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Complications of Parenteral Nutrition

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CONTENTS

Objectives

Identify potential acute and long-term metabolic complications associated with parenteral nutrition (PN).

Describe the laboratory and clinical monitoring parameters required to identify metabolic complications associated with PN.

List clinically relevant metabolic complications that develop from administration of inadequate or excessive nutrients.

Develop strategies to avoid and treat metabolic complications associated with PN.

Test Your Knowledge Questions

1. Which of the following is the most common metabolic complication associated with PN?

A. Hyperglycemia
B. Essential fatty acid deficiency (EFAD)
C. Azotemia
D. Hyperammonemia

2. One day after initiating PN in a critically ill adult patient, the patient's laboratory values are as follows: serum potassium, 3.1 mEq/L (normal: 3.4–4.8 mEq/L); serum phosphorus 1.6 mg/dL (normal: 2.5–4.8 mg/dL); and serum magnesium, normal. The PN regimen is providing protein 90 g, dextrose 150 g, no lipid, minimum volume, potassium 80 mEq, phosphate 40 mmol, and standard doses of sodium, magnesium, calcium, vitamins, and trace elements. The patient weighs 60 kg and has a body mass index (BMI) of 18. The most appropriate response to these laboratory data is:

A. Increase potassium and phosphate in the PN, and decrease macronutrient doses with tonight's PN bag.
B. Provide supplemental intravenous (IV) doses of potassium and phosphate today, but do not change the macronutrient doses with tonight's PN bag.
C. Increase potassium and phosphate in the PN, and advance dextrose to 225 g with tonight's PN bag.
D. Provide supplemental IV doses of potassium and phosphate today, and advance dextrose to 225 g with tonight's PN bag.

3. Which of the following measures would be considered most beneficial in a patient who develops cholestasis while receiving long-term PN that is infused over 12 hours nightly?

A. Stop all oral and enteral intake.
B. Switch from a cyclic to continuous method of PN administration.
C. Decrease lipid injectable emulsion (ILE) dose from 1.5 g/kg/d to 1 g/kg twice weekly.
D. Increase protein dose from 1 g/kg/d to 2 g/kg/d.

4. Which of the following PN modifications is recommended to help prevent and/or treat osteoporosis in a long-term PN patient?

A. Maintain protein intake of at least 2 g/kg/d.
B. Provide more than 20 mEq calcium per day.
C. Add injectable vitamin D to the PN formulation.
D. Provide 20 to 40 mmol phosphorus per day.

Test Your Knowledge Answers

1) The correct answer is A. Hyperglycemia is the most common metabolic complication that occurs with PN. Hyperglycemia is associated with overfeeding but is also common in appropriately fed patients, where it is attributed to insulin suppression and resistance as well as gluconeogenesis from stress and infection. Nondiabetic hospitalized patients receiving IV dextrose infusions at rates greater than 4 mg/kg/min have a 50% chance of developing hyperglycemia.1 EFAD is associated with fat-free PN and can be avoided by administering minimal amounts of ILE. Azotemia is usually associated with renal or hepatic dysfunction or protein overfeeding. Hyperammonemia rarely occurs now that crystalline amino acids are used in PN.
2) The correct answer is B. Management and prevention of refeeding syndrome and refeeding hypophosphatemia involve (1) identifying patients at risk, (2) serum electrolyte monitoring with aggressive replacement, and (3) slowly increasing energy intake.2–5 In this critically ill patient who experiences hypophosphatemia and hypokalemia after the initiation of PN, the electrolyte abnormalities should be treated quickly with supplemental, IV replacement doses. Energy intake from PN should not be advanced until the electrolyte deficiencies are corrected.
3) The correct answer is C. Cholestasis has been associated with ILE doses greater than 1 g/kg/d in adult patients receiving long-term PN,6 and the patient may therefore benefit from a trial of lowering the ILE dose. Cyclic infusion has been shown to reduce serum liver enzyme and conjugated bilirubin concentrations when compared with continuous infusion.7 Enteral feeding should be attempted to promote enterohepatic circulation of bile acids. The protein dose does not seem to play a role in the development of cholestasis in adults.
4) The correct answer is D. An inadequate phosphorus dose may increase urinary calcium excretion; therefore, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends that phosphorus doses of 20 to 40 mmol/d be added to the PN formulation.8 Although patients receiving PN are vulnerable to a negative calcium balance, calcium supplementation in the PN formulation is limited by calcium's physical compatibility with phosphorus, and higher calcium doses are offset by higher urinary losses. ASPEN recommends that calcium gluconate 10 to 15 mEq/d be added to the PN formulation.8 High protein doses (2 g/kg/d vs 1 g/kg/d) in PN formulations have been associated with increased urinary calcium excretion in adult patients. Excessive vitamin D doses can be detrimental to the bone because they can suppress parathyroid hormone (PTH) and promote bone resorption, and individual forms of parenteral ergocalciferol or cholecalciferol are not available.

Background

Parenteral nutrition–associated complications can be categorized as mechanical, metabolic, and infectious. Metabolic complications are more commonly associated with PN rather than enteral nutrition. Therefore, patients receiving PN require close monitoring for prevention and early detection of complications. Mechanical complications related to the venous access device and infectious complications are discussed in Chapter 16. This chapter focuses on the recognition, prevention, and treatment of metabolic complications associated with PN in the adult patient. Refer to Table 17-1 for an overview of monitoring recommendations to identify or prevent such complications.

TABLE 17-1 Monitoring to Identify/Prevent Metabolic Complications in Patients Receiving Parenteral Nutrition

	Frequency of Monitoring	
Parameter	**Initiation of Therapy (Acute Care)**	**Long-Term Therapy**
Capillary glucose	Every 6 hours until patient is advanced to PN goal and as needed to maintain glucose level of 140–180 mg/dL	Not routine; done on as-needed basis to coordinate with PN infusion cycle
Basic metabolic panel, phosphorus, magnesium	Daily, until patient is advanced to PN goal and stable; then 1–2 times/wk	Weekly; then decrease frequency in stable patients
CBC (with differential)	Baseline; then 1–2 times/week	Monthly; then decrease frequency in stable patients
Liver function: ALT, AST, ALP, total bilirubin, INR	Baseline; then weekly	Monthly; then decrease frequency in stable patients
Serum triglycerides	Baseline if patient is at risk for hypertriglyceridemia; then as needed	Not routine; done on as-needed basis
Iron studies, 25-hydroxyvitamin D	Not routine	Baseline; then every 3–6 months
Zinc, copper, selenium, manganese	Not routine	Baseline; then every 6 months
Weight	Daily	Daily
Total fluid intake/output	Daily until stable; then as needed	As-needed basis

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; INR, international normalized ratio; PN, parenteral nutrition.

