NAG-AMA) recommended in 1975 the daily parenteral supplementation of 13 essential (four fat-soluble and nine water-soluble) vitamins for pediatric and adult patients based on requirements for healthy people.[46]

Since these original recommendations, the NAG-AMA has revised the guidelines for children to primarily reflect changes for preterm infants requiring PN.[46] The FDA also mandated in 2000 changes in adult parenteral vitamin formulations (inclusion of vitamin K and higher doses of vitamins B_1, B_6, and C).[46] Vitamin K was not included in early multivitamin formulations due to the potential for drug-nutrient interactions in patients receiving anticoagulants. Although the NAG-AMA recommendation for vitamin K for adults is 2 to 4 mg weekly, only 150 µg/day was mandated to be included in newer formulations by the FDA.[47] However, in adult patients receiving long-term SO-ILE-containing PN with vitamin K–free parenteral multivitamins at

home, supplemental vitamin K may not be necessary to maintain normal prothrombin times and plasma vitamin K concentrations.[48] Indeed, SO used in ILEs is a natural source of phylloquinone (vitamin K1). However, the other commercially available mixed-oil ILE formulations contain phylloquinone as well.[49] SO-ILE formulations contain the highest amount of vitamin K and the concentration is generally dependent on the SO concentration in the ILE.[35,47-49] Although current vitamin K-containing multiple-vitamin products should provide sufficient amounts to prevent adverse effects associated with vitamin K deficiency, supplemental vitamin K may be given intramuscularly or subcutaneously or added to the PN solution if needed.[47]

The 2012 ASPEN recommendations advocate for the continued availability of multivitamin products with and without vitamin K so that clinicians have the ability to withhold vitamin K supplementation in patients receiving warfarin therapy. Most adult parenteral multiple-vitamin products which are available commercially contain vitamin K. MVI-12, multivitamin infusion without vitamin K is available from Hospira, Inc. Lake Forest, IL. Two parenteral multiple-vitamin products are commercially available for use for pediatric patients. MVI-Pediatric (Hospira Inc.) and Infuvite Pediatric (Baxter Healthcare Corporation) are formulated to meet the revised NAG-AMA guidelines for infants weighing less than 1 kg (2.2 lb) and children up to 11 years. However, there are no commercially available injectable multivitamin products designed to specifically meet the unique requirements of premature infants, including higher vitamin A and lower doses of vitamins B_1, B_2, B_6, and B_{12}.

Vitamin requirements may be altered in malnutrition and other specific disease states or with certain medication therapies. Individual and combination products are available to provide additional or tailored supplementation, which may be necessary to prevent development of vitamin toxicities or deficiencies caused by altered metabolism or medication therapy.

The 2012 ASPEN recommendations question whether the vitamin D content of parenteral multivitamins is adequate to meet current Recommended Dietary Allowances (RDA) and advocate for the addition of a parenteral vitamin D product for PN-dependent patients who are unresponsive to additional enteral vitamin D supplementation.[46] In addition, the recommendations support the continued production of adult-injectable multivitamin products with and without vitamin K and for the supplementation of carnitine (2-5 mg/kg/day) in neonatal PN and choline in all patients receiving PN.[46]

Trace Elements

Many trace elements are an important part of metalloenzymes and function as cofactors in a variety of regulatory metabolic pathways.[50] Although 17 trace elements have demonstrated biologic importance, clear deficiency syndromes in humans have been described only for cobalt (as vitamin B_{12}), copper, iodine, iron, and zinc.[50-52] In 1979, the NAG-AMA recommended chromium, copper, manganese, and zinc supplementation for patients receiving PN.[46,50] Recommendations followed in 1984 to also supplement with selenium.[46,50] Although there is not a clear deficiency syndrome for manganese, the NAG-AMA considered manganese essential based on case reports of patients receiving PN with metabolic complications that corrected after manganese supplementation. Reports of deficiency syndromes associated with selenium and molybdenum suggest that they may also be essential.[46,50,51] Although iodine deficiency does not occur for patients receiving short-term PN, it has been observed in patients receiving long-term PN and may be related to the use of chlorhexidine for central-line care instead of povidone-iodine.[46,50,52]

Injectable trace elements are available as single-trace element solutions and as multiple-trace element combinations.[22] The use of single-entity injectable products allows for individualization of trace mineral supplementation of chromium, copper, iodine, manganese, selenium, and zinc. Requirements for trace elements vary on the basis of the patient's clinical condition. For example, higher doses of supplemental zinc are likely necessary for patients with high-output ostomies or diarrhea because the GI tract is the predominant excretion route for zinc. Whereas manganese and copper are excreted through the biliary tract, chromium, molybdenum, and selenium are excreted renally. Hence, these trace elements should be restricted or withheld from PN solutions for patients with cholestatic liver disease and kidney disease, respectively. ASPEN recommended formulation changes to the available injectable multiple-trace element preparations for PN patients.[46] In general, the recommendations support overall decreased trace element contamination in large- and small-volume PN products.[46] The recommendations advocate for decreased copper and manganese, no (or decreased) chromium, and inclusion and increased dose of selenium in all injectable adult multiple-trace products.[46] The recommendations also support products with no chromium, decreased manganese, and the inclusion of selenium in all injectable pediatric multiple-trace products.[46] These recommendations were recognized by injectable trace element manufacturers and reformulated products for adults and pediatric patients are now available.[22] The trace element combination product for adults provides the daily requirements for the trace elements considered essential by the NAG-AMA except chromium (ie, copper, manganese, selenium, zinc).[53] Chromium amounts provided as a contaminate in PN injectable products are

considered adequate to meet daily requirements.[46] The combination product approved for use in the United States for neonates and pediatric patients contains zinc, copper, manganese, and selenium.[54] The addition of single-entity zinc, copper, and selenium is required in many pediatric weight ranges to meet recommended needs when using these combination products.

Electrolytes

Electrolytes such as sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate are necessary PN components for the maintenance of many cellular functions. Electrolytes may be given to maintain normal serum concentrations or to correct deficits. Patients who have "normal" organ function and relatively normal serum concentrations of any electrolyte should receive "normal" maintenance electrolyte doses when PN is initiated and daily thereafter. Specific electrolyte requirements vary according to the patient's age, disease state, organ function, previous and current medication therapy, nutrition status, and extrarenal losses. Electrolytes are available commercially as single- and multiple-nutrient solutions.[22] Multiple-electrolyte solutions are useful for stable patients with normal organ function who are receiving PN. Concentrated multiple-electrolyte solutions designed for addition to PN solutions generally contain only sodium, potassium, calcium, and magnesium. Phosphorus must be added as a separate additive. Further information regarding metabolism and requirements of vitamins, trace elements, and electrolytes is given elsewhere.[55]

DESIGNING A PARENTERAL NUTRITION REGIMEN

5 Several factors, including the patient's venous access, fluid status, and macronutrient and micronutrient requirements, are important considerations when designing the PN regimen. A patient's venous access and fluid status determines the maximum PN osmolar concentration, which will impact the nutrient amount that may be provided. PN solutions may be administered by central or peripheral venous access. The patient's clinical condition determines which route is most appropriate.

PN formulations may be provided as a two-in-one admixture that contains dextrose, CAA, and other necessary micronutrients or as a three-in-one admixture or TNA that contains dextrose, CAA, and ILE, as well as other necessary micronutrients. Use of TNA solutions offers several potential advantages, including reduced inventory (infusion pumps, tubing, and other related supplies), decreased time for compounding and administration, a potential decrease in manipulations of the infusion line (which should correspond with a decreased risk of catheter contamination), and ease of delivery and storage for patients receiving home PN.[40] Potential disadvantages include increased risk of infections and stability and compatibility concerns. For example, the stability of TNA admixtures is less predictable than that of two-in-one admixtures, which makes their use less desirable in some patient populations such as neonates and infants.[41,56]

Routes of Parenteral Nutrition Administration

Peripheral Route

Peripheral parenteral nutrition (PPN) is an option for mild-to-moderately stressed patients in whom adequate GI tract function is expected to return within 10 to 14 days.[11] PPN may also be used as a temporary source of PN, or as a bridge therapy during transition periods where oral intake or EN is suboptimal or clinical circumstances do not justify placing a central venous catheter (CVC) access.[11] In general, potential PPN candidates should not be fluid-restricted or require large nutrient amounts. Lower concentrations of amino acids (3%-5% final concentration), dextrose (5%-10% final concentration), and micronutrients compared with central parenteral nutrition (CPN) must be used for peripheral administration. Because PPN solutions are relatively dilute, larger volumes are usually necessary to provide nutrient requirements. Additionally, many patients who receive PPN likely will require ILE to achieve the desired caloric intake at levels consistent with CPN regimens. The primary advantages of PPN include a potentially lower risk of infectious and technical complications associated with CVC access.[11] Patients who are likely to be poor candidates for PPN include those with poor venous access as the result of multiple courses of chemotherapy, malnutrition, illness of long duration that has required multiple venous accesses for fluid and medication administration, premature infants, and the elderly. PPN use is also limited by relatively poor peripheral vein tolerance to hypertonic solutions. Thrombophlebitis is a common complication for patients receiving PPN.[56] Although the risk of phlebitis is greater with solution osmolarities greater than 600 to 900 mOsm/L, peripherally administered TNA with much higher osmolarities to adults has been associated with low infusion-site complications in some centers.[56,57] Efforts to minimize development of phlebitis or infiltration sequelae for patients receiving PPN include addition of ILE as a possible venous lumen protectant, subtherapeutic heparin doses (0.5-1 unit/mL) to prevent thrombus

formation, or small doses of hydrocortisone (5 mg/L) to minimize access site inflammation.[56,57] However, the co-infusion of ILE with PPN (ie, not provided as a TNA) does not reduce phlebitis. In addition, heparin does not reduce catheter-related thrombosis and is not compatible for use in TNAs.[56] Midline catheter use may offer some advantage and has been associated with a reduced risk of thrombophlebitis.[11,58] Although these catheters are not central venous access devices, they are longer and infuse into larger venous vessels that may dilute the PPN solution to a more tolerable osmolarity. The osmolarity of a PN solution may be estimated by using the guidelines for osmolarities of selected PN components listed in Table 165-4.

TABLE 165-4

Osmolarities of Selected Parenteral Nutrients

Nutrient	Osmolarity
Amino acid	100 mOsm/%
Dextrose	50 mOsm/%
Lipid 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

Central Route

CPN is the preferred route for PN delivery and is used predominantly for patients who require PN for periods of more than 7 to 14 days during hospitalization or indefinitely at home.[11,59,60] These patients may have large nutrient requirements; poor peripheral venous access; or fluctuating fluid requirements, such as metabolically stressed patients with extensive surgery, trauma, sepsis, multiple-organ failure, or malignancy. CPN solutions are highly concentrated hypertonic solutions that must be administered through a large central vein. Unlike peripheral veins, central veins have a higher blood flow, which quickly dilutes the hypertonic solutions. Disadvantages of CPN include risks associated with catheter insertion, routine catheter use, and care of the access site. Relative to peripheral venous access, CVC access is associated with a greater potential for infection. In addition, the risk of more serious catheter-induced trauma and related sequelae and other serious technical or mechanical problems is greater than that with peripheral access.

