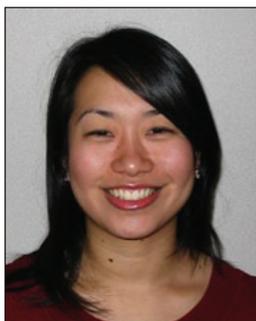


Carol Rees Parrish, R.D., M.S., Series Editor

Liver Dysfunction Associated with Parenteral Nutrition: What Are the Options?



Vanessa Lee

Although parenteral nutrition (PN) may be a life-saving therapy for patients who cannot support their nutritional needs via the enteral route, it poses significant complications in the form of PN-associated liver dysfunction. Clinical and pathologic presentations include steatosis, steatohepatitis, cholestasis, cholelithiasis and decompensated liver disease. It is often difficult to separate direct PN-related hepatic injury from the other liver toxic factors that complicate the course of PN-reliant patients. Presentation of liver dysfunction differs between adults and infants; steatosis is the most common complication of adults, whereas cholestasis occurs frequently with children. Since there is no definitive therapy, the prevention and treatment of PN-associated liver dysfunction requires a multifaceted approach.

Discerning an optimal treatment plan for PN-associated liver dysfunction is complicated by the multitude of therapy options and often varied, non-standardized original treatment studies. The purpose of this comprehensive review is to aid in the development of a treatment plan for PN-associated liver dysfunction in adult patients.

INTRODUCTION

Patients who cannot support their nutritional needs via the enteral route due to intestinal failure often require parenteral nutrition (PN). Prolonged PN

may be necessary in patients suffering from a variety of gastrointestinal motility, malabsorptive, or metabolic disorders (1). As the number of patients relying on prolonged PN support increases, associations between PN and an array of hepatobiliary complications emerge. There are differing categories of PN-associated liver dysfunction affecting infants and adults (Table 1). Cholestatic syndromes occur more

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frequently with children, whereas steatosis and steatohepatitis complications are noted more commonly with adults. Both age groups will suffer complications of biliary sludge and cholelithiasis (2).

The mechanisms of liver dysfunction and its relation to PN are poorly understood. Due to differences in liver pathology and pathophysiology, extrapolating pediatric research to the adult population, and alternatively adult research to infant care, is controversial (2,3). Many possible causes for PN-associated liver dysfunction have been proposed, however guidelines for clinical management are not clearly defined in the literature. The purpose of this review is to develop a prevention and treatment plan for liver complications associated with PN in the adult population based on current evidence to date.

PN-ASSOCIATED HEPATIC DYSFUNCTION IN ADULTS

As many as 22% of long-term PN patient deaths are related to PN-related liver failure (4). PN-related liver dysfunction in adults is primarily diagnosed by elevated liver bilirubin and enzymes. Rarely do studies include liver biopsy and histological evaluation. The incidence of abnormal liver enzymes varies from 25% to 100%. Incidence data differ from studies with populations suffering from inflammatory bowel disease, cancer, sepsis, and others (2,5).

The content of PN has evolved over the last 20 years thus making disease incidence difficult to evaluate. For example, alterations in total calorie content, addition of certain amino acids, and the introduction of lipid emulsion infusions may have significantly changed the presentation of liver disease. The evaluation of hepatic injury from PN is also a difficult task due to the inconsistency of data from diverse patient populations and the evolution of PN content (1,5-7).