Macronutrient-Related Complications

Hyperglycemia

Hyperglycemia is the most common complication associated with PN administration and can be caused by various factors. Stress-associated hyperglycemia in acutely ill and septic patients often develops as a result of insulin resistance, increased gluconeogenesis and glycogenolysis, and suppressed insulin secretion.1 Excess carbohydrate administration has been associated with hyperglycemia, hepatic steatosis, and increased carbon dioxide production. ASPEN recommends target blood glucose concentrations between 140 to 180 mg/dL in adult hospitalized patients receiving nutrition support.9

Similarly, the Society of Critical Care Medicine (SCCM) recommends blood glucose concentrations be maintained between 150 to 180 mg/dL for the general intensive care unit (ICU) population.10 PN should be initiated at half of the estimated energy needs, or approximately 150 to 200 g dextrose, for the first 24 hours. Delivery of less dextrose (approximately 100 g) may be warranted if the patient has a low BMI or poor glucose control. Carbohydrate administration should not exceed a rate of 4 to 5 mg/kg/min or 20 to 25 kcal/kg/d in acutely ill patients.11

Blood glucose concentrations can be controlled with insulin therapy, which may be administered subcutaneously, intravenously via an insulin infusion, or directly in the PN solution. Capillary blood glucose concentrations should be monitored every 6 to 8 hours in patients receiving short-acting subcutaneous insulin and more frequently in critically ill patients receiving insulin infusion therapy. An initial insulin regimen of 0.05 to 0.1 units per gram of dextrose in the PN solution is common, or 0.15 to 0.2 units per gram of dextrose may be used in patients who are already hyperglycemic. Supplemental short-acting or rapid-acting insulin may be administered subcutaneously if needed, using a sliding scale regimen. Two-thirds of the total amount of sliding scale insulin required over 24 hours may then be added to the next day's PN formulation. Only regular insulin should be added to the PN formulation. When administering repeat doses of insulin, clinicians must take into account the duration of action of the insulin formulation previously provided before administering the next dose. Giving the subsequent dose too soon is referred to as "stacking" insulin and can result in hypoglycemia.

The dextrose dose in the PN formulation should not be advanced until the patient's blood glucose concentrations are controlled. The insulin dose should be proportionally increased and decreased with respect to the PN dextrose dose. Alternatively, an insulin infusion may be instituted to provide consistent and safe glucose control. A proportional increase in fat content or frequency may be necessary to increase energy from PN.

Rarely, hyperglycemia may be related to chromium deficiency. Insulin is less effective in patients with chromium deficiency. Increasing the chromium dose in the PN formulation beyond the standard amount in commercially prepared multiple trace element injections may be necessary.12,13

Hyperglycemia is associated with worsened clinical outcomes, such as increased risk of infection, poor wound healing, and inability to gain weight. Uncontrolled hyperglycemia may result in hyperosmolar hyperglycemia, nonketotic dehydration, coma, and death secondary to osmotic diuresis.14 Refer to Chapter 34 for additional information on hyperglycemia and the administration of insulin.

Hypoglycemia

PN-associated hypoglycemia can occur from excess insulin administration via the PN solution, IV infusion, or subcutaneous injection. Excessive or erroneous administration of insulin is a severe medication error, and resulting hypoglycemia may be life-threatening. Treatment includes initiation of a 10% dextrose infusion, administration of an ampule of 50% dextrose, and/or stopping any source of insulin administration. Treatment with oral carbohydrate, such as glucose gel or chewable tablets, can be considered for management of mild hypoglycemia in suitable patients who are likely to tolerate it.

Abrupt discontinuation of PN solutions has been associated with rebound hypoglycemia.15 Studies have not reported symptomatic hypoglycemia after abruptly stopping PN infusions given over 16 to 24 hours.16,17 However, some patients had asymptomatic hypoglycemia.

Patients requiring large doses of insulin have a greater propensity for rebound hypoglycemia, but predicting which patients will experience rebound hypoglycemia is difficult. Therefore, to reduce the risk of rebound hypoglycemia in susceptible patients, a 1- to 2-hour taper down of the infusion, or half the infusion rate, may be necessary. If a PN solution must be discontinued quickly, a dextrose-containing fluid should be infused for 1 or 2 hours following PN discontinuation to avoid a possible rebound hypoglycemia. Obtaining a capillary blood glucose concentration 30 minutes to 1 hour after the PN solution is discontinued will help identify rebound hypoglycemia. See Chapter 34 for additional discussion of this topic.

Essential Fatty Acid Deficiency

ILE is generally provided as a source of essential fatty acids and as a nonprotein energy source (see Chapters 5 and 15). Depending on the length of the PN therapy and the nutrition status of the patient, ILE-free PN may result in EFAD. Two polyunsaturated fatty acids, linoleic and α-linolenic, cannot be synthesized by the body and are considered essential. Clinical manifestations of EFAD include scaly dermatitis, alopecia, hepatomegaly, thrombocytopenia, fatty liver, and anemia.18 A triene:tetraene ratio of more than 0.2 indicates EFAD and can occur within 1 to 3 weeks in adults receiving ILE-free PN.19 The adult requirements for linoleic acid are met through exogenous sources or endogenously through the lipolysis of adipose tissue. However, when hypertonic dextrose is infused, insulin is secreted and lipolysis is reduced. Thus, an exogenous source of fat must be provided.

To prevent EFAD, 1% to 2% of daily energy requirements should be derived from linoleic acid and about 0.5% of energy from linolenic acid.8 This goal translates to approximately 250 mL of 20% or 500 mL of 10% soy-based ILE administered over 8 to 10 hours, twice a week. Alternatively, 500 mL of a 20% soy-based ILE can be given once a week. When using an alternative oil–based ILE, such as those containing medium-chain triglycerides, olive oil, and fish oil, a greater amount of ILE is required to meet essential fatty acid requirements because these non-soy-based products contain lower quantities of linoleic and linolenic acid. In patients who do not tolerate ILE, a trial of topical skin application or oral ingestion of oils may be given to alleviate biochemical EFAD.20,21

Immunosuppression

Soy-based ILEs have been associated with immunosuppressive effects, reticuloendothelial system dysfunction, and exaggerated systemic inflammatory response. The 18-carbon ω-6 fatty acid preparation (ie, linoleic acid) has been postulated to suppress the immune response by activating the arachidonic pathway. Evidence suggest that certain long-chain fatty acids may impair immune function by interfering with phagocytosis and chemotaxis and may increase the patient's risk of infection. The alternative oil–based ILEs now available in the United States have demonstrated fewer proinflammatory and immunosuppressive properties compared with soy-based ILEs (see Chapter 5). Although alternative

oil–based products are safe and effective, further research is necessary to determine which patient populations and medical conditions will benefit from them.22

Withholding or limiting soy-based ILE in critically ill patients for the first week of PN has been suggested as a strategy to reduce immunosuppression complications. The 2016 ASPEN and SCCM guidelines for nutrition support therapy in the adult critically ill patient support this recommendation; however, ASPEN and SCCM gave the quality of evidence a very low rating.23 The recommendation is primarily based on research from one study involving trauma patients receiving fat-free PN over the first 10 days of hospitalization.24 The study reported that the elimination of ILE from the PN improved clinical outcomes (eg, decreased infectious morbidity, decreased hospitalization, shortened ICU length of stay, and shortened duration of mechanical ventilation). However, the study is more than 20 years old and has not been duplicated. Also, it has been criticized, in part because the goals for energy delivery in the study were based on nonprotein calories (not total calories). Consequently, the total amount of energy delivered was greater than reported, and overfeeding may have contributed to the complications associated with the PN with ILE.23,24

Hypertriglyceridemia

Hypertriglyceridemia can occur with dextrose overfeeding or with rapid administration rates of ILE (greater than 0.11 g/kg/h).8 Hyperlipidemia may impair immune response, alter pulmonary hemodynamics, and increase the risk of pancreatitis.25,26 Reducing the dose and/or lengthening the infusion time of ILE will help minimize these effects. ILE intake should be restricted to less than 30% of total energy, or 1 g/kg/d; also, if ILE is administered separately, it should be provided slowly over at least 8 to 10 hours.25 Serum triglyceride concentrations should be checked prior to ILE administration in any patient with a known history of hyperlipidemia or risk of hypertriglyceridemia. ASPEN recommends that serum triglyceride concentrations greater than 400 mg/dL be avoided when infusing ILE, and clinicians should reduce the ILE dose or discontinue ILE if this level of hypertriglyceridemia occurs.8 The dose of ILE should also be reduced or discontinued in mechanically ventilated patients receiving propofol for sedation because propofol is supplied as a 10% ILE.