The choice of central venous access site depends on a number of factors, including the patient's age and anatomy. CVCs vary in composition, lumen size, number of injection ports, and other features that affect ease or convenience of care and maintenance. CVCs for short-term use for adults are commonly inserted percutaneously into the subclavian vein and advanced so that the tip is at the superior vena cava.[58] If this approach is not possible, the internal jugular vein can be used. Frequently, short-term central venous access is obtained for critically ill neonates via a catheter placed in the umbilical vein. Other sites for central venous access in infants and older children are similar to those in adults. When therapy is expected to last longer than 4 weeks, the catheter is tunneled subcutaneously before entering the central vessel, secured initially with retaining sutures, and anchored in place with a felt cuff that promotes subcutaneous fibrotic tissue growth around the catheter. The injection port may remain external or may be

concealed entirely beneath the skin. Implanted CVCs have a larger port or reservoir that is surgically placed beneath the skin surface and anchored in the chest wall muscle. Peripherally inserted central catheters (PICCs) are venous access devices that are inserted into a peripheral vein (basilic, cephalic, or brachial) and advanced so that the tip is at the superior vena cava.[58] PICCs are increasingly used for both short- and long-term central venous access in acute or home care settings because of ease and economy of bedside placement.[11,58,60]

Constructing a Parenteral Nutrition Regimen

After the route of delivery is chosen, the components of the PN regimen are determined based on the patient's nutritional assessment. Although not recommended due to increased potential for errors, some healthcare systems may require the entire PN order to be written in individual components and additives on traditional paper order forms without the use of a standard order form. Standardized electronic PN orders suitable for computerized prescriber order entry (CPOE) are recommended for all patients to minimize risk of errors associated with the ordering process.[5,61] Standardized order forms or clinical decision support within electronic PN ordering systems promote education of practitioners by providing brief guidelines for initiating PN and foster cost-efficient nutrition support by minimizing errors in ordering, compounding, and administration.[5,56,61] Standardized order forms also may include options for ordering certain related procedures, laboratory tests, protocols for patient management, or consultations with other medical services related to the patient's nutrition support.

Adult Parenteral Nutrition Solutions

6 In general, there are two methods for ordering adult PN. The "standard formula approach" offers a variety of admixtures with a fixed nonprotein-calorie-to-nitrogen ratio. This method usually includes different formulas for mild-to-moderately stressed patients, and those who have kidney or liver failure or are fluid-restricted. Because the nonprotein-calorie-to-nitrogen ratio is fixed, the daily amount of nutrient delivered depends solely on the volume infused. Standard institutional PN formulations may be compounded; however, standardized commercial PN products or multichamber bag PN solutions are available from several manufacturers.[62] A standard institutional formula may promote clinician prescribing of a complete, balanced formulation and promote consistent provision of stable and compatible admixtures. However, efficiencies associated with use of the standard formula approach may be hindered if there is a frequent need to modify the PN formulation. Finally, standard PN formulations may be difficult to use in complicated patients, such as neonatal or pediatric patients, and those with severe malnutrition, organ failure, glucose intolerance, large GI losses, or critical illness.[62]

The "individualized formula approach" permits compounding of patient-specific admixtures. Compounding of the PN admixture is limited only by the concentrations of stock solutions and stability of the additives. The nutrient amount delivered depends on the daily volume of the PN solution infused and the nutrient amounts in the PN solution. The total daily amount of PN solution may be prepared in multiple bags or more cost-effectively in a single container.[40]

Historically, adult PN formulations were ordered by expressing the final concentrations of each component in the solution. However, this inconsistency may promote confusion and misinterpretation of PN admixture contents that may result in harm, especially when patients are transferred between health system environments. To ensure that PN labels in all health system environments clearly and accurately reflect the PN admixture contents, guidelines for standardized adult PN labeling have been recommended.[5,61] In addition to including a variety of other information on the label such as dosing weight and administration route, the guidelines recommend expressing PN ingredients in amounts per daily volume, which minimizes the need for pharmaceutical calculations to determine the nutrient value of the admixture. For example, macronutrients ordered in grams per day and electrolytes in milliequivalents or millimoles per day in an adult patient. Commercially available computer software for calculating PN formulations include the recommended ASPEN labeling guidelines (Baxter Healthcare, Deerfield, Il.; B. Braun Medical Inc., Bethlehem, PA).[5,61] Pharmaceutical calculations of an adult TNA PN regimen are briefly reviewed in Fig. 165-1.

FIGURE 165-1

Calculation of an adult PN regimen. To convert to energy units of kilojoules (kJ) multiply values with kilocalories as the numerator (kcal, kcal/mL, kcal/kg, kcal/g) by 4.18 to give the corresponding value in kilojoules (kJ, kJ/mL, kJ/kg, kJ/g). (CAA, crystalline amino acids; ILE, lipid injectable emulsion; PN, parenteral nutrition; TNA, total nutrient admixture.)

Calculation of an Adult PN Regimen

Patient case: A patient's daily nutritional requirements have been estimated to be 105 g protein and 2,200 total kcal. The patient has central venous access and reports no history of diabetes, hyperlipidemia, or egg allergy. The patient is not fluid-restricted. The PN formulation will be compounded as an individualized regimen using a single-bag, 24-hour infusion of a TNA. Determine the total PN volume and administration rate by calculating the macronutrient solution volumes required to provide the desired daily nutrients. The PN products used for this regimen are 10% CAA, 70% dextrose, and 30% ILE.

1. Determine the daily ILE calories and volume.
   - 2,200 kcal/day × 30%-40% of total calories as fat = 660-880 kcal/day
   - Choose 660 kcal to minimize ILE calories; calculate 30% ILE volume

     660 kcal ÷ 3 cal/mL 30% ILE = X mL X = 220 mL 30% ILE

   - Calculate ILE gram amount
     30 g/100 mL = X g/220 mL 30% ILE X = 66 g ILE
2. Determine the appropriate volume of 70% dextrose to deliver the desired dextrose calories
   - Dextrose calories = Total kcal – ILE kcal – Protein kcal
     = 2,200 kcal – 660 kcal ILE – (4 kcal × 105 g CAA) = 1,120 kcal
   - Calculate required dextrose (grams):

     1,120 kcal ÷ 3.4 kcal/g dextrose = 329 g dextrose

   - Determine 70% dextrose volume
     70 g/100 mL = 329 g/X mL 70% dextrose; X = 470 mL 70% dextrose
3. Determine the appropriate volume of 10% CAA
   10 g/100 mL = 105 g/X mL 10% CAA X = 1,050 mL 10% CAA
4. Determine the TNA PN volume and administration rate
   - Calculate CAA/dextrose/ILE volume:
     470 mL 70% dextrose + 1,050 mL 10% CAA + 220 mL 30% ILE = 1,740 mL
   - Add 100-200 mL for additives:
     Total TNA volume = approximately 1,840-1,940 mL/day
   - Calculate the administration rate:
     1,840 to 1,940 mL/day ÷ 24 h = 77 to 81 mL/h; round up to 80 to 85 mL/h
5. Choose final TNA regimen and determine final concentrations of CAA, dextrose, and ILE
   - Final TNA regimen
     105 g CAA/329 g dextrose/66 g ILE in 1,920 mL/d to infuse at 80 mL/h
   - Calculate final concentrations of CAA, dextrose, and ILE
     - 105 g CAA/1,920 mL = X g/100 mL X = 5.5% CAA
     - 329 g dextrose/1,920 mL = X g/100 mL X = 17.1% dextrose
     - 66 g ILE/1,920 mL = X g/100 mL X = 3.4% ILE

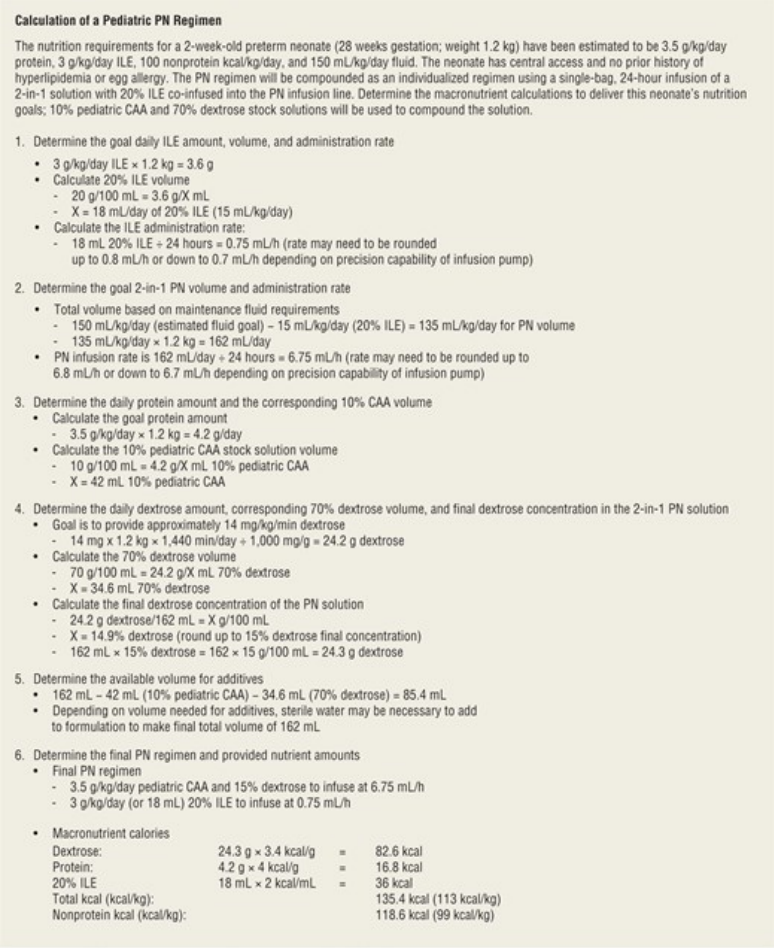
Several guidelines are available to help simplify calculation of a PN regimen after a patient's nutritional requirements have been decided. For example, adult patients receiving only PN therapy may need larger volumes of fluid to provide maintenance requirements and replace extrarenal losses. However, patients requiring other IV medication therapy may receive adequate fluid from an additional IV maintenance solution (eg, 0.45% NaCl in 5% dextrose) or co-infused medications (or both). Depending on individual institutional practices, maximally concentrating the PN admixture and using an inexpensive maintenance fluid to manage hydration may provide a cost-effective regimen that requires fewer adjustments. Another guideline that may be helpful in designing a PN regimen is to allow a volume of approximately 100 to 150 mL/L of base solution (~200-300 mL/day) for electrolytes and other additives. PN regimens for patients who require small amounts of additives, such as patients with kidney failure, may need further concentration.