The diagnosis of liver dysfunction in association with PN is often a diagnosis by exclusion. Many of the patients who require PN will already have hepatic complications from their underlying diseases. It is paramount to first differentiate liver dysfunction consequent to primary medical problems, mechanical obstructions, or metabolic disorders. Liver enzyme elevations usually peak within one to four weeks of

Table 1
Hepatobiliary Disorders Reported in Patients on PN

Adults

- *Steatosis*
- *Steatohepatitis*
- Cholestasis
- Fibrosis
- Micronodular cirrhosis
- Phospholipidosis
- *Biliary sludge*
- *Cholelithiasis and its complications*
- Acalculous cholecystitis

Infants

- *Cholestasis*
- Fibrosis
- Cirrhosis
- Hepatocellular carcinoma
- Biliary Sludge
- *Abdominal pseudotumor (distended gallbladder)*
- Cholelithiasis and its complications

NOTE: The more common disorders are italicized

Quigley EMM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology*, 1993; 104: 286-301.

initiation of PN (7). Markers of liver dysfunction include gamma glutamyl transpeptidase, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase. Elevated levels of bilirubin are less common (8).

Steatosis is the most common histologic liver abnormality. Histological evaluation reveals periportal fat accumulation that extends into a panlobular or centrilobular distribution in more severe cases (6,8,9). Abnormal intracellular fat droplets within Kupffer cells form even without significant alterations in hepatic function (10). Other presentations of disease include intrahepatic cholestasis, steatohepatitis, and varying degrees of fibrosis including cirrhosis (Table 1). Fatty infiltration appears to be the predominant early hepatic histological finding that will progress to signs of persistent intrahepatic cholestasis and periportal inflammation in PN courses greater than three weeks (9).

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In a long-term histologic study, Bowyer, et al followed 60 patients on PN over an average of 29 months (11). Nine patients (15%) had persistent hepatic laboratory abnormalities. Liver biopsies revealed eight patients with steatohepatitis, three patients with centrilobular fibrosis, three patients with cholestasis, and one patient with early nodular regeneration. The range of liver pathology further highlights the difficulty in classifying and understanding this disease process.

PN-ASSOCIATED DISORDERS OF THE GALLBLADDER AND BILIARY TREE

In addition to intrahepatic dysfunction, extrahepatic cholelithiasis and biliary sludge develop in proportion to duration of PN therapy. Messing, et al noted biliary sludge via ultrasound in 6% of patients by three weeks, and an increase to 50% within four to six weeks of PN usage (12). With PN durations greater than six weeks, 100% of patients had biliary sludge. Eventually six of 14 patients had courses complicated by cholelithiasis.

Potential therapies for managing PN-associated cholelithiasis focus on stimulating biliary flow and avoiding gallbladder stasis. Current proposed therapies include the introduction of enteral feedings, use of ursodeoxycholic acid (UDCA), administration of exogenous cholecystokinin (CCK), and prophylactic cholecystectomy.

PREDISPOSING FACTORS

Several predisposing factors have been associated with a higher incidence of PN-associated liver disease. Unfortunately, incidence data have been difficult to interpret due to the inherent disease processes of the studied populations.

Short bowel syndrome, especially in cases with small bowel length less than 50 cm, increases the risk of PN-associated liver disease and cholestasis (4,13,14). It is unclear whether it is the loss of bowel alone or the combination with PN-use that predisposes patients to developing hepatic cholestasis and fibrosis (14). This may be related to interruption of the enterohepatic circulation with subsequent abnormal bile acid metabolism (2).

When comparing rates of PN-associated cholestasis, Nanji and Anderson observed a higher rate of

cholestasis in patients with hematologic malignancy (87%) compared to those with inflammatory bowel disease (56%) (15). It is uncertain why patients with hematologic malignancies would be more predisposed to hepatic dysfunction. Underlying disease processes or chemotherapy toxicities may contribute to these results.

Several studies suggest that the duration of PN dependence correlates with the frequency of liver complications (4). With PN duration greater than six weeks, the majority of patients develop biliary sludge (12). A study of 90 patients with no previous liver disease noted that 55% of patients developed chronic cholestasis within two years (4). At two years of PN dependence, 26% had complicated liver disease as defined by extensive portal fibrosis, cirrhosis, hyperbilirubinemia with jaundice, ascites, and liver failure. These numbers increased to 50% at six years.