Pancreatitis due to ILE-induced hyperlipidemia is rare unless serum triglyceride concentrations exceed 1000 mg/dL. ILE is considered safe for use in patients with pancreatitis without hypertriglyceridemia.27 See Chapter 28 for further discussion of pancreatitis.

Adverse Reactions to Lipid Injectable Emulsions

Although the incidence of complications associated with ILE use is low, potential complications include allergic or infusion-related adverse reactions. Allergic reactions to ILE are rare, but they can occur, especially in patients with history of egg allergy. The allergic reaction is most likely a result of the egg phospholipid that is used as an emulsifier. Other acute, infusion-related adverse reactions associated with ILE include dyspnea, cyanosis, flushing, sweating, dizziness, headache, back or chest pain, nausea, and vomiting.

Azotemia

When protein administration is excessive, the metabolic demand of disposing of the byproducts of protein metabolism increases. Prerenal azotemia can result from dehydration, excess protein, and/or inadequate energy from nonprotein sources (eg, in patients with anorexia nervosa). Intolerance to the protein load is exhibited by an increase in blood urea nitrogen. Patients with hepatic or renal disease are prone to developing azotemia because their ability to metabolize and eliminate urea is impaired. When urea clearance is impaired, patients may require dialysis to help eliminate urea and allow for the adequate intake of protein.

Hyperammonemia was a greater risk when protein hydrolysates contained excessive amounts of ammonia and insufficient arginine for urea cycle metabolism. This complication has become a rare occurrence since the advent of crystalline amino acid solutions, although it has been observed with the new crystalline amino acid solutions in patients with urea cycle defects, such as ornithine transcarbamylase deficiency.28,29

Patients who develop prerenal azotemia may benefit from a reduction in the amount of amino acids provided. Protein restriction in patients in liver failure with hyperammonemia and encephalopathy has not been demonstrated to improve outcomes and thus is discouraged. In patients with hepatic failure and hepatic encephalopathy, the use of high branched-chain, low aromatic amino acid formulations has provided inconsistent results and is not recommended (see Chapter 27 for discussion of the appropriate use of specialized amino acid formulations in liver disease). Protein should not be restricted in critically ill patients with acute kidney injury receiving continuous renal replacement therapy or hemodialysis, especially in the setting of malnutrition (see Chapter 29 for more information on acute kidney injury).

Micronutrient-Related Complications

Fluid and Electrolytes

Once macronutrient tolerance has been established, the routine management of the patient receiving PN centers on fluid and electrolytes (see Chapter 7). The requirements vary depending on the patient's renal, fluid, and electrolyte status when starting PN, as well as the underlying disease process and any losses he or she may incur.30,31 To identify necessary adjustments in the PN solution composition and volume, clinicians must routinely monitor patients for fluid and electrolyte shifts between the intracellular and extracellular space or changes in total body water or electrolyte status.

When determining the patient's fluid and electrolyte status, clinicians also need to evaluate concurrent IV fluids and medications provided during PN therapy. All fluids being infused should be considered when the PN formulation is prescribed. If the patient has excessive losses, fluid and electrolyte replacement with separate IV fluids outside of the PN formulation may be necessary. Treatment involves replacing the lost fluids with IV fluid of similar electrolyte composition. Accurate intake and output records are necessary to show the amount of loss from various body fluids. See Chapter 7 for a complete review of fluid and electrolytes and Practice Scenario 17-1 for a discussion of metabolic monitoring during PN.

Practice Scenario 17-1

Question: What parameters should be monitored, and with what frequency, to help identify and prevent metabolic complications in a patient initiating parenteral nutrition (PN)?

Scenario: A 52-year-old woman, postoperative Day 7, presents with a small bowel obstruction. She has elevated gastric residual volumes, abdominal distention, and hypoactive bowel sounds. She is 165 cm in height and weighs 63 kg, with no muscle or adipose tissue wasting or signs of edema noted. Serum laboratory values include the following: albumin, 3.7 g/dL; prealbumin, 16 mg/dL; sodium, 139 mmol/L; potassium, 3.9 mmol/L; chlorine, 101 mmol/L; carbon dioxide, 25 mmol/L; blood urea nitrogen, 10 mg/dL; creatinine, 0.7 mg/dL; glucose, 112 mg/dL; ionized calcium, 4.7 mg/dL; phosphate, 3.3 mg/dL; and magnesium, 1.9 mg/dL. Vital signs include heart rate, 74 bpm; blood pressure, 118/70 mm Hg; input, 2400 mL/d; and output, 2370 mL/d.

Intervention: The patient's maintenance intravenous fluid is discontinued, and PN is initiated.

Answer: Before PN is initiated, the nutrition support team should evaluate the patient's vital signs, intake/output, and physical examination data to determine her fluid status, and a complete metabolic panel as well as phosphate, and magnesium levels should be obtained and assessed. If electrolytes, specifically potassium, phosphate, and magnesium, are depleted, they should be repleted before PN is administered. After PN is initiated, electrolytes should be evaluated daily until levels are stable, in part to assess for potential refeeding syndrome. PN may be administered slowly and titrated to goal over a period of days to prevent hyperglycemia. Glucose levels should be monitored at least every 6 hours until the patient is euglycemic. If insulin is administered, more frequent glucose monitoring may be necessary because the patient is at increased risk for hypoglycemia. Prealbumin can be evaluated initially and serially during PN administration. Below-normal prealbumin can be a useful indicator of inflammatory metabolism, and normal levels can indicate that normal postprandial metabolism and anabolism are possible (see Chapter 9 for further discussion).

Rationale: Initial presentation of the patient does not suggest any additional concerns beyond the standard considerations of fluid status, electrolytes, and glucose levels. Her electrolytes are within normal values, her vital signs and fluid status are appropriate, and she has no signs of wasting. The complication of hyperglycemia must be considered when PN is initiated. Additionally, until she is stable, daily electrolyte monitoring is necessary.

Vitamins

Vitamins are essential for effective nutrient utilization, and a sustained exogenous intake of vitamins is essential to avoid deficiency (see Chapter 8). However, excessive amounts of lipid-soluble vitamins A, D, E, and K can be toxic. Provision of adequate vitamin intake in the PN patient may be complicated by conditions that increase requirements, such as sepsis, trauma, or recovery following surgery. Identifying vitamin deficiency or toxicity can be difficult because serum vitamin concentrations do not always

directly correlate with body stores and clinical symptoms are often nonspecific. Therefore, adult patients receiving PN should receive a standard daily dose of parenteral multivitamins.32 Clinicians should not delay IV multivitamin therapy until a patient develops clinical signs of vitamin deficiency and must take measures to address product shortages.