Pediatric Parenteral Nutrition Solutions

Pediatric PN admixtures are typically ordered using an individualized approach because current safe clinical practice guidelines recommend nutrient intakes based on the patient's weight.[5] To simplify pediatric PN ordering, many institutions use a pediatric-specific PN order form that expresses daily nutrient amount based on weight. For example, protein and fat are ordered as grams per kilogram per day, dextrose as milligrams per kilogram per minute, and electrolytes as milliequivalents per kilogram per day. However, some institutions may order macronutrients by expressing the final concentration of each component in the solution. Current safe practice guidelines recommend ordering all PN ingredients based on weight as "amount per kilogram per day."[5] The PN bag label should accurately reflect the weight-based order as well. Calculations for determining a pediatric PN admixture are reviewed to illustrate fundamental concepts for ordering pediatric PN formulations (Fig. 165-2). Additional features of the pediatric PN label include the dosing weight, administration date and time, expiration date, infusion rate, and duration of infusion. Because infants and children generally receive daily maintenance fluid from the PN regimen, supplemental IV solutions are rarely needed. Pediatric PN may be provided as a two-in-one admixture or TNA. However, the TNA system is not recommended for compounding neonatal and infant PN because of ILE instability with the often needed higher calcium and phosphorus concentrations.[41,56] The ILE labeling guidelines for pediatric PN are similar to adult ILE labeling recommendations.

FIGURE 165-2

Calculation of a pediatric PN regimen. To convert to energy units of kilojoules, multiply values with kilocalories as the numerator (kcal, kcal/mL, kcal/kg, kcal/g) by 4.18 to give the corresponding value in kilojoules (kJ, kJ/mL, kJ/kg, kJ/g). (CAA, crystalline amino acids; ILE, lipid injectable emulsion.)



Calculation of a Pediatric PN Regimen

The nutrition requirements for a 2-week-old preterm neonate (28 weeks gestation; weight 1.2 kg) have been estimated to be 3.5 g/kg/day protein, 3 g/kg/day ILE, 100 nonprotein kcal/kg/day, and 150 mL/kg/day fluid. The neonate has central access and no prior history of hyperlipidemia or egg allergy. The PN regimen will be compounded as an individualized regimen using a single-bag, 24-hour infusion of a 2-in-1 solution with 20% ILE co-infused into the PN infusion line. Determine the macronutrient calculations to deliver this neonate's nutrition goals; 10% pediatric CAA and 70% dextrose stock solutions will be used to compound the solution.

1. Determine the goal daily ILE amount, volume, and administration rate
   - 3 g/kg/day ILE × 1.2 kg = 3.6 g
   - Calculate 20% ILE volume
     - 20 g/100 mL = 3.6 g/X mL
     - X = 18 mL/day of 20% ILE (15 mL/kg/day)
   - Calculate the ILE administration rate:
     - 18 mL 20% ILE ÷ 24 hours = 0.75 mL/h (rate may need to be rounded up to 0.8 mL/h or down to 0.7 mL/h depending on precision capability of infusion pump)
2. Determine the goal 2-in-1 PN volume and administration rate
   - Total volume based on maintenance fluid requirements
     - 150 mL/kg/day (estimated fluid goal) – 15 mL/kg/day (20% ILE) = 135 mL/kg/day for PN volume
     - 135 mL/kg/day × 1.2 kg = 162 mL/day
   - PN infusion rate is 162 mL/day ÷ 24 hours = 6.75 mL/h (rate may need to be rounded up to 6.8 mL/h or down to 6.7 mL/h depending on precision capability of infusion pump)
3. Determine the daily protein amount and the corresponding 10% CAA volume
   - Calculate the goal protein amount
     - 3.5 g/kg/day × 1.2 kg = 4.2 g/day
   - Calculate the 10% pediatric CAA stock solution volume
     - 10 g/100 mL = 4.2 g/X mL 10% pediatric CAA
     - X = 42 mL 10% pediatric CAA
4. Determine the daily dextrose amount, corresponding 70% dextrose volume, and final dextrose concentration in the 2-in-1 PN solution
   - Goal is to provide approximately 14 mg/kg/min dextrose
     - 14 mg x 1.2 kg × 1,440 min/day ÷ 1,000 mg/g = 24.2 g dextrose
   - Calculate the 70% dextrose volume
     - 70 g/100 mL = 24.2 g/X mL 70% dextrose
     - X = 34.6 mL 70% dextrose
   - Calculate the final dextrose concentration of the PN solution
     - 24.2 g dextrose/162 mL = X g/100 mL
     - X = 14.9% dextrose (round up to 15% dextrose final concentration)
     - 162 mL × 15% dextrose = 162 × 15 g/100 mL = 24.3 g dextrose
5. Determine the available volume for additives
   - 162 mL – 42 mL (10% pediatric CAA) – 34.6 mL (70% dextrose) = 85.4 mL
   - Depending on volume needed for additives, sterile water may be necessary to add to formulation to make final total volume of 162 mL
6. Determine the final PN regimen and provided nutrient amounts
   - Final PN regimen
     - 3.5 g/kg/day pediatric CAA and 15% dextrose to infuse at 6.75 mL/h
     - 3 g/kg/day (or 18 mL) 20% ILE to infuse at 0.75 mL/h
   - Macronutrient calories

Dextrose:	24.3 g × 3.4 kcal/g	=	82.6 kcal
Protein:	4.2 g × 4 kcal/g	=	16.8 kcal
20% ILE	18 mL × 2 kcal/mL	=	36 kcal
Total kcal (kcal/kg):			135.4 kcal (113 kcal/kg)
Nonprotein kcal (kcal/kg):			118.6 kcal (99 kcal/kg)

Administration Techniques

PN admixtures should be administered with an infusion pump. The IV administration line for CAA-dextrose solutions should include a 1.2 µm inline filter to remove any particulate matter that may be present in the solution.[63] This filter size also removes *Candida albicans.* ILE's may be administered separately from the CAA-dextrose solution by co-infusion into the PN line. However, co-infused ILE should also be filtered with a 1.2 µm filter.[31-35,41,63] A single 1.2 µm filter may be placed below the Y-site of the IV administration line where the dextrose-amino acid admixture and the ILE co-infuse to simplify PN filtering practices.[63] TNA solutions should be filtered with a 1.2 µm filter placed as close to the IV catheter hub as possible.

INITIATING AND ADVANCING THE PARENTERAL NUTRITION INFUSION

Adult Parenteral Nutrition

The patient's nutrition status, current clinical status, history of glucose tolerance, and dextrose concentration in the formula will dictate the infusion rate at which the adult PN solution should be initiated. Stable patients with normal organ function and stable baseline serum glucose concentrations have demonstrated minimal effect on serum glucose concentrations when PN is abruptly initiated or discontinued.[5,64] However, another approach is to begin the PN infusion and increase the rate gradually over 12 to 24 hours to the desired rate. The infusion rate may likewise be reduced in a stepwise fashion, such as decreasing the rate by 50% for 1 hour before discontinuation.[5,64] This approach should prevent development of hyperglycemia and

rebound hypoglycemia, respectively. Alternatively, the PN regimen may be initiated at the goal infusion rate but with a hypocaloric dextrose dose. The dextrose dose can be increased daily to the goal based on patient response. Tapered initiation and cessation should be considered for patients receiving intermittent subcutaneous regular insulin; patients with severe kidney or liver disease; and patients with other disease states who have an increased risk for development of hyperglycemia or hypoglycemia, such as severe diabetes mellitus or pancreatic malignancy.

The SO-ILE dose should not exceed 2.5 g/kg/day or 60% of total daily calories, lower doses of 1 g/kg/day not to exceed 30% of calories have been recommended to minimize negative effects associated with long-chain fatty acids.[12,31,35] Higher doses of mixed-oil ILE up to 2.5 g/day may be necessary to prevent EFAD in patients with larger energy requirements. Manufacturer's dosing and administration recommendations differ depending on the product.[31-35] However, co-infusion over 12 hours as a separate infusion with two-in-one admixtures and infusion over no longer than 24 hours in a TNA formulation is the best clinical strategy to promote ILE clearance and minimize risk of negative effects on infection control and pulmonary and immune function.[5]

The manufacturer's guidelines recommend initiating SO-ILE and SMOF ILE with a test dose of 0.5 to 1 mL/min for the first 15 to 30 minutes because of the potential for an immediate hypersensitivity reaction.[31,37] For most adult patients, this is probably not necessary because of the relatively low incidence and benign nature of acute adverse reactions. In addition, infusion over 12 to 24 hours eliminates the need for a test dose because the infusion rate is within the range of the recommended test dose rates. Appropriate electrolytes should be provided to patients with normal organ function based on standard nutrient ranges Adjustments may be necessary depending on the patient's clinical condition. Adults and children older than 11 years should receive daily amounts of trace elements and an adult vitamin formulation.

Pediatric Parenteral Nutrition

Pediatric PN solutions are typically initiated with a volume calculated to provide the patient's daily maintenance fluid requirements on the first day of therapy. Individual nutrient substrates are then advanced daily as tolerated with the goal PN regimen generally being achieved by day 3 of therapy. However, the PN formulation should be initiated with the goal of achieving the desired protein dose on day 1. The initial dextrose dose for older infants and children is based on their previous glucose tolerance. Although practices may vary, one approach is to start with 10% dextrose and advance the concentration in 5% increments daily, as tolerated, to goals of 10 to 14 mg/kg/min in infants, 8 to 10 mg/kg/min in children, or 5 to 6 mg/kg/min in adolescents.[16] Initial dextrose doses for premature infants should approximate fetal nutrient delivery rates of 5 to 6 mg/kg/min. Frequently, this results in a final PN dextrose concentration of 5% to 10%. The dextrose concentration for the neonatal PN should be advanced daily by 1% to 2.5% or by 2 to 4 mg/kg/min increments to a goal of 10 to 14 mg/kg/min (maximum, 14-18 mg/kg/min).[16] SO-ILE is usually initiated at 0.5 g/kg/day for neonates and 0.5 to 1 g/kg/day for infants and children and increased daily by 0.5 to 1 g/kg/day. Incremental increases of SO-ILE dose allow daily serum triglyceride evaluation and early detection of those with impaired fat clearance. The SO-ILE dose should not exceed 60% of total daily calories for neonates and 30% of total calories for children, and the maximum SO-ILE dose should not exceed 3 g/kg/day (approximately 30 kcal/kg/day [126 kJ/kg/day]) for infants and 2.5 g/kg/day for children.[16] The maximum dose for FO-ILE is 1 g/kg/day.[34] The best clinical strategy for minimizing the risk of adverse medication reactions associated with SO-ILE administration and promoting ILE clearance is to infuse SO-ILE over 20 to 24 hours, not exceeding 1 g/kg in 4 hours. FO-ILE may be infused over 8 to 12 hours.[34,41]