CAUSES

PN-associated liver disease presents in a wide spectrum from steatosis and hepatosteatorosis to intrahepatic cholestasis and extrahepatic cholelithiasis. Clinical and animal studies suggest that PN-related hepatic steatosis is primarily related to the effects of excess caloric intake, usually in the form of dextrose or glucose, and impaired hepatic secretion of triglycerides. Increased hepatic fat deposition may begin with infusions of highly concentrated glucose and amino acids stimulating increased insulin secretion. Subsequent hyperinsulinemia promotes lipogenesis and synthesis of acylglycerol from glucose while inhibiting mitochondrial carnitine acyltransferase, which is a rate-limiting enzyme in fatty acid oxidation. In rats, step-wise increases of hepatic lipid accumulation were noted when given increasing caloric amounts of PN (16,17). Mismatched carbohydrate:nitrogen ratios, such as in high-fat and low-protein solution, and inadequate amino acids may also play a role by impairing lipoprotein synthesis and triglyceride secretion (18). Essential fatty acid-poor PN infusion or secondary specific amino acid deficiencies may cause essential fatty acid deficiencies that contribute to hepatic steatosis (Table 2).

Intrahepatic cholestasis is the predominant presentation of PN-related liver disease in children and

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infants. However in adults, biliary dysfunction more often takes the form of cholelithiasis and gallbladder disease. Although there is significant research within the pediatric literature investigating PN-associated intrahepatic cholestasis, it is beyond the scope of this review. Certainly there may be some disease processes that correlate between adult and pediatric populations, but further studies are needed to elucidate those points.

Sheldon, et al noted that abnormal liver biopsies were significant for steatosis within five days of beginning PN (9). In subsequent biopsies, progression to cholestasis and periportal inflammation was the common finding. The pathogenesis of PN-associated cholestasis is poorly understood. Many different hypotheses have been proposed including the duration of PN, continuous rather than cyclic PN infusions, septic episodes, ileal disease and other contributing disease processes. Several studies suggest an association between inflammatory bowel disease (19), short bowel syndrome (14), and hematologic malignancies (15) with PN-associated cholestasis.

Fouin-Fortunet, et al suggested that lithocholate plays a toxic role in cholestasis after they noted elevated biliary lithocholic acid in their PN-reliant patients suffering from inflammatory bowel disease without previous bowel resections (5). Lithocholic acid is a hepatotoxic secondary bile acid formed by bacterial conjugation within the small intestines. Elevated lithocholic acid has been shown to impair bile flow and induce intrahepatic cholestasis, biliary duct hyperplasia and gallstone formation. Increased lithocholic production may also be related to intestinal stasis which promotes small bowel bacterial colonization from colonic bacteria (20).

PN has been implicated in the development of gut mucosal atrophy and decreased immunity (21). As a result, overgrowth of anaerobic intestinal bacteria may encourage further production of lithocholic acid and release of hepatoxins in the form of endotoxins (5).

TREATMENT

No single pathway has been elucidated as the primary etiology of this disease process. Given the multiple hypotheses, one may infer that it may be the combination of multiple factors that subsequently predisposes a patient to

developing PN-associated liver dysfunction. Many recommendations have emerged in the prevention and treatment of PN-associated liver disease. These recommendations represent varying opinions on the mechanism and progression of this disease. Comparing studies and treatment options is difficult due to the variability of patient demographics, definitions of disease, and primary endpoints from study to study. Recommendations include altering PN cycles, adding macronutrient supplementation, treating small bowel bacterial overgrowth, and considering prophylactic cholecystectomy (Table 3).

Liver function abnormalities are often the first sign of PN-associated liver dysfunction. If PN is discontinued, serum laboratory abnormalities usually resolve within one to four months (9). In some studies, liver dysfunction resolves on its own despite continuing PN (19,22). Despite these trends, using PN for the shortest possible duration is the best route to prevent hepatic complications. Unfortunately in many patients, long-term PN is unavoidable.