Certain clinical situations warrant special attention. Patients receiving both PN and warfarin therapy require close monitoring because the vitamin K (150 mcg) included in the 13-vitamin preparation interacts with warfarin and can result in therapeutic failure. Patients with a history of prolonged poor dietary intake or alcohol abuse are at risk for developing thiamin deficiency, especially with initiation of carbohydrate. Acute thiamin deficiency can result in alterations in mental status and peripheral nervous system dysfunction (ie, Wernicke's encephalopathy). Several cases of lactic acidosis due to thiamin deficiency, including 3 deaths, were reported in patients receiving PN without thiamin during a period of parenteral multivitamin shortage.33 Supplemental thiamin (50 to 100 mg/d) and folic acid (1 mg/d) beyond what is provided in the parenteral multivitamin preparation for the initial 5 to 7 days of PN therapy has been recommended in patients with a history of prolonged poor dietary intake.34

Vitamin toxicity, particularly of the fat-soluble vitamins, is a potential complication of PN. Vitamin A toxicity has been reported in patients with chronic renal failure receiving PN, and some clinicians have recommended reducing the frequency of fat-soluble vitamin administration to twice per week in these patients. However, because there are no injectable multivitamin preparations available without fat-soluble vitamins, water-soluble vitamin deficiency is a risk with restricted dosing. Furthermore, because some water-soluble vitamins may be lost with hemodialysis, provision of water-soluble vitamins to patients receiving dialysis has been recommended.35 An oral vitamin B complex supplement or individual parenteral vitamin B supplementation, as available, can be used to address this recommendation.

Several vitamins are known to undergo substantial degradation after addition to the PN formulation. This issue is not considered a significant problem in the acute care setting because of the relatively short time period between compounding and administration. However, because PN formulations are compounded in a batch fashion for patients in the home setting, degradation is a risk with these solutions. Vitamin A degradation was clearly demonstrated in a home PN patient who developed night blindness within 6 months of receiving PN that was prepared on a weekly basis with the vitamins added to the PN formulation by the pharmacy before delivery.36 Although the patient's night blindness resolved after a therapeutic dose of vitamin A, the source of the problem was not identified until symptoms returned 6 months later. Substantial amounts of vitamin A were likely lost to degradation and adsorption to the plastic matrix of the bag because the vitamins were added to the PN formulation up to a week before administration. To avoid this problem, the patient or caregiver must perform the task of adding vitamins to the PN formulation prior to administration in the home setting.8 Home nutrition support is further discussed in Chapter 38.

Interruptions in parenteral multivitamin product supply have been an ongoing issue in the United States and could possibly harm patients if not appropriately managed (see Chapter 15). ASPEN offers the following advice to help clinicians cope with parenteral multivitamin product shortages:37

- Reserve a supply of IV multivitamins for those patients receiving solely PN.
- Use oral or enterally administered multivitamins whenever possible.
- To ensure fair allocation of products nationwide, do not stockpile parenteral multivitamins.
- Do not use pediatric IV multivitamins for adult patients.
- When all options to obtain IV multivitamins have been exhausted, ration use by reducing the dose by 50% or giving 1 dose 3 times a week.
- If IV multivitamins are no longer available, administer individual thiamin, ascorbic acid, pyridoxine, and folic acid daily.

Trace Elements

Trace element deficiencies are relatively uncommon in patients receiving PN, but they can occur when intake is insufficient or utilization or excretion is increased over a prolonged period. For example, a patient with high intestinal losses may become zinc deficient. Cardiomyopathy caused by selenium deficiency has been reported in patients receiving long-term PN without selenium supplementation.38,39 Trace element toxicity is also a potential complication in patients receiving long-term PN and those with hepatobiliary disease. Available parenteral multi–trace element preparations may exceed actual requirements in many patients receiving PN.40 In addition, many of the components of the PN formulation may be contaminated with trace elements such as zinc, copper, manganese, chromium, selenium, and aluminum.41 Tissue elevations of copper, manganese, and chromium have been noted on autopsy in patients receiving long-term PN.42 Although serum trace element monitoring is recommended at baseline and routine follow-up in patients receiving long-term PN, serum levels are unreliable measures of total body balance.43 Empiric adjustments in trace element intake may be warranted. Clinicians should consider reducing manganese and copper dosing in patients with hepatobiliary disease because the disease impairs excretion. Removal of supplemental manganese from the PN formulation and reduction in the copper dose are often necessary in long-term PN patients to minimize the risk for toxicity.

Interruptions in the supply of IV multi–trace element and individual trace element products have resulted in shortage situations in the United States. To address parenteral multi–trace element shortages, ASPEN suggests rationing the supply by reducing doses by half, limiting the frequency of administration to 3 times a week, and using the oral/enteral route when feasible. Withholding multi–trace element products for the first month of PN therapy from newly initiated adult patients who are not critically ill and do not have preexisting deficits could also be considered. If a multi–trace element supply is no longer available, individual trace element components should be given parenterally, as available, or otherwise provided by the oral/enteral route.44

Iron is not a component of the PN formulation, primarily because of compatibility limitations. Parenteral iron supplementation at repletion doses is warranted in conditions of iron deficiency when the oral route is ineffective or not tolerated and can be provided as an infusion separate from the PN formulation. Delivery of parenteral iron to replete iron stores to patients receiving PN may be provided

on an as-needed basis as determined by routine monitoring of iron status.45,46 See Chapters 8 and 15 for more information about trace elements in PN.

Refeeding Syndrome

Refeeding syndrome refers to the adverse effects of metabolic and physiological shifts of fluid, electrolytes, vitamins, and minerals (eg, phosphorus, magnesium, potassium, thiamin) that can occur as a result of aggressive nutrition support or nutrition repletion of a malnourished patient; it is a risk during the first 2 to 5 days after the start of nutrition support.47 In periods of prolonged starvation, the body adapts by deriving energy from fat (ketone production), reducing energy expenditure, decreasing insulin secretion, and utilizing intracellular minerals and electrolytes. With the reintroduction of carbohydrate during nutrition repletion, glucose again becomes the primary fuel source. Insulin release is stimulated and results in enhanced update of glucose, electrolytes, minerals, and water into cells. The carbohydrate administration increases the demand for intracellular phosphorus to synthesize adenosine triphosphate, resulting in a further depletion of phosphorus. Additionally, carbohydrate administration results in an increased need for thiamin, potassium, and magnesium. These resulting electrolyte and vitamin deficits cause symptoms of neuromuscular, cardiovascular, and respiratory compromise. Moreover, fluid and sodium from the nutrition delivery further burdens the compromised organs, resulting in fluid overload and edema. Because these deleterious effects are the result of aggressively feeding a malnourished or starved patient, energy and fluid should be initiated and advanced slowly and electrolytes and vitamins administered as aggressively as necessary in at-risk patients (see Practice Scenario 17-2).47–50

Practice Scenario 17-2

Question: How can the complications of refeeding syndrome be minimized when providing parenteral nutrition (PN) to a nutritionally depleted patient?

Scenario: A 54-year-old man with a history of gastric cancer is status post partial gastrectomy and small bowel resection. His nasogastric output is 1250 mL/d with absent bowel sounds. A kidney, ureter, and bladder x-ray is consistent with a small bowel ileus. The patient's height is 180 cm and he weighs 66 kg (body mass index: 20). His usual body weight was 75 kg, and he shows signs of moderate wasting of lean muscle and adipose stores as well as slight edema postsurgery. His prealbumin is 10 mg/dL and his albumin is 3.1 g/dL.

Intervention: Intravenous fluids are tapered as PN is initiated on postoperative Day 8.