IV electrolytes, vitamins, and trace elements should be initiated on the first day of therapy and continued as a daily component of the PN solution.[5,16] Children younger than 11 years should receive a vitamin product formulated for pediatric patients. Two multivitamin dosing schemas may be used for infants and children.[16] One method recommends 2 mL/kg/day for infants weighing less than 2.5 kg (15.5 lb) and 5 mL/day for infants and children weighing 2.5 kg (5.5 lb) or greater. The other suggests 30% of a vial (1.5 mL/day) for infants weighing less than 1 kg (2.2 lb), 65% of a vial (3.25 mL/day) for infants weighing 1 to 3 kg (2.2-6.6 lb), and 100% of the vial (5 mL/day) for children weighing more than 3 kg (6.6 lb) (up to 11 years of age). Adult injectable vitamin products should not be used for infants because of potential neurotoxicity from accumulation of polysorbate and propylene glycol preservatives. Dosage recommendations for the reformulated multiple trace element products approved for use in pediatric patients are 0.2 mL every other day for neonates weighing less than 0.6 kg and 0.3 mL/kg/day for neonates and infants at least 0.6 kg and less than 10 kg (maximum daily dose of 1 mL) using the product approved for pediatric patients less than 10 kg. The daily dose for the product approved for pediatric patients 10 kg and greater is 0.2 mL, 0.4 mL, 0.6 mL, or 0.8 mL (based on weight range). Children weighing 50 kg (110 lb) or greater should receive the adult dose of 1 mL daily. Weight-based doses of the multiple trace element products do not provide the recommended daily intake for all trace elements, so additional supplementation or individual dosing with single-entity products is necessary. Individualized dosing allows for dose adjustment based on serum trace element assessment, individual patient characteristics (eg, cholestasis, stool losses, wounds), and the provision of the recommended intake across the

pediatric age spectrum from a single source for each trace element supplemented. And while the amounts of chromium and manganese are lower in the reformulated multiple trace element products, individualized dosing allows for the need to minimize or remove these trace elements in patients with evidence of accumulation. Pediatric patients receiving PN commonly transition from PN support to EN gradually, over a period of days to weeks, by decreasing the PN infusion rate while increasing the enteral intake. The PN infusion rate should be reduced for 1 to 2 hours before stopping the infusion for neonates and infants because of their immature counter-regulatory mechanisms that contribute to an increased risk for developing rebound hypoglycemia.[5] Blood glucose concentrations should be measured within 15 to 60 minutes after the PN infusion ends.

Continuous Versus Cyclic Infusions

7 Continuous infusions are attractive for patients with unstable fluid balance or glucose homeostasis. The intermittent or cyclic infusion of PN over less than 24 hours, usually for 12 to 18 hours each day, is useful for hospitalized patients with limited venous access in whom administration of multiple other medications requires interruption of the PN infusion.[64] Cyclic PN may also minimize the incidence or reverse the liver injury associated with continuous PN therapy. In addition, this delivery mode allows patients receiving PN at home the ability to resume a relatively normal lifestyle.[16,60,64] Various protocols suggest incremental increases to the maximum infusion rate for a desired period of time followed by a gradual taper to discontinue the solution.[64] However, metabolically stable adults and children older than 2 years receiving ILE-based PN regimens are likely candidates for abrupt initiation and discontinuation of their intermittent PN regimen.[5,64,65] Cyclic PN should be used with caution for those with severe glucose intolerance, diabetes mellitus, or unstable fluid balance.

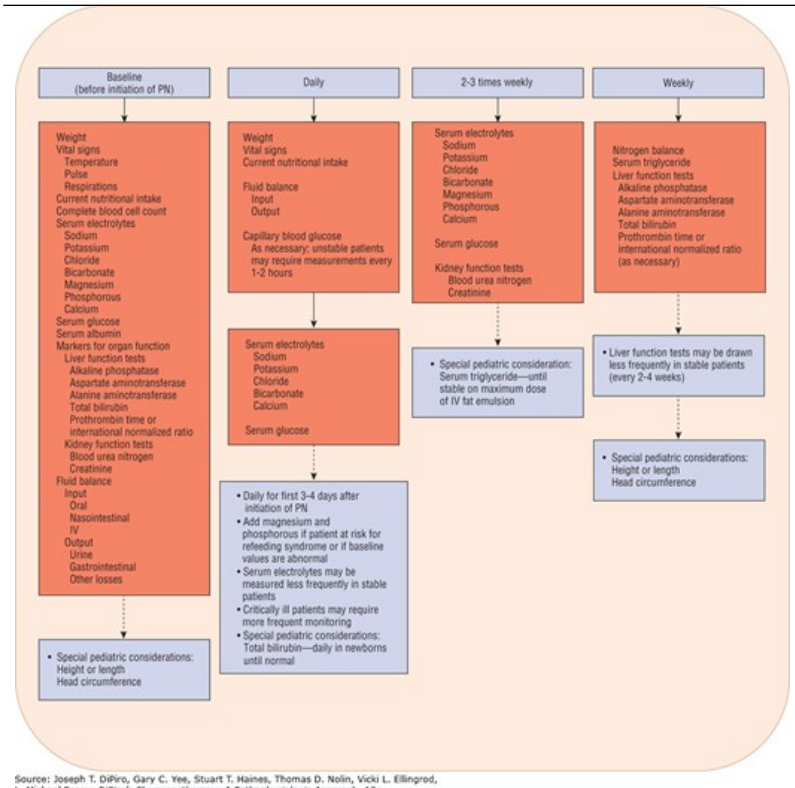
EVALUATION OF THERAPEUTIC OUTCOMES

8 Thorough and consistent monitoring of patients who are receiving PN is necessary to ensure that the desired nutritional outcomes are achieved and to prevent the occurrence of adverse effects or complications. Routine evaluation should include the assessment of the patient's clinical condition with a focus on nutritional and metabolic effects of the PN regimen. Serial documentation of a patient's response to their PN regimen is a helpful guide for determining appropriate adjustments in fluid, electrolyte, and nutrient therapies.

Serum concentrations of electrolytes, hematologic indices, and biochemical markers for kidney and liver function, and nutrition status should be measured before PN initiation and periodically thereafter depending on the patient's age, nutrition status, and clinical condition. The frequency of blood laboratory measurements for neonates and infants tends to be more conservative because of their smaller blood volumes and, in some cases, lack of central vascular access. Other important clinical measurements include vital signs, weight, total fluid intake and output, and nutritional intakes. Weekly measurements of height, length, and head circumference are helpful for monitoring nutritional changes in neonates. Monitoring parameters considered important for patients receiving PN and the suggested frequency of measurement for each are outlined in Fig. 165-3. Appropriate assessment and evaluation of patient data can identify potential complications that may be avoided or treated early. Monitoring protocols should be developed and tailored for the patient population, medical practices, and resources of individual practice settings.

FIGURE 165-3

Monitoring strategy for patients receiving parenteral nutrition (PN).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

COMPOUNDING, STORAGE, AND INFECTION CONTROL

The USP Chapter 797 details the procedures and requirements for compounding sterile preparations, including PN admixtures.[66] These standards apply to all healthcare settings in which sterile preparations are compounded and are used by boards of pharmacy, the FDA, and accreditation organizations such as The Joint Commission. Compounded sterile preparations are defined by risk level (immediate use, low, low with 12-hour beyond-use date, medium, and high) based on the probability of microbial, chemical, or physical contamination. PN solutions are classified as a medium-risk compounded sterile preparation. In general, PN solutions should be prepared using aseptic technique in a device or room that meets International Organization for Standardization (ISO) class 5 standards that is located in an ISO class 7 buffer area with an ISO class 8 ante area.[66] Preparation of PN formulations should be supervised by a pharmacist experienced in compounding IV solutions and knowledgeable about the stability, compatibility, and storage of PN admixtures. Quality assurance procedures should be developed to maintain safe and accurate admixture preparation. A standardized process for PN ordering, labeling, determining nutrient requirements, screening of the PN order, PN administration, and monitoring has been recommended to minimize risk of potentially life-threatening compounding errors.[5,62] The potential risk of infectious complications associated with PN solution contamination can be decreased greatly when pharmacy-based admixture programs follow specific guidelines developed to ensure proper compounding of PN solutions.[5,66] USP Chapter 797 is under revision.[67] However, the published version of the chapter, which became official on June 1, 2008, is enforceable.

In general, the type of solution being prepared dictates the compounding, storage, and infusion methods. The two most commonly used types of PN solutions are two-in-one admixtures with or without ILE co-infused into the PN administration line and TNAs. Methods for compounding PN admixtures vary based on a healthcare system's patient population and medical practices and the number of PN admixtures that need to be prepared. PN base admixtures may be prepared by using gravity-driven transfer of CAA stock solutions to partially filled bags of concentrated dextrose stock solutions.[5,68] Other practice settings may use standardized commercial PN products with CAA and dextrose, and ILE separated within a single bag that must be mixed before use.[5,44,62] Advances in compounding technology have facilitated the use of ACDs for preparing PN solutions. ACD systems usually include computer software that communicates calculated volumes of nutrient stock solutions directly to a transfer pump device that delivers fluid from the source container to the final container by either a volumetric or gravimetric fluid pumping system.[5,68] Advantages of ACDs include reduced personnel time and compounding materials and improved compounding accuracy. Disadvantages include the potential for equipment failure.

Because of their acidic pH and hypertonicity, two-in-one PN admixtures are poor media for microbial growth.[5,40] However, several characteristics of ILE, such as isoosmotic tonicity, near neutral to alkaline pH, glycerol content, and preservative-free formulations favor microbial growth, particularly at room temperature.[35,41,56] Other factors contributing to the potential for compromised ILE stability or sterility include the container material, length of ILE co-infusion with PN, length of time between administration set change, effect of infusion from the source container such as the original container, and infusion of ILE transferred to a secondary container. When ILEs are added to dextrose-CAA solutions to make TNAs, the growth potential is decreased, presumably because of the protective effects of the hypertonic dextrose-CAA solution and decreased pH.[35,41,56]

Because of the risk for microbial contamination, manufacturers recommend storage of PN solutions for as little time as possible after preparation. The USP 797 standards recommend storage times of not more than 30 hours at controlled room temperature (20°C-25°C [68°F-77°F]) and not more than 9 days at refrigerated temperatures (2°C-8°C [36°F-46°F]) for all medium-risk compounded sterile preparations, including PN admixtures.[66]

When co-infusing ILE with PN (ie, not as a TNA), the appropriate ILE dosage form (original packaging or re-packaged doses) and administration time to minimize risk of contamination is controversial. Unfortunately, the Centers for Disease Control and Prevention (CDC) guidelines offer no guidance for administration times.[58] Instead, the guidelines recommend administration tubing replacement every 24 hours for both ILE infused separately or when given as part of a TNA. The guidelines also recommend administration tubing replacement no more frequently than at 96-hour intervals but at least every 7 days for tubing used continuously for infusion of IV solutions other than blood, blood products, or ILE. More conservative recommendations have been presented.[5,56] The ASPEN 2013 PN Safety Consensus suggests a 24-hour infusion time and administration tubing replacement every 24 hours for TNAs and two-in-one PN formulations and a 12-hour infusion time and administration tubing replacement every 12 hours for ILE co-infused separately.[5]

Compliance with ASPEN recommendations in pediatric patients is problematic. For example, an infant receiving 3 g/kg/day ILE at the recommended infusion rate of 0.15 g/kg/hr to promote lipid clearance and minimize metabolic complications, would require at least a 20-hour infusion.[16,69] To accommodate prolonged ILE infusions, many institutions routinely infuse ILE separately over 24 hours and change administration tubing for the ILE and PN solution with each new bag because the use of TNA formulations is not recommended in neonates and infants. In addition, since commercially available ILE products are not manufactured in unit volumes suitable for safe use in neonates and infants, institutions commonly transfer ILE from the original container into another container to accommodate the smaller patient-specific volume to decrease risk of adverse events from infusion-related errors. A variety of methods have been utilized for repackaging ILE. Syringe repackaging and aseptic transfer into sterile bags with the use of an ACD are not recommended because of higher contamination rates. Other methodologies, such as aseptic withdrawal of an appropriate ILE volume resulting in a patient-specific dose in the original manufacturer's container (drawing-down) has been recommended as a potential option.[41,56,69] These multifactorial concerns with providing ILE to pediatric patients have been addressed by the ASPEN Safety Consensus Recommendations.[5] When prolonged ILE infusions are required in neonates and infants, the daily dose should be divided in two separate 12-hour infusions. The ILE container and administration tubing should be replaced every 12 hours.[5] When utilizing repackaged ILE, the infusion time should not exceed 12 hr/Unit and the administration tubing should be changed with each new infusion.[5,41,56,69]

Stability and Compatibility

Comprehensive current information regarding compatibility and stability of PN solutions can be found in several reference sources such as *ASHP Injectable Drug Information*[70] and *King Guide to Parenteral Admixtures*.[71] In many cases, the answer to a compatibility question may not be readily available, and a review of the primary literature may be necessary. When information is not available, clinical judgment and experience must be used to resolve the situation.

The stability of a PN formulation is determined by the rate or degree of component degradation and any resulting changes in chemical integrity or pharmacologic activity that may render the formulation unsuitable for safe administration.[22] In general, the sterile combination of PN components accelerates the rate of physicochemical destabilization of all of the components in the formulation; certain amino acids, vitamins, and ILE are the most susceptible nutrients.[5,22,28,46] When compounded and stored appropriately, the degree of degradation is usually not clinically relevant for most patients receiving short-term PN because many patients have sufficient stores of those susceptible nutrients to support any short-term periods of suboptimal intake. However, nutrient degradation that is more extensive may be problematic for patients with marginal nutrient stores who receive long-term PN. TNAs present additional stability challenges because of the presence of ILE in the solution. ILE stability in TNAs is affected by the amino

acid and dextrose concentration, solution pH, order of mixing, electrolyte amounts, and final TNA volume as well as container material, storage conditions, and addition of non-nutrient medications. Information on the effect of specific electrolyte concentrations on TNA stability is limited. In general, ILE stability is affected by the PN cation content. Divalent and trivalent cation additives such as calcium and magnesium have a greater destabilizing potential compared with monovalent cation additives such as sodium and potassium. However, when given in sufficiently high concentrations, monovalent cation additives may also increase instability. Cations act to reduce the surface potential of the emulsion droplet, thereby enhancing tendency to aggregate and ultimately, in some cases, destabilize the solution to coalescence or a "cracked" admixture.[5,22,40] When a cracked ILE occurs, the oil phase separates from the water phase, resulting in the appearance of free oil fat globules. Early stages may appear as subtle changes in the uniformly white appearance of the TNA, which may progress to yellow oil streaks throughout the bag or development of an amber oil layer at the top of the admixture bag. TNA formulations with any visible free oil should be considered unsafe for parenteral administration because infusion of circulating fat globules may be of sufficient size to accumulate in the pulmonary vasculature and potentially compromise respiratory function. In general, the likelihood of preparing an unstable TNA formulation can be minimized by maintaining the final concentrations of CAA greater than 4%, dextrose greater than 10%, and ILE greater than 2%.[5] Specific guidelines for compounding TNAs are reviewed elsewhere.[2,5,31-35,56]

Because of differences in pH among various CAA products and phospholipid content among ILE products, the manufacturer of each product should be consulted for compatibility and stability information before routinely admixing components. One approach to compounding TNAs manually is to combine CAA, dextrose, and sterile water (if necessary) followed by the addition of electrolytes, vitamins, and trace elements. Then the solution should be visually inspected for precipitate or other particulates. Finally, ILE may be added and the solution should then be visually inspected again to ensure a uniform emulsion exists.[31-34] Mixing components in this specific order may not be possible with the use of ACDs. Although CAA, dextrose, and ILE may be simultaneously transferred to an admixture container, the ACDs manufacturer should be consulted for the optimal mixing sequence to ensure safe compounding of TNA formulations.

The precipitation of calcium and phosphorus is a common interaction that is potentially life-threatening.[16,22,72] The risk of precipitate formation is greater with increased solution temperature and pH, higher concentrations of calcium and phosphorus, lower concentrations of amino acids and dextrose, use of the chloride salt of calcium, improper mixing sequence when adding calcium and phosphorus salts, and the presence of other additives (including ILEs).[16,22,72] In general, steps to minimize risk of calcium and phosphate precipitation in PN admixtures include the use of calcium gluconate instead of calcium chloride because it is less reactive, adding phosphate salts early in the mixing sequence, adding calcium last or nearly last, and agitating the mixture throughout the admixture process to achieve homogeneity. PN admixtures with a lower final pH should be used when clinically appropriate. Higher final concentrations of dextrose and CAA and lower final concentrations of ILE favor a lower admixture pH. CAA product-specific solubility curves that are available from the manufacturer or primary literature should be consulted to project calcium and phosphorous solubility. The calculation of a sum or product of calcium and phosphate concentrations should not be used as the sole criterion for determining solubility because the product of calcium and phosphate concentrations vary inconsistently as calcium concentration decreases and phosphate concentration increases.[72]

Electrolyte stability in TNA solutions is difficult to assess because of poor visualization of a precipitate if one occurs. PN solutions for neonates and infants tend to contain larger amounts of calcium and phosphorus, as well as other divalent cations, that limit the use of TNAs. Because of the limited amount of published stability information, the use of a two-in-one admixture with separate administration of ILEs is recommended for neonates and infants.[56] In general, alternative methods of delivering electrolytes or medications should be pursued in any clinical situation in which TNA compatibility information is lacking. Because the addition of bicarbonate to acidic PN admixtures may result in the formation of carbon dioxide gas and insoluble calcium and magnesium carbonates, sodium bicarbonate use in PN admixtures is not recommended. Use of a bicarbonate precursor salt such as acetate usually is preferred.[22]

Vitamins may be affected adversely by changes in solution pH, presence of other additives, storage time, solution temperature, and exposure to light.[22,28] Because of variable stabilities of individual vitamins, IV vitamin solutions should be added to the PN solution as near to the time of administration as is clinically feasible and should not be in the PN solution longer than 24 hours.

Peroxide concentrations are increased in ILE and dextrose-amino acid solutions after addition of injectable multivitamins or exposure to air or light.[73] Peroxides and associated metabolites have negative effects on organ and immune function. Specifically, peroxides are associated with neonatal hypoxic-ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, retinopathy of prematurity, and necrotizing enterocolitis.[73] Neonates and infants are at increased risk for harmful effects of peroxides because they receive a higher daily peroxide

load from PN solutions compared to adults and they have lower endogenous antioxidant levels. However, premature infants are more vulnerable to consequences of peroxide formation in PN admixtures.[73] Complete PN photoprotection from light (admixture and administration line) beginning as soon as possible during the PN compounding process and continued until the entire PN admixture and ILE infusion is complete is recommended to minimize risk of peroxides formation and by-products of lipid peroxidation.[73]

Many patients receiving PN also receive other IV medications. The compatibility of these medications with the PN solution is an important consideration for safe and effective medication delivery. Although some medications may be added directly to the PN solution and administered at the same rate as the PN infusion, most are administered as a separate admixture co-infused in the PN line. Several criteria should be considered before medications are added directly to the PN solution because of the potential for ineffective medication therapy or other complications associated with physiochemical incompatibility and stability of the PN solution.[22,56] First, the medication should be stable for at least 24 hours and should have pharmacokinetic properties appropriate for continuous infusion. Second, the chemical and physical compatibility of the medication with PN admixture components and other medications that may be co-infused concomitantly into the PN line should be verified. Advantages of using PN admixtures as medication vehicles include consolidation of dosage units, improved pharmacodynamics for certain medications, conservation of fluid in volume-restricted patients, fewer venous catheter violations, and decreased compounding and administration times. However, a major disadvantage to the use of PN solutions as medication-delivery vehicles is the lack of compatibility and stability data. Medications frequently added to PN solutions include regular insulin and histamine-2 receptor antagonists.[22,56]

COMPLICATIONS OF PARENTERAL NUTRITION

Mechanical and Technical Complications

Mechanical and technical complications include malfunctions in the system used for IV delivery of the solution, such as infusion pump failure, problems with administration sets or tubing, or the CVC. Although problems associated with infusion pumps and administration sets can be decreased by appropriate equipment selection and routine care and monitoring, CVC-related complications are potentially life-threatening. Pneumothorax, catheter misdirection or migration into the wrong vein or improper positioning within the cardiac chambers, arterial puncture, bleeding, and hematoma formation may occur during surgical placement of the catheter. Many of these complications, in addition to venous thrombosis and air embolism, can occur after insertion. CVCs occasionally occlude or break during use and if these problems cannot be rectified easily, the catheter may need to be surgically replaced.

Infectious Complications

Infectious complications can be a major hazard for patients receiving CPN because of the increased risk associated with the presence of an indwelling CVC. The source of a CVC infection may be skin organisms from the catheter insertion site, contamination of the catheter hub, or hematogenous seeding of the catheter from a distant site. In addition, patients receiving PN therapy are often predisposed to infection because of compromised immunity or concomitant infection. Frequent use of broad-spectrum antibiotic therapy and malnutrition are also predisposing factors for development of infection. The risk of catheter infection is increased for those who require multiple manipulations of the line used for PN administration as well as those who experience, poor catheter placement technique, and poor CVC and insertion site care.[58]

Infection rarely develops secondary to solution contamination.[58,63] Strict adherence to protocols for preparation of PN admixtures should minimize this occurrence.[66,74] Catheter-related bloodstream infections (CRBSIs), defined as the presence of clinical manifestations of infection (eg, fever, chills, hypotension) associated with bacteremia or fungemia resulting from no apparent source other than the catheter, are common sources of systemic infection.[74] Before this diagnosis can be made, there should be evidence of more than one positive blood culture result obtained from the peripheral vein with growth of the same organism from a blood culture obtained from the catheter or catheter segment. When a CRBSI is suspected or confirmed, appropriate antimicrobial therapy should be initiated. Retention or removal of the CVC depends on the patient's severity of illness, the suspected or identified pathogen, and the type of catheter involved. The catheter may be removed and replaced in the same site, the catheter may be removed and replaced at a different anatomic location, or it may not be replaced.[74] Filling the catheter with antimicrobials such as vancomycin or antiseptics such as 70% alcohol and allowing the solution to dwell for a period of time while the catheter is not in use is referred to as a catheter lock.[58] Antimicrobial catheter locks have been used to prevent and treat CRBSI in patients with long-term catheters such as those receiving home PN.[58,59]