Answer: The nutrition support team should start nutrition slowly by providing half of the goal energy requirements, or approximately 15 kcal/kg/d, on the first day of PN. The first bag should contain about 1000 kcal. Recommendations differ with regard to initial protein dosing. Since the effect of protein on glycolysis is not as concerning as dextrose, starting at the goal protein dose (1.2 to 1.5 g/kg/d) is recommended.47 Dextrose and fat should comprise the rest of the formulation, although dextrose should not exceed approximately 200 g/d. Nutrition should be slowly increased to the full nutrition goal

over the next 2 to 5 days, based on the patient's tolerance. Clinicians should monitor electrolytes daily, paying close attention to sodium, potassium, phosphorous, and magnesium. Daily intake and output, as well as the patient's weight, must be assessed. Vitamins and trace elements should be administered daily.

Rationale: The patient is at risk for refeeding syndrome complications because he is severely malnourished; his lean muscle and adipose stores are moderately wasted, and he has experienced significant weight loss. He should be monitored closely for electrolyte abnormalities and volume overload. The monitoring parameters suggested in Table 17-1 can help identify and prevent metabolic complications when initiating PN therapy.

The term refeeding hypophosphatemia has been used to describe decreased serum phosphorus concentrations after the initiation of nutrition in patients who do not have the other metabolic abnormalities associated with refeeding syndrome.50 Hypophosphatemia may also result from other causes, including cellular phosphate redistribution, poor phosphate intake, or renal tubular phosphate loss. Even without the other complications associated with refeeding syndrome, hypophosphatemia is concerning, and phosphorus should be replaced as needed; however, labeling the complication refeeding syndrome is arguably not necessary.48–51

Hepatobiliary Complications

Disorders of the liver and biliary system are commonly reported in patients receiving PN. These complications may be life-threatening and are particularly concerning in patients who depend on long-term PN support. We do not yet fully understand how PN influences the development of liver disease. Historically, it was thought that some existing component of the PN formulation or a nutrient not provided by the PN formulation caused the liver disease. However, that simplistic concept has been replaced. Today, we recognize that liver dysfunction can result from a complex set of risk factors that affect patients receiving PN, such as the primary risk factor of intestinal failure. The term PN-induced liver disease has therefore been replaced with the interchangeable terms PN-associated liver disease (PNALD)52 and intestinal failure–associated liver disease53 to refer to hepatic dysfunction secondary to intestinal failure that occurs in the setting of PN.

Types of Hepatobiliary Disorders

The types of hepatobiliary disorders associated with PN in adult patients are usually different from those seen in pediatric patients, although age-related distinctions become less evident in patients receiving long-term PN. The 3 types of hepatobiliary disorders associated with PN therapy are steatosis, cholestasis, and gallbladder sludge/stones; these disorders may coexist.54 Steatosis (hepatic fat accumulation) is more common in adults than in pediatric patients and is generally benign. It typically presents as modest elevations of serum aminotransferase concentrations that occur within 2 weeks of PN therapy, and concentrations may return to normal even when PN is continued. Most patients are asymptomatic. Steatosis seems to be a complication of overfeeding and has probably decreased in

prevalence over the years as estimates of PN energy requirements have been lowered. Although steatosis is generally thought to be a nonprogressive lesion, it may progress to fibrosis or cirrhosis in patients receiving long-term PN.6

PN-associated cholestasis (PNAC) is a condition of impaired secretion of bile or frank biliary obstruction that occurs predominantly in children, but it may also occur in adult patients receiving long-term PN. PNAC typically presents as elevated alkaline phosphatase, γ-glutamyl transpeptidase, and conjugated (direct) bilirubin concentrations with or without jaundice. Although both γ-glutamyl transpeptidase and alkaline phosphatase are sensitive markers for hepatobiliary disease, they lack specificity because levels may be elevated in other diseases as well. An elevated serum conjugated bilirubin (eg, greater than 2 mg/dL) is considered the prime indicator for cholestasis. PNAC is a serious complication because it may progress to cirrhosis and liver failure.

Gallbladder stasis during PN therapy may lead to the development of gallstones or gallbladder sludge with subsequent cholecystitis. This complication is related more to the lack of enteral stimulation than the PN infusion itself. The lack of oral intake results in decreased cholecystokinin (CCK) release and impaired bile flow and gallbladder contractility. The duration of PN therapy seems to correlate with the development of biliary sludge.55 Biliary sludge may progress to acute cholecystitis in the absence of gallstones. This condition is also referred to as acalculous cholecystitis.

Prevalence

Prevalence rates of PNALD vary greatly. In adult patients receiving PN, the reported incidence of abnormal enzyme elevations ranges from 25% to 100%.54 However, few studies have correlated enzyme changes to permanent hepatic function or histological damage. The risk for and severity of liver disease seem to increase as the duration of PN usage lengthens. The prevalence of chronic cholestasis in a group of 90 patients receiving home PN for permanent intestinal failure was 55% at 2 years, 64% at 4 years, and 72% at 6 years.6

Many studies evaluating the prevalence of PNALD have also attempted to identify risk factors unrelated to the PN therapy. Bacterial and fungal infections are associated with cholestasis. Sepsis likely causes liver inflammation because of the release of proinflammatory cytokines that are activated by endotoxins. This point is especially relevant in the long-term PN patient, who may experience recurrent central line–associated bloodstream infections. Many patients receiving PN have disorders that predispose them to small intestinal bacterial overgrowth (SIBO), which is another risk factor for liver disease. SIBO occurs when large amounts of bacteria normally confined to the colon and lower small bowel populate the upper small intestine (see Chapter 26). It has been postulated that these anaerobic bacteria in the small intestine may produce hepatotoxins. Massive intestinal resection has also been identified as a risk factor for PNALD.6,56 A small bowel remnant less than 50 cm in length has been significantly associated with chronic cholestasis.6

Parenteral Nutrition–Related Risk Factors

Although supporting data are limited, various factors related to the nutrient composition of the PN formulation could contribute to the development of liver complications. Therefore, it is important to evaluate the merits of these potential risk factors to design a PN formulation that minimizes risk of PNALD.

Energy

Clinical studies suggest that the development of steatosis during PN administration is primarily related to excessive energy intake.42 Overfeeding in general or an excess of individual energy substrates (carbohydrate, fat, protein) can contribute to liver complications. The administration of excessive energy is thought to promote hepatic fat deposition by stimulating insulin release, which, in turn, promotes lipogenesis and inhibits fatty acid oxidation.54

Carbohydrate

Dextrose-based PN regimens that contain little or no fat have been implicated in the development of steatosis. Excess carbohydrates deposit in the liver as fat, and a dextrose-based PN regimen may result in EFAD, which may lead to impaired lipoprotein formation and triglyceride secretion, resulting in steatosis. Providing balanced amounts of energy from dextrose and fat seems to decrease the incidence of steatosis, possibly by decreasing hepatic triglyceride uptake and promoting fatty acid oxidation.54 A balanced PN formulation should provide 70% to 85% of nonprotein energy as carbohydrate and 15% to 30% as fat.8 In addition, the carbohydrate content of PN should not exceed 7 g/kg/d in adults.8

Protein

Early sources of amino acids for parenteral use included protein hydrolysates contaminated with significant amounts of aluminum. Animal studies suggest that high levels of aluminum exposure may lead to the development of cholestasis. The replacement of protein hydrolysates with crystalline amino acids has significantly reduced the overall aluminum contamination in PN formulations. Amino acid–associated aluminum toxicity is no longer considered a risk factor for the development of liver complications.57 Although the role that amino acids play in the development of cholestasis in adults is unclear, it does not seem to be as significant as the role they play in cholestasis in infants.

Lipid Injectable Emulsion

The role of ILE in the development of liver complications may involve the fat source, the phytosterol content, or the dose. The most commonly used ILE in the United States is soybean oil–based and contains high concentrations of ω-6 fatty acids and significant amounts of phytosterols. Phytosterols are inefficiently metabolized to bile acids by the liver, and it has been postulated that they may impair bile flow and cause biliary sludge and stones. Adult patients with short bowel syndrome (SBS) receiving ILE-containing PN have been shown to have much higher serum phytosterol levels than other patients with SBS or healthy controls.58 Case reports of children with PN-related cholestasis have documented high serum phytosterol levels.59 In addition, the high ω-6 fatty acid content of soybean-based ILE may

potentially initiate or worsen inflammatory states and can have immunosuppressive effects.60 The presence of phytosterols and proinflammatory ω-6 fatty acids may contribute to the hepatotoxic effects seen in patients receiving long-term PN with a soybean oil–based ILE. The use of a fish oil–based ILE, primarily composed of ω-3 fatty acids and containing no phytosterols, has shown promising results in reversing PNALD in pediatric patients when used in place of soybean oil–based ILE.61,62 Further study evaluating the safety and efficacy of fish oil–based ILE for the prevention and treatment of PNALD is needed before its use can be recommended.22,63,64 A newer-generation ILE product containing a combination of soybean, medium-chain triglyceride, olive, and fish oils has recently become available (see Chapters 5 and 15). Compared with soybean oil alone, it offers a shift in the ω-6:ω-3 ratio toward an anti-inflammatory effect, which, theoretically, may reduce the risk for PNALD or provide a treatment option for patients with PNALD. However, further study is required to investigate these hypotheses.64,65

The ILE dose is another concern when evaluating PN options. Although liver complications have been associated with EFAD, they can also occur when the ILE dose is excessive. Steatosis can occur when the ILE infusion rate exceeds the liver's ability to clear the phospholipids and fatty acids, leading to direct deposition in the liver. Cholestasis may also be associated with high ILE doses, especially with long-term use. Multivariate analysis demonstrated that chronic cholestasis and severe PNALD were strongly associated with ILE intake greater than 1 g/kg/d in patients receiving long-term PN.6 The results demonstrated no association between dextrose intake or nonprotein energy intake and PNALD.

Carnitine

Carnitine plays an important role in fat metabolism (see Chapters 5 and 15). Primary carnitine deficiency has been associated with the development of steatosis. Because carnitine is not routinely added to PN, a patient's plasma carnitine concentrations may decrease below the reference range within a few weeks of starting PN therapy. Carnitine supplementation has been shown to help mobilize hepatic fat stores and prevent steatosis in neonates receiving PN.59 However, low serum carnitine concentrations do not necessarily correlate with hepatic dysfunction in adults. Bowyer and colleagues studied carnitine supplementation in adult patients receiving home PN who had abnormal serum liver enzymes and low serum carnitine concentrations. The investigators found no improvement in liver enzymes after carnitine was supplemented for 1 month, despite normalization of serum carnitine concentrations.66 The role of carnitine in the prevention and treatment of PN-associated liver complications in adults remains to be established.

Choline

Choline is essential for normal function of all cells and required for lipid transport and metabolism. This nutrient is found in many foods, but it is not a component of PN formulations because it is assumed that endogenous synthesis is possible from methionine contained in the crystalline amino acid solution. However, the conversion of methionine to choline may be less efficient when methionine is given parenterally than when given orally.67 Low plasma-free choline concentrations have been reported in patients receiving long-term PN and have been associated with elevated serum hepatic

aminotransferase concentrations.68 Steatosis resolved following choline supplementation in a small group of adult patients receiving long-term PN but did not resolve in a control group.69

At present, an injectable choline preparation is not commercially available. ASPEN recommends that a commercially available parenteral choline product be developed for routine addition to adult and PN formulas, either as an individual product or incorporated into a multivitamin product.40

Strategies to Manage Parenteral Nutrition–Associated Hepatobiliary Complications

When a patient receiving PN develops liver complications, clinicians should review all aspects of care to identify and eliminate or treat the various contributing factors. Table 17-1 provides monitoring parameters, and Table 17-2 outlines strategies to consider when a patient receiving PN develops liver complications. See Practice Scenario 17-3 for a discussion of management of cholestasis in an adult patient on long-term PN.

TABLE 17-2 Strategies to Manage Parenteral Nutrition–Associated Liver Complications

- Rule out non-PN etiologies for liver problems, such as hepatotoxic medications, herbal supplements, biliary obstruction, hepatitis, and sepsis.
- Consider PN modifications:

– Decreasing dextrose.

– Decreasing ILE (<1g/kg/d).

– Providing a balance of dextrose and ILE.

– Cyclic PN infusion.

- Maximize enteral intake:

– Encourage oral diet.

– Tube feeding, even at slow rate.

- Prevent/treat bacterial overgrowth:

– Use enteral antibiotics, such as metronidazole, neomycin, doxycycline, ciprofloxacin, or rifaximin.

– In CIPO patients, consider agents to enhance motility, such as metoclopramide or erythromycin.

- Pharmacotherapy:

– Aggressively treat infection.

– Prescribe ursodeoxycholic acid (ursodiol).

– Treat pruritus with cholestyramine, rifampin, or phenobarbital.

- Consider intestinal transplantation for patients with PN failure.

CIPO, chronic intestinal pseudo-obstruction; ILE, lipid injectable emulsion; PN, parenteral nutrition.

Practice Scenario 17-3

Question: How can a parenteral nutrition (PN) formulation be modified to minimize and manage the development of cholestasis in an adult patient requiring long-term PN?

Scenario: A 72-year-old woman with a history of ovarian cancer and short bowel syndrome due to intestinal ischemia presents to the intestinal failure clinic for home PN management after receiving home PN for the past year. She has approximately 120 cm of small bowel remaining with an end jejunostomy. A recent liver biopsy shows cholestasis and steatosis, and laboratory studies show elevated levels of serum transaminase, alkaline phosphatase, and conjugated/direct bilirubin (8 mg/dL). The patient is eating a regular diet and empties the ostomy appliance 10 times daily. Her weight is 50 kg and has been stable; her body mass index is 18.9. The home PN regimen provides protein 60 g, dextrose 250 g, and lipid 50 g; standard amounts of electrolytes, vitamins, and trace elements; and a volume of 2500 mL cycled over 15 hours nightly through a single-lumen tunneled catheter.

Intervention: The frequency of lipid injectable emulsion (ILE) is reduced from daily to twice weekly, and the amount of dextrose is increased proportionally to account for the decrease in energy from lipid. A trial of stopping ILE for 1 to 2 weeks could also be considered. The infusion cycle is shortened from 15 to 12 hours. Trace element levels are obtained, and supplemental copper and manganese are removed from the PN formulation.

Answer: Because the patient's weight is stable and the PN formulation provides 32 kcal/kg/d, neither the amount of dextrose nor the overall energy dose from PN seems excessive. Although the dose of ILE does not exceed 1 g/kg/d, a trial to decrease the dose/frequency may be beneficial. Infusing PN over a cyclic period rather than a continuous, 24-hour infusion rate may reduce risk for PN-associated liver disease (PNALD). The impact of changing the PN cycle from 15 to 12 hours may be minimal, but all efforts to minimize risk are warranted as long as the patient tolerates the changes. Finally, the dose of copper and manganese should be reduced or eliminated and levels monitored in this patient because her excretion of these elements is impaired.