Metabolic and Nutritional Complications

Metabolic and nutritional complications associated with PN therapy are numerous, frequently multifactorial in origin, and potentially fatal if left untreated. Metabolic abnormalities related to substrate intolerance, fluid and electrolyte disorders, and acid-base disorders are summarized in multiple recent review articles and their management is briefly summarized in the following sections.[28-30,39,55,75-82]

Liver Disease

PNALD presents as elevations in total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase. Both adult and pediatric patients who receive PN are at risk for developing PNALD; it occurs in approximately 50% to 60% of children who receive long-term PN, with a higher incidence in premature infants.[28,29,75] No single etiology has been identified, although several risk factors have been described, such as degree of prematurity, sepsis, hypoxia, lack of EN, small bowel bacterial overgrowth, GI conditions requiring surgical intervention, duration of PN therapy, and long-term administration of excessive calories.[29,39,75] PNALD in infants is characterized clinically by a serum direct bilirubin concentration greater than 2 mg/dL (more than 34.2 µmol/L).[29] Taurine deficiency has been proposed as an etiology of cholestasis for preterm infants and neonates.[29,39] Taurine is a conditionally essential amino acid that is not present in standard CAA solutions but is important for neonatal and infant bile metabolism. However, the preventative or therapeutic benefit of PN regimens with CAA solutions containing supplemental taurine is unclear. SO-based ILEs contain large concentrations of plant sterols or phytosterols, which are inefficiently metabolized to bile acids by the liver and may impair bile flow. Improvement or reversal of PNALD may occur for patients who receive FO-ILE.[37,39] Other PNALD treatments that have been investigated include providing reduced doses of SO-based ILE and use of enteral fish oil in patients with limited oral intake.[39,76]

Risk factors for PNALD in adults include preexisting liver disease, sepsis, preexisting malnutrition, extensive bowel resection, prolonged duration of PN therapy, lack of enteral intake, nutrient deficiencies such as choline deficiency, and long-term administration of excessive calories.[28,29,39,75] PNALD in adults typically presents as steatosis and steatohepatitis on biopsy. Clinically, PNALD is characterized by mild elevations in serum liver enzymes, usually less than three times the upper limit of normal, with peak enzyme levels usually occurring between 1 and 4 weeks after initiating PN. In many cases, the liver abnormalities improve or resolve with manipulation of substrate intake or discontinuation of PN therapy. However, in severe cases, liver dysfunction may progress to overt failure and death despite use of traditional therapies such as using cyclic PN, ursodiol, and oral antibiotics for bacterial overgrowth; maximizing enteral feeding; and avoiding sepsis and parenteral overfeeding.[28,29,75] Intestinal transplant with or without liver transplantation has become a treatment option for PN-dependent patients who have progressive PNALD.

Hypertriglyceridemia

Hypertriglyceridemia, defined as serum triglyceride concentrations greater than 400 mg/dL (4.52 mmol/L) for adults and 150 mg/dL (1.70 mmol/L) to 200 mg/dL (2.26 mmol/L) for preterm infants, neonates, and older pediatric patients, may occur in patients receiving ILE-based PN. Risk factors include preexisting liver or pancreatic dysfunction, sepsis, multiple-organ failure, degree of prematurity, ILE infusion rate, and dose.

ILE-associated hypertriglyceridemia is generally caused by defective lipid clearance or an excessive rate of ILE administration.[28] Premature infants and neonates have relatively slower lipid clearance than do adults because of immature metabolic pathways, including decreased lipoprotein lipase activity.[16,41] Reducing the ILE infusion rate or dose or withholding ILE therapy should be considered when patients present with hypertriglyceridemia or lipemic serum.[28] Use of low-dose heparin (1 unit/mL of two-in-one PN formulation) to stimulate lipoprotein lipase activity may be a potential therapeutic intervention to treat ILE-associated hypertriglyceridemia in neonates.[16] However, the risk associated with heparin delivery via PN may outweigh the clinical benefits because of the potential for compounding errors associated with confusion between heparin and insulin doses.[77] Carnitine does not have a defined role for treatment of ILE-associated hypertriglyceridemia.[16,28]

Hyperglycemia

Hyperglycemia is one of the most common complications of PN administration and is associated with a history of diabetes mellitus, metabolic stress, adverse medications reactions to agents such as glucocorticoids, and excessive carbohydrate administration. In the pediatric population, additional risks for hyperglycemia include prematurity and surgery. The optimal blood glucose concentration for acutely ill hospitalized patients receiving PN is not known. However, a target range of 140 to 180 mg/dL (7.8-10 mmol/L) has been suggested for adults, and less than 150 mg/dL (8.3 mmol/L) has

been suggested for neonates.[78,79] Clinical management of PN patients with hyperglycemia has not been well studied and is largely empiric.[80,81] Blood glucose concentrations can be controlled with regular insulin, which may be given subcutaneously or added to the PN formulation. One approach for adult PN patients requiring insulin or oral hypoglycemic agents before starting PN therapy is to initiate PN with approximately 100 to 200 g of dextrose and add 0.05 to 0.1 Units of regular insulin per gram of dextrose in the PN solution for those patients with mild hyperglycemia (140-180 mg/dL [7.8-10 mmol/L]). The insulin dose may be increased to 0.15 to 0.2 Units/g of dextrose for patients with moderate hyperglycemia (181-200 mg/dL [10-11.1 mmol/L]).[28,80,81] Others have suggested continuing preadmission basal insulin with long-acting insulin (detemir or glargine). Response to blood glucose monitoring prior to initiating PN therapy can be useful in determining initial insulin dosing. Blood glucose concentrations should be monitored every 4 to 6 hours. Blood glucose measurements above the goal range should be treated with short-acting insulin administered subcutaneously according to an appropriate sliding scale (see Chapter 94). The insulin dose is modified daily by adding 60% to 100% of the sliding-scale insulin given over the previous 24 hours to the PN formulation daily until blood glucose concentrations are stable and within the target range. When blood glucose measurements are stable, the dextrose dose may be advanced to achieve the therapeutic goal and the frequency of monitoring blood glucose concentrations may be decreased after blood glucose concentrations are stable within the target range at the goal dextrose dose. Use of a separate IV insulin infusion is most commonly used for pediatric patients, but it may also provide better and safer glycemic control for patients with large insulin requirements or those with unstable marked fluctuations in their blood glucose concentrations.

Refeeding Syndrome

Severe and rapid declines in serum phosphate, potassium, and magnesium concentrations; fluid retention; and other micronutrient deficiencies are common features of the refeeding syndrome.[82] Individuals at greatest risk for refeeding syndrome are severely malnourished patients with considerable weight loss who receive aggressive nutritional supplementation. In addition, those who are unfed for 7 to 10 days with evidence of stress or nutritional depletion; those with chronic diseases causing undernutrition such as cancer, cardiac cachexia, chronic obstructive pulmonary disease, or cirrhosis; and individuals who were previously morbidly obese and have experienced massive weight loss are at heightened risk for this syndrome.[82] Electrolyte abnormalities are related to acute provision of macronutrient substrates that promote anabolism in an environment of depleted total body stores of phosphorus, potassium, and magnesium. Recommendations for initiating PN in adults at risk for refeeding syndrome include providing 100 to 150 g of dextrose or 10 to 20 kcal/kg (42-84 kJ/kg) for the first 24 hours and advancing calories by 33% of goal every 1 to 2 days. Recommendations for initiating PN in pediatric patients include providing a maximum of 40% to 50% goal, and initiating the glucose infusion rate at approximately 4 to 6 mg/kg/min. The dextrose dose should be advanced by 1 to 2 mg/kg/min daily to a maximum dose of 14 to 18 mg/kg/min depending on blood glucose response. Other non-PN sources such as IV fluids or EN should be considered as well. Supplemental thiamine 100 mg/day for adults and 2 mg/kg/day to a maximum of 100 to 200 mg/day for pediatric patients should be considered before feeding or before initiating dextrose-containing IV fluids in patients at risk.

Because the metabolic abnormalities described with refeeding syndrome are related primarily to acute provision of large amounts of dextrose, the goal protein dose may usually be provided with the initial PN infusion. Pediatric PN regimens are usually advanced over several days as a general practice for all pediatric patients.

Complications Associated with Long-Term Parenteral Nutrition

Other nutritional complications of PN therapy may develop over a prolonged course of therapy (weeks to months) as a result of inappropriate intake of a particular nutrient. Certain conditions, such as metabolic stress in a previously malnourished patient, may elicit symptoms of deficiency much earlier if a nutrient is not appropriately provided. For example, lactic acidosis and other life-threatening complications associated with severe thiamine deficiency may occur in patients who received PN solutions without multivitamin supplementation.[46] Maintenance doses of vitamins, trace elements, and essential fatty acids should be provided to all patients with normal age-related organ function receiving PN.

Essential Fatty Acid Deficiency

Patients receiving PN regimens without ILEs for weeks to months are at risk for development of EFAD. Clinical signs of EFAD include hair loss, desquamative dermatitis, thrombocytopenia, malabsorption, and diarrhea resulting from changes in intestinal mucosa.[28,36] EFAD may also be diagnosed by evaluating plasma fatty acid profiles. Although this assessment is not routinely available, it can be provided by several larger regional laboratories. Historically, a triene-to-tetraene ratio more than 0.4 was considered biochemical evidence for EFAD; however, individual laboratory

reference ranges should be used when evaluating patients for EFAD.[16,36] Although the time in which EFAD may develop depends on the patient's nutrition status, disease state, and age, these manifestations may occur 2 to 4 weeks after initiation of lipid-free PN in adults and within 48 hours in newborn infants.[36,37]

Metabolic Bone Disease

Metabolic bone disease may occur in adults and children receiving long-term home PN.[28,29] This disorder in adults is characterized by osteomalacia with or without osteoporosis that may present without associated clinical, radiologic, or biochemical abnormalities. The diagnosis may not be made for premature infants until after the development of bone fractures or overt rickets. The etiology is poorly understood and likely multifactorial. Treatment options include pharmacologic intervention, calcium and vitamin D supplementation, and exercise. Because excessive vitamin D has also been implicated in the development of metabolic bone disease, others have recommended removal of vitamin D from the PN for patients with a normal 25-hydroxyvitamin D concentration and low serum parathyroid hormone and 1,25-hydroxyvitamin D concentrations.[28,29]

Trace Element and Vitamin Complications

Clinical symptoms of trace element deficiencies, although rare, may occur for patients receiving long-term PN. More commonly, decreased serum trace element concentrations are seen in a variety of patient populations. However, the clinical significance of abnormally low concentrations of many trace elements is unknown because serum concentrations often do not correlate with total body stores.[46] Occasionally, patients may develop clinical toxicities from elevated vitamin or trace element concentrations as the result of increased intake or decreased metabolism. These abnormalities are frequently associated with an underlying disease state such as severe kidney or hepatic failure and may necessitate reduction in vitamin and trace element intake.