Rationale: The PN formulation should be reviewed whenever liver complications develop. Although the PN therapy may not be implicated as the cause of the complication, it may contribute to or exacerbate the problem. Overfeeding should be avoided, and a trial of a lower-energy regimen may be warranted. Infection has been identified as a risk factor for development of PNALD; therefore, efforts to minimize the risk of infection are especially crucial. In the long-term patient who develops cholestasis, limiting the ILE dose may be beneficial.

Oral and Enteral Nutrition

Oral and enteral nutrition should be optimized whenever feasible in the patient on long-term PN because even small amounts of dietary or enteral intake may promote enterohepatic circulation of bile acids. Oral nutrition is generally preferable to tube feeding, for obvious reasons, but tube feeding may offer certain advantages in select patients. For example, patients with chronic intestinal pseudo-obstruction who depend on PN and require gastric decompression may tolerate jejunal feeding at a slow rate during a portion of the day or night. These patients may need medications to enhance motility, and multiple trials may be required before they achieve feeding tolerance. During periods of acute illness, enteral tolerance may be more difficult to achieve, and setbacks can be expected; however, clinicians should attempt to restart enteral feeding as soon as possible once the patient's condition has stabilized.

Patients with SBS should be encouraged to maximize oral intake because at least some of their intake will be absorbed. Depending on the severity of the SBS, a reduction in energy from PN may be necessary to prevent unwanted weight gain. However, the patient's fluid requirements generally remain high because stool output tends to increase when oral intake increases. See Chapter 30 for further discussion of nutrition support for patients with SBS.

Cyclic Infusion

Cyclic PN infusion refers to the infusion of a PN formulation over a period of less than 24 hours (generally 8 to 12 hours). This type of regimen gives the patient time off PN. Continuous PN infusion can result in hyperinsulinemia and fat deposition in the liver, thereby potentially increasing the risk of liver complications. Cyclic PN infusion has been shown to reduce serum liver enzyme and conjugated bilirubin concentrations when compared with continuous PN infusion.7 Allowing time off PN each day may reduce the risk of PNALD, especially in patients who depend on long-term PN.

Pharmacotherapeutic Options

In addition to enteral intake, medications can be used to help stimulate bile flow and maintain gallbladder contractility. Ursodiol (ursodeoxycholic acid) is a form of bile acid widely used to treat various chronic cholestatic liver diseases, and it has been shown to improve biochemical markers of cholestasis. When given orally at therapeutic doses, it becomes the predominant biliary bile acid and is thought to displace potentially hepatotoxic bile salts. Data about using ursodiol to treat PNAC are limited. The medication may improve biochemical markers and symptoms of pruritis,70 but there is no evidence that the progression of disease is delayed. No IV form of ursodiol is available; therefore, the use of ursodiol is limited to patients who can absorb oral medications.

CCK-octapeptide is a synthetic fragment of CCK that produces the biologic activities of CCK. It is available in an injectable form, but there is not enough evidence to support its use in the prevention or treatment of PNAC.

Phenobarbital has been used to relieve pruritus in patients with cholestasis and treat other types of cholestatic liver disease. However, evidence supporting its use to treat PNAC is lacking.

Transplantation

In the long-term PN patient with significant or progressive liver disease, an isolated intestinal or combined liver/intestinal transplant may be the only treatment option.71,72 The Centers for Medicare and Medicaid Services (CMS) have approved reimbursement of intestinal transplantation for patients with intestinal failure who fail PN therapy. One of the CMS criteria to define PN failure is the development of impending or overt liver failure. The choice of an isolated small bowel transplantation vs a combined small bowel and liver transplantation depends on the extent of liver disease. Although many patients can stop PN after an intestinal transplantation, other life-threatening complications and quality-of-life issues must be considered before deciding on this intervention (see Chapter 31).

Metabolic Bone Disease

Osteoporosis and osteomalacia are associated with long-term PN use. Osteoporosis is the most common form of metabolic bone disease and is characterized by low bone mass, compromised bone strength, and deterioration of bone tissue and architecture.73 It is a silent disease until it is complicated by fractures. According to World Health Organization criteria, the diagnosis of osteoporosis is based on a bone mineral density measurement that is more than 2.5 standard deviations below the mean score for young-adult, ethnicity- and sex-matched controls. It is reported as a T-score below –2.5. A T-score that ranges between –1 and –2.5 is considered low bone mass (osteopenia).

Osteomalacia is characterized as softening and bending of the bones that occurs because the bones contain osteoid tissue that has failed to calcify. This problem is generally caused by vitamin D deficiency. The diagnosis of osteomalacia requires a bone biopsy for histologic examination of bone tissue. Therefore, this condition is difficult to identify. Some patients may have a combination of osteoporosis and osteomalacia.

Prevalence

The prevalence of PN-associated metabolic bone disease is unknown, but compromised bone health is of concern in all patients requiring long-term PN. Pironi and colleagues reported osteoporosis in 41% of patients after at least 6 months of home PN,74 and Cohen-Solal and associates identified osteoporosis in 67% of patients on long-term PN because of intestinal failure.75 Many diseases, conditions, and medications increase the risk for bone loss (Table 17-3). Because almost all patients receiving long-term PN manifest at least 1 of these risk factors, it is unclear whether PN itself contributes to accelerated bone loss. In a follow-up study in a relatively large patient group receiving long-term PN according to more current protocols, participants had moderate bone loss that was not statistically different from bone loss in age- and sex-matched, healthy subjects.76

TABLE 17-3 Risk factors for Bone Loss

Postmenopausal osteoporosis

Long-term parenteral nutrition

Endocrine disease:

- Cushing's syndrome
- Hypogonadism
- Amenorrhea
- Hyperthyroidism
- Hyperparathyroidism

Gastrointestinal disease:

- Crohn's disease
- Short bowel syndrome
- Malabsorption

Malignancy:

- Multiple myeloma
- Leukemia

Medications:

- Corticosteroids
- Heparin
- Warfarin
- Levothyroxine overreplacement
- Phenytoin
- Phenobarbital
- Leuprolide
- Methotrexate

Genetic disease:

- Osteogenesis imperfecta

Immobilization:

- Spinal cord injury
- Prolonged bed rest

Other:

- Alcohol abuse
- Anorexia nervosa
- Roux-en-Y gastric bypass

Parenteral Nutrition–Related Factors

Various factors related to the nutrient composition of the PN formulation could potentially interfere with bone metabolism.77,78 Therefore, the PN formulation should be designed to minimize the risk for bone problems.

Calcium

Calcium plays a vital role in maintaining bone integrity by decreasing bone turnover and slowing bone loss. Patients receiving PN are at risk for negative calcium balance because of limited intake and increased urinary calcium loss. Calcium supplementation in the PN formulation is limited by the mineral's physical compatibility with phosphorus, and there seems to be a threshold for calcium uptake when given parenterally. Higher calcium doses provided in the PN formulation are offset by higher urinary calcium losses. Therefore, ASPEN recommends daily intake of 10 to 15 mEq calcium gluconate from the PN formulation.8

An inadequate phosphorus dose may increase urinary calcium excretion. Phosphorus seems to enhance calcium reabsorption by the renal tubules and thereby promote a positive calcium balance. The ASPEN recommendation for intake of phosphorus from the PN formulation is 20 to 40 mmol/d.8

Higher protein doses (2 g/kg/d vs 1 g/kg/d) in PN formulations have been associated with increased urinary calcium excretion. For this reason, reducing protein intake to maintenance doses whenever possible has been recommended.77,79

Chronic metabolic acidosis is associated with hypercalciuria and metabolic bone disease.80 Correction of the acidosis with acetate in the PN formulation can reduce urinary calcium excretion; therefore, adequate acetate amounts should be added to the PN formulation to avoid metabolic acidosis.77

Finally, cyclic PN infusion results in higher urinary calcium losses when compared with continuous infusion.81 However, this potential disadvantage associated with cyclic infusion should be weighed against its potential benefits to the liver and quality of life in long-term PN patients.