Many trace elements are present in PN components as contaminants.[46,56] In patients with normal organ function who receive PN supplemented with commercially available parenteral multiple trace element solutions, elevated serum concentrations of trace elements such as chromium and manganese may develop.[46,56] Aluminum is a common contaminant of many sterile IV solutions, including those used for compounding PN. Calcium and phosphorus solutions are among those components with the highest levels of aluminum contamination.[83,84] Aluminum accumulation may occur during long-term PN therapy, especially for patients with reduced kidney function, and is associated with abnormal neurologic and hematologic function and metabolic bone disease in adults and premature infants.[28,83,84] Preterm infants are at higher risk of aluminum toxicities because they receive larger doses (µg/kg) from PN solutions than adults.[84] Preterm infants are also more likely to retain aluminum because of immature kidney function. Although the maximum safe level of IV aluminum intake is unknown, parenteral doses of 4 to 5 µg/kg/day may be associated with central nervous system and bone toxicity.[85] Even smaller amounts may result in tissue accumulation but no documented toxicity.

The FDA implemented a mandate in 2004 to restrict aluminum content in large-volume PN stock solutions (CAA, dextrose, sterile water for injection, ILE) to a maximum of 25 µg/L and for manufacturers to indicate the maximum aluminum concentration at expiration for both large- and small-volume parenteral products used for PN.[85] Actual aluminum concentrations in parenteral products should be lower than the amounts described on the manufacturer's label; however, aluminum amounts in PN solutions still exceed FDA guidelines.[83,84] In addition, the aluminum content of parenteral products varies considerably during the shelf life of the products and increases with time because of leaching from glass containers. The amount of aluminum contamination delivered to patients receiving long-term parenteral therapy such as chronic PN patients or dialysis patients, can be substantially reduced if newer stock solutions are used to prepare their PN.[83,84]

HOME PARENTERAL NUTRITION

Advances in technology for the delivery of IV solutions have allowed medically stable patients who require extended PN therapy to be maintained indefinitely on IV nutrition. An increasing concern for cost containment of healthcare services has fostered use of sophisticated infusion devices to provide PN at home. Numerous programs are now available outside the traditional healthcare setting to support patients who require long-term or permanent PN. Standards have been developed to promote safe and effective care.[60] Home PN services may be coordinated and administered through a hospital or by a commercial home care company.[59]

Many factors are considered in selecting candidates for home PN therapy. Meaningful benefit must be expected from the therapy. Examples of patients who have been maintained successfully with home PN include those with severe GI dysfunction secondary to Crohn's disease, ischemic bowel disease, severe GI motility disorders, extensive intestinal obstruction, and congenital bowel dysfunction.[59] The patient and the patient's caregiver must be willing to complete training and assume numerous responsibilities for managing the new daily routine. Other logistics such as funding, procurement of solutions and supplies, and clinical management and follow-up must be individualized for each patient in order to achieve the desired outcomes.[59]

Patients commonly receive PN solutions from their home care provider. IV vitamins or other additives may be added daily by the patient or caregiver, depending on the arrangement with the home care provider. The solution is administered through the night by infusion pump over 8 to 20 hours.[59,64] A cycled regimen allows the patient time away from the pump during daylight hours and provides many patients with the freedom to have a reasonably normal daily routine. Clinical management and follow-up are performed periodically according to the needs of the patient and the protocol of the home care provider or the managing healthcare team. A coordinated effort among several healthcare professionals, including physicians, pharmacists, nurses, dietitians, social workers, and the patient and the patient's caregiver, as well as the suppliers, is paramount to providing safe and effective management. Home PN affords some patients the potential for an ambulatory lifestyle while maintaining an IV feeding regimen that was previously only available in the hospital setting. For others, home PN may contribute to a better quality of life in the comfort of their homes.[59]

PHARMACOECONOMIC CONSIDERATIONS

Determining the true cost of PN support is difficult because numerous variables affect the provision of PN and the clinical response to therapy. PN therapy cost variables include the underlying indication for treatment, the administration setting (home or acute care), timing of PN initiation, therapy associated complications, and the type of PN formulation provided (compounded or standardized commercial PN product).[59,86-91] Expenses associated with PN therapy may be categorized as direct and indirect costs.[89] Direct costs may be further categorized as fixed or variable costs. Fixed costs do not depend on the volume of patients receiving therapy. For example, an ACD and the tubing sets required to transfer volumes of stock solutions to the administration bag would be considered fixed costs in many practice settings. These costs per patient tend to be highest in low-volume environments. Variable costs such as PN administration bags or standard commercial PN products depend directly on the number of patients receiving PN. Other direct costs include ancillary services required by patients receiving PN and costs related to the management of PN associated complications.

Clinical benefits and other clinical effects of PN (ie, reduction in hospital length of stay and frequency of complications) in specific patient populations have been evaluated but few investigations include a comprehensive economic assessment of PN therapy. Attempting to measure the cost or cost savings associated with the benefits of PN therapy and other clinical effects is difficult.[87,88] Clinical outcome measurements and hence economic outcomes are influenced by multiple factors, including experimental design, sample size, and specific health system practices.[87,89-93] More recent cost analyses for PN therapy have focused on timing of initiating therapy in critically ill patients and choice of PN formulation (compounded or standard commercial PN product). The cost advantage of supplemental PN in critically ill patients unable to meet nutritional goals within 24 to 48 hours of intensive care unit (ICU) admission is unclear.[91] Similarly, the cost advantage of using standard commercial PN products compared to PNs compounded with an ACD is uncertain.[93,94]

Although the results of economic analyses of PN remain controversial, similarities among several reports provide a basis for minimizing the costs of PN therapy:

1. Use PN only for the most appropriate patients as described by institution-specific criteria based on current consensus statements. EN should be used whenever feasible because the associated costs and complications are demonstrated to be less than those associated with PN.[90,92,95]
2. Reassess the need for routine laboratory monitoring measurements used for PN therapy. In general, the level of laboratory monitoring should decrease as a patient's clinical condition stabilizes.
3. Minimize the direct cost of PN by using efficient purchasing practices for PN solutions and compounding supplies through contract purchasing, streamlined compounding procedures, standardized administration times, single-bag PN solutions, and optimized monitoring plans. Some institutions may realize direct cost savings with use of standardized, commercial PN products depending on the usual daily PN census and patient population.[94,96] Others may reduce direct costs by outsourcing PN compounding to a third-party compounding pharmacy facility.

PHARMACOTHERAPY CONSIDERATIONS

10 11 Considerations for individualizing a patient's PN regimen include goals determination based on a patient-specific nutrition assessment, selection of the optimal type of available vascular access, and macronutrient and micronutrient requirements. In general, both macronutrient and micronutrient doses are age and weights based but are also affected by the patient's degree of metabolic demand, organ function, other medication therapy, exogenous losses, and acid-base status. Nutrient amounts provided by the PN may also require adjustment based on enteral intake either orally or by feeding tube in patients with recovering GI tract function.

Patient-specific caloric goals include (a) adequate energy intake to promote normal growth and development in neonates, infants, and children; (b) energy equilibrium and preservation of fat calorie stores in well-nourished adults; and (c) positive energy balance in malnourished patients with depleted endogenous fat stores. Overweight patients with a BMI above 30 kg/m^2 may require less caloric support than nonobese patients with the same clinical condition.[12] Critically ill adults may also benefit from a hypocaloric regimen.[12] Specific nitrogen goals are positive nitrogen balance or nitrogen equilibrium and improvement in the serum concentration of visceral protein markers such as transferrin or prealbumin in patients without systemic inflammation. Routine monitoring is necessary to ensure that the nutrition regimen is suitable for a given patient as the patient's clinical condition changes and to minimize or treat complications. The PN component doses usually require individualized adjustments as the patient's clinical condition affects further changes in metabolic stress, organ function, fluid and electrolyte balance, and acid-base status.

Appropriate patient selection, assessment, and monitoring are key to successful PN therapy and the prevention of unnecessary complications. Because pharmacists are actively involved in the provision of PN at many levels, including order verification, PN compounding and dispensing, direct patient care, education, and research, nutrition support is recognized as a pharmacy practice specialty.[97] In addition, as the interprofessional team-based approach to specialized nutrition support has evolved, standards of practice have been defined for pharmacists as well as for other healthcare professionals.[4,8-10] Standardized order forms and monitoring protocols are useful tools to ensure safe administration and monitoring of PN therapy. The future of PN therapy and the role of nutrition-support clinicians will be affected primarily by new insights from clinical research and economic challenges in the evolving healthcare environment.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	body mass index
CAA	crystalline amino acid
CDC	Centers for Disease Control and Prevention
CPN	central parenteral nutrition
CRBSI	catheter-related bloodstream infection
CVC	central venous catheter
EN	enteral nutrition
EFAD	essential fatty acid deficiency
FO	fish oil

FDA	Food and Drug Administration
GI	gastrointestinal
ICU	intensive care unit
ILE	lipid injectable emulsion
IV	intravenous
LCT	long-chain triglyceride
MCT	medium-chain triglyceride
NAG-AMA	Nutrition Advisory Group of the American Medical Association
NF	National Formulary
PICC	peripherally inserted central catheter
PN	parenteral nutrition
PNALD	parenteral nutrition-associated liver disease
PPN	peripheral parenteral nutrition
PUFA	polyunsaturated fatty acid
SO	soybean oil
SMOF	soybean oil, medium chain triglyceride oil, olive oil, fish oil
TNA	total nutrient admixture
USP	United States Pharmacopeia

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SELF-ASSESSMENT QUESTIONS

Questions 1 through 8 refer to the following patient case:

A 65-year-old woman was admitted to the hospital after a 3-week history of nausea, vomiting, diarrhea, and increasing abdominal girth. The initial physical examination revealed a pelvic mass, which was confirmed by a computed tomography (CT) scan. A barium enema revealed an obstruction of the sigmoid colon. The patient was subsequently taken to surgery for exploratory laparotomy at which time the patient underwent an omentectomy, a jejunal-ileal anastomosis, and CVC placement. After surgery, the patient developed hypotension and respiratory failure requiring mechanical ventilation. The patient continued to have a distended abdomen on postoperative day 9. A nasogastric tube was placed for low continuous intermittent gastric suction with approximately 600 to 800 mL/day output. The patient has no kidney or liver function laboratory abnormalities and remains hemodynamically stable requiring continuous IV norepinephrine for blood pressure support. She is receiving propofol 25 mL/hr IV for sedation. The Nutrition Support Team is consulted to begin PN. The patient's goal regimen was determined to be (final concentrations) 6% amino acids and 20% dextrose at 75 mL/hr continuous infusion with 20% lipid injectable emulsion (ILE) 250 mL/day co-infused with the PN.

Pertinent Data:

- Height: 6 ft, 1 in (185 cm)
- Admission weight: 71 kg (156.5 lb)
- Weight 2 months prior to admission: 84 kg (185 lb)
- Present weight: 74 kg (163 lb)

1. Which of the following PN regimens is the *best* to initiate for this patient?
   A. Goal estimated caloric and protein requirements beginning PN day 1
   B. 100% Dextrose calories on PN day 1 and advance protein dose over 3 to 4 days
   C. 100 to 150 g Dextrose on PN day 1 and advance by 33% of goal to the goal regimen every 1 to 2 days until goal regimen is achieved
   D. 75% to 100% calculated caloric requirements PN day 1 and cycle the infusion over 16 hours
2. What is the daily amount of protein in grams provided by this patient's goal regimen?
   A. 60 g
   B. 71 g
   C. 86 g
   D. 108 g
3. What is the daily amount of dextrose in grams provided by this patient's goal regimen?