Vitamin D

Data regarding vitamin D requirements in patients receiving PN are controversial. Both vitamin D deficiency and vitamin D toxicity can result in bone disease. The adult multivitamin preparation used for PN formulations contains 200 IU of vitamin D (ergocalciferol or cholecalciferol). Vitamin D can be detrimental to the bone when excessive doses are given because it can suppress PTH secretion and directly promote bone resorption. There are reports that short-term removal of vitamin D from the PN

formulation resulted in decreased hypercalciuria and an improvement in osteomalacia, although the results may have been influenced by the presence of significant aluminum contamination. In 9 patients receiving long-term PN who had low serum PTH and low 1,25-hydroxyvitamin D, long-term (average of 4.5 years) removal of vitamin D resulted in normal PTH and 1,25-hydroxyvitamin D concentrations and improved bone mineral density of the spine.82 Although vitamin D removal may benefit certain patients, such as those with a low serum PTH concentration, it is impractical because there are no commercially available injectable multivitamin preparations without vitamin D. Certainly, excessive supplementation of vitamin D should be avoided.

Vitamin D status should be monitored to identify deficiency states, which can result in bone disease and poor mineralization. The prevalence of vitamin D deficiency is higher in patients with intestinal malabsorption syndromes than in the general population.83,84 It is reasonable to provide PN patients with the maintenance vitamin D dose contained in the injectable multivitamin preparation. However, when supplemental doses of vitamin D are required to treat deficiency, the oral route is required because individual parenteral ergocalciferol or cholecalciferol products are not commercially available.

Aluminum

Osteomalacia was associated with PN formulations that contained significant aluminum contamination from protein hydrolysates. A low-turnover bone disease and decreased bone formation were described in patients with elevated plasma, urine, and bone aluminum concentrations. Aluminum contamination of PN formulations is significantly lower now that crystalline amino acids have replaced protein hydrolysates. However, aluminum contamination is still a concern and has prompted the US Food and Drug Administration (FDA) to establish labeling requirements. Manufacturers of large-volume parenteral products, small-volume parenteral products, and pharmacy bulk packages used in PN compounding are required to measure the aluminum content of the product and disclose the concentration on the label.85 Large-volume parenteral products, including amino acid and concentrated dextrose solutions, ILE, and sterile water for injection, are required to contain no more than 25 mcg aluminum per liter. The FDA does not limit the aluminum content in small-volume parenteral products (ie, electrolyte salts) and pharmacy bulk packages (ie, parenteral multivitamins and trace element solutions), but manufacturers are required to state the maximum aluminum level at expiry in the product labeling.

Magnesium

Hypocalcemia is a prominent manifestation of magnesium deficiency. Magnesium deficiency results in decreased mobilization of calcium from bone through several mechanisms. Hypomagnesemia causes an increased release of magnesium ions at the bone surface in exchange for increased bone uptake of calcium ions from the serum. In addition, chronic severe hypomagnesemia inhibits PTH release, resulting in inappropriately low PTH levels for the degree of hypocalcemia. The response of bone to PTH can also be diminished, resulting in functional hypoparathyroidism. Hypomagnesemic hypocalcemia should be treated with magnesium supplementation because it is often refractory to calcium therapy alone. Magnesium deficiency can also lead to hypophosphatemia because of increased phosphorus excretion.

Copper

Copper deficiency impairs bone formation and can cause osteoporosis (see Chapter 8). Bone disease has been reported in infants receiving a copper-free PN formulation.78

Prevention and Management

Because most patients with osteoporosis are asymptomatic, a screening process is important to identify patients at risk. Clinicians should perform a thorough history, physical examination, and laboratory assessment to identify risk factors. Patients receiving long-term PN may lose height because of compression fractures of the vertebral bodies. A baseline dual-energy x-ray absorptiometry scan is recommended for all patients who require long-term PN therapy. In addition to routine laboratory monitoring, patients with low bone mineral density may require further diagnostic testing, including measurement of thyroid-stimulating hormone, intact PTH, 25-hydoxyvitamin D, 24-hour urine calcium and magnesium, urine markers of bone turnover (such as N-telopeptide collagen), and serum markers of bone turnover (such as osteocalcin and C-telopeptide collagen).

Strategies to prevent and treat osteoporosis should be considered in all patients who require long-term PN therapy, as outlined in Table 17-4. The PN formulation should be designed to minimize hypercalciuria; provide adequate magnesium, calcium, and phosphorus; avoid metabolic acidosis; provide vitamins and trace elements; and minimize aluminum contamination.71 Individual products with the lowest-reported maximal aluminum content should be used in PN compounding whenever possible; for example, sodium phosphate is preferable to potassium phosphate.86 Patients with osteoporosis should be educated on lifestyle modifications, low-intensity exercises, and fall prevention measures to minimize risk. Medications that improve bone mineral density and decrease fracture risk in patients with osteoporosis may also be used to prevent or treat osteoporosis. Medications that decrease bone resorption include bisphosphonates, raloxifene (a selective estrogen-receptor modulator), calcitonin, estrogen, and the monoclonal antibody denosumab. Teriparatide is the only FDA-approved medication that stimulates bone formation.74

TABLE 17-4 Strategies to Prevent and Treat Osteoporosis in Patients Receiving Long-Term Parenteral Nutrition

Strategy	Considerations
PN modifications	• Avoid high doses of protein. • Avoid excessive doses of sodium. • Calcium: 10 to 15 mEq/d. • Phosphorus: 20 to 40 mmol/d. • Treat metabolic acidosis. • Maintain adequate magnesium intake. • Maintain adequate copper intake. • Minimize aluminum contamination. • Avoid adding heparin.
Lifestyle modifications	• Weight-bearing exercises. • Stop smoking. • Reduce caffeine intake. • Reduce alcohol intake.
Fall prevention measures	• Increase safety of home. • Discontinue medications that may increase risk of falls, if possible.
Calcium	• Consider oral supplementation.
Vitamin D	• Consider oral supplementation, if patient has vitamin D deficiency.
Pharmacological treatment	• Perform a comprehensive risk assessment after the initial treatment period. • Do not consider any pharmacotherapy to be indefinite in duration. • Individualize treatment decisions. • Avoid oral route for bisphosphonate therapy due to malabsorption and tolerance issues in PN patients. • Consider endocrinology referral for management.

PN, parenteral nutrition.

Summary

A thorough monitoring plan is required to identify and prevent short- and long-term metabolic complications in all patients receiving PN. Refeeding syndrome and hyperglycemia are significant risks in patients receiving PN in the acute care setting. In patients receiving long-term PN, potential complications include micronutrient abnormalities, hepatobiliary problems, and metabolic bone disease. Even though the PN itself may not be the sole cause of these complications, efforts to minimize contributing risk factors from the PN formula should be taken.