A. 150 g

B. 242 g

C. 360 g

D. 410 g

4. What is the approximate daily amount of nitrogen in grams provided by this patient's goal regimen?

A. 12 g

B. 17 g

C. 25 g

D. 34 g

5. What volumes of 10% amino acids and 70% dextrose stock solutions are required to provide daily protein and carbohydrate amounts for the goal regimen?

A. 108 mL amino acids; 200 mL dextrose

B. 540 mL amino acids; 275 mL dextrose

C. 720 mL amino acids; 360 mL dextrose

D. 1,080 mL amino acids; 514 mL dextrose

6. What is the daily total calories (energy) provided by the patient's goal PN regimen?

A. 1,420 kcal (5941 kJ)

B. 1,820 kcal (7515 kJ)

C. 2,156 kcal (9021 kJ)

D. 2,552 kcal (10678 kJ)

7. What is the total daily amount of ILE provided by the patient's goal PN regimen?

A. 50 g

B. 60 g

C. 110 g

D. 250 g

8. Given the patient's current clinical status and therapeutic regimen, what is the *most* appropriate intervention to make at this time?

A. Reduce the PN infusion rate to 35 mL/hr

B. Discontinue the ILE

C. Reduce the amino acid concentration to 4.25%

D. Increase the dextrose concentration to 30%

9. Which statement is *true* regarding ILE when administered with a two-in-one PN formulation?

   A. Used to prevent fatty acid deficiency

   B. Usually the major source of calories in a PN regimen

   C. Should be infused as a single bag for no longer than 24 hours

   D. Cannot be administered via a peripheral vein

10. What is the rationale for cysteine addition to neonatal PN formulations?

   A. Increase pH of PN formulations

   B. Provide a conditionally essential nutrient

   C. Improve long chain fatty acid utilization

   D. Extend the beyond use date

11. Which of the following combinations of additives in a PN solution that provides 105 g amino acids and 350 g dextrose in 1,920 mL/day is *most likely* to result in an incompatibility?

   A. Sodium phosphate 40 mmol/L, calcium gluconate 5 mEq/L (2.5 mmol/L), and sodium bicarbonate 50 mEq/L (50 mmol/L)

   B. Potassium phosphate 60 mmol/day, calcium gluconate 10 mEq/day (5 mmol/day), and sodium acetate 125 mEq/day (125 mmol/day)

   C. Potassium phosphate 20 mmol/L, magnesium sulfate 8 mEq/L (4 mmol/L), and ranitidine 150 mg/day

   D. Magnesium sulfate 32 mEq/day (16 mmol/day), calcium gluconate 10 mEq/day (5 mmol/day), and cysteine 160 mg

12. What is the United States Pharmacopeia–assigned beyond use date for PN formulations?

   A. 30 hours at room temperature; 9 days refrigerated

   B. 36 hours at room temperature; 12 days refrigerated

   C. 48 hours at room temperature; 7 days refrigerated

   D. 48 hours at room temperature; 14 days refrigerated

13. Which statement is *true* regarding nutrition support in a very low birth weight premature neonate?

   A. Dextrose should be initiated at 14 mg/kg/min

   B. Protein should be initiated within the first 24 hours of life

   C. ILE should be withheld for the first day of PN support

   D. Fluid should be initiated at 50 mL/kg/day

14. A 6-week-old infant who was born at 28 weeks of gestation weighs 2 kg and has been receiving PN since birth. The infant's hospital course is significant for necrotizing enterocolitis that required an extensive small bowel resection. The infant is now 1 week post-surgery and is not receiving any enteral feedings. The morning laboratory measurements are noteworthy for a direct bilirubin concentration of 3.2 mg/dL (54.7 µmol/L) and elevated aminotransferases. All other laboratory measurements are within normal limits. PN was initiated and the regimen provides (final concentrations) 2.5% amino acids, 15% dextrose, with standard electrolytes, minerals, vitamins and trace elements infusing at 10 mL/hr continuous infusion and 20% ILE infusing at 1.3 mL/hr. Which of the following interventions is *most appropriate* regarding this infant's PN

regimen?

A. Increase dextrose to 17%; decrease ILE rate to 0.8 mL/hr

B. Increase dextrose to 20%; continue same ILE

C. Decrease dextrose to 12.5%; decrease ILE to 0.5 mL/hr

D. Continue same dextrose; increase ILE to 1.5 mL/hr

15. A product shortage of injectable cysteine has been announced and is expected to continue for at least the next 6 months. Which of the following is a rational consideration to ensure PN safety for pediatric patients requiring cysteine-supplemented PN during the shortage?

A. None, because cysteine is not usually added to pediatric PN formulations

B. All two-in-one admixtures should be converted to TNAs

C. Calcium and phosphate solubility limits must be reassessed for PNs previously formulated with cysteine

D. PN CAA doses must be increased to accommodate cysteine loss

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** According to the ASPEN Consensus Recommendations for Refeeding Syndrome (ASPEN CRRS), the patient has two diseases and clinical conditions associated with an increased risk of refeeding syndrome, cancer and postoperative patients with complications. The patient also has clinical features consistent with criteria for Significant Risk for developing refeeding syndrome. The patient's weight loss history exceeds the 7.5% in 3 months criteria (~15% weight loss over 2 months prior to admission). The patient had none or negligible oral intake for greater than 7 days, as well. ASPEN CRRS recommendations include initiating PN with 100 to 150 g of dextrose or 10 to 20 kcal/kg (42-84 kJ/kg) for the first 24 hours and advance by 33% of goal every 1 to 2 days. This includes enteral as well as other sources of parenteral dextrose such as maintenance IV fluids or medications administered in dextrose-containing IV fluids. Delaying PN initiation or advancing dextrose dose after PN initiation should be considered in patients with moderate-to-high risk of RS with low electrolyte levels until normal serum concentrations are achieved.

2. **D.** Total daily PN volume = 75 mL/hr × 24 hr = 1,800 mL or 1.8 L; amino acids 6% = 6 g/100 mL = 60 g/L; 60 g/L × 1.8 L = 108 g Protein.

3. **C.** Total daily PN volume = 75 mL/hr × 24 hr = 1,800 mL or 1.8 L; Dextrose 20% = 20 g/100 mL = 200 g/L; 200 g/L × 1.8 L = 360 g Dextrose.

4. **B.** 1 g Nitrogen = 6.25 g protein; 108 g protein ÷ 6.26 g protein/1 g nitrogen = 17.28 g nitrogen.

5. **D.** First, determine the appropriate volume of 10% CAA: 10% AA = 10 g/100 mL; 10 g/100 mL = 108 g/X mL 10% CAA; X = 1,080 mL 10% CAA; next, determine 70% dextrose volume: 70% dextrose = 70 g/100 mL; 70 g/100 mL = 360 g/X mL 70% dextrose; X = 514 mL 70% dextrose.

6. **C.** Protein calories = 108 g CAA × 4 kcal/g = 432 kcal; dextrose calories = 360 g dextrose × 3.4 kcal/g = 1,224 kcal; 20% ILE calories = 250 mL × 2 kcal/mL = 500 kcal; 2,156 kcal. Multiply values expresed in units of kcal by 4.18 for equivalent values in kJ.

7. **C.** 20% 250 mL ILE provided by PN regimen: 20 g/100 mL = X g/250 mL, X = 50 g; ILE provided by propofol: 25 mL/hr × 24 hr = 600 mL/day; propofol contains 10% ILE, 10 g/100 mL = X g/600 mL, X = 60 g; 50 g + 60 g = 110 g/day total ILE.

8. **B.** Sufficient calories and essential fatty acids are provided by the daily propofol dose, so additional ILE is not necessary and results in total daily calories that exceed estimated requirements. Distractors A and C result in a PN regimen that provides insufficient protein. Distractor D results in a PN regimen that provides excessive dextrose.

9. **A.** ILE is a source of essential fatty acids and is used as a part of PN regimens to provide calories and to prevent or treat essential fatty acid deficiency. ILE is rarely the major source of calories, particularly in critically ill patients. While some ILE products are FDA approved to provide up to 60% total calories, maintaining a weight-based dose has been recommended that usually provides less than approximately 30% to 50% total calories. ILE may be administered in its original packaging for less than 12 hours or as a part of total nutrient admixture which may infuse up to 24

hours. ILE may be administered via peripheral or central venous access device because they are isotonic solutions.

10. **B.** Cysteine is a conditionally essential nutrient in infants due to enzymatic immaturity of the trans-sulfuration pathway (eg, biosynthesis of taurine). In addition to protein supplementation to the primary parenteral protein source, the addition of cysteine to PN solutions decreases solution pH thereby improving calcium and phosphate solubility.

11. **A.** Bicarbonate salts should be avoided in PN admixtures to avoid potential for precipitation of multiple salts including calcium and magnesium.

12. **A.** According to the current USP 797 guidelines, PN admixtures are considered Medium Risk compounded sterile preparations (CSPs), which have a 30-hour beyond use date (BUD) at room temperature and 9 day BUD refrigerated.

13. **B.** When initiating PN support in neonates and infants, all macronutrients should be given on day 1 (and optimally protein should be given within the first 24 hours of life for very low birthweight premature neonates). Dextrose and ILE are advanced daily over several days to achieve goal calories. Goal protein doses should be given from day 1. Dextrose is generally started at 6 to 8 mg/kg/min and advanced by 2 to 4 mg/kg/min to a goal of 10 to 14 mg/kg/min. ILE are started at 0.5 to 1 g/kg/day and advanced by 0.5 to 1 g/kg/day to a goal of 3 g/kg/day. PN is prescribed to provide daily fluid requirements (150 mL/kg/day in premature neonates).

14. **A.** Phytosterol content of SO-based ILE have been associated with the development of PN associated liver disease (PNALD) or cholestasis. Dose reduction of SO-based ILE is a potential treatment option for PNALD. An ILE rate of 1.3 mL/hr in a 2 kg infant provides 3.1 g/kg/day which is slightly above the maximum recommended dose of 3 g/kg/day. Reducing the ILE rate to 0.8 mL/hr decreases the daily ILE dose to 1.9 g/kg/day which is an appropriate initial dose reduction. Dextrose calories should be increased to offset the reduction in calories from the ILE. An increase from 15% (12.5 mg/kg/min) to 17% dextrose (14 mg/kg/min) provides additional calories without exceeding the maximum dextrose requirements for this patient.

15. **C.** Cysteine may be added to PN solutions as a conditionally essential amino acid due to enzymatic immaturity of the trans-sulfuration pathway in neonates and infants. Cysteine also decreases PN solution pH thereby improving calcium and phosphate solubility. If cysteine is removed from a PN solution, the calcium and phosphate solubility curve must be reassessed to ensure solubility limits are not exceeded. There is no need to increase the dose of CAA when removing cysteine from PN solutions as its addition only provides a negligible amount of protein.