Avoidance of Excessive Caloric Administration

Excess caloric administration, from either dextrose or lipid sources, has been implicated in the development of hepatic steatosis. In cases of dextrose overfeeding, the excess dextrose causes hyperinsulinemia, which then enhances glucose conversion to fat within the liver (23). Gramlich and Bistrain recommend hypocaloric feedings (glucose calories infused < resting energy expenditure) and avoidance of dextrose cycling to prevent hyperinsulinemia (24). When evaluating 90 patients on home PN, Cavicchi, et al noted increased incidence of liver dysfunction in patients with longer duration of PN and those with dextrose infusions greater than 4 g/kg/day (4).

Whether from combined or separate macronutrients, excessive calories are linked to PN-associated liver complications (25). PN caloric intake greater than 80% of basal energy expenditure (BEE) is associated with a higher incidence of liver disease and chronic cholestasis (4). Burstyne and Jensen recommend limiting PN calories to $1.3 \times$ BEE or less to avoid hepatic complications (26).

Schloerb and Henning reported that a quarter of surveyed academic centers used a high glucose infu-

Table 2
Adult Patient Factors and Parenteral Nutrition-Related Effects Proposed to Contribute to the Pathophysiology of Hepatobiliary Dysfunction on Parenteral Nutrition

<i>Complication</i>	<i>Patient Factors</i>	<i>PN Effects</i>	
		<i>Major</i>	<i>Minor/controversial</i>
Steatosis	Starvation Protein-calorie malnutrition Glucose intolerance	Calorie excess Carbohydrate excess Carbohydrate-nitrogen imbalance	Essential fatty acid deficiency Carnitine deficiency Impaired drug oxidation Absence of dietary "protective factor" L-glutamine deficiency Lipid excess
Cholestasis	Loss of enteric stimulation Sepsis Ileal disease or resection Short bowel syndrome Malignant disease Bacterial overgrowth Lithocholate toxicity	Duration of PN	Low energy-to-nitrogen ratio Continuous administration Bacterial translocation L-glutamine deficiency Copper in PN solution Lipid content Lithocholate toxicity
Gallbladder disease and gallstones	Fasting → loss of enteric stimuli → gallbladder stasis and impaired bile flow	Decreased bile flow	Altered bile composition

Adapted from Quigley EMM, Marsh MN, Shaffer JL, Markin RS. Hepatobiliary complications of total parenteral nutrition. *Gastroenterology*. 1993; 104: 286-301.

sion rate of 4.5 mg/kg/min, which produced a respiratory quotient (RQ) greater than 1.0 (27). A RQ greater than 1.0 is associated with significant net lipogenesis. The benefit of providing extra calories may not outweigh the risks of hypercaloric complications. Their final recommendation included limiting glucose infusion rates to less than 4 mg/kg/min and PN formulation of a maximum of 15% dextrose calories.

Rapid lipid infusion boluses were first suggested as a means to stimulate bile flow and reduce the risk of gallstones. Subsequent evaluation failed to show that rapid lipid infusions would be beneficial. There is some evidence that rapid lipid infusions of long chain triglycerides may impair immune function, increase the incidence of bacteremia, and even worsen cirrhosis and intrapulmonary shunting (1,24).

In spite of this data, lipid emulsion infusions should not be avoided and its exclusion in PN is detri-

mental. Zagara and Locati noted that of patients who received only dextrose-based PN, 53% patients developed steatosis (28). In comparison, 17% of patients developed steatosis while receiving a lipid-dextrose PN infusion (at a 30:70 ratio).

Addition of Lipid Emulsion Infusion

Essential fatty acid deficiencies likely contribute to the development of hepatic steatosis and cholestasis in patients on long-term PN. Richardson, et al used fat-free PN to induce essential fatty acid deficiency within six to eight weeks in four adults (29). Interestingly, two of the four patients experienced elevations in liver enzymes, AST and ALT, which resolved with linoleic acid supplementation.

Essential fatty acid deficiencies are avoided with the use of lipid emulsions in addition to PN. A mini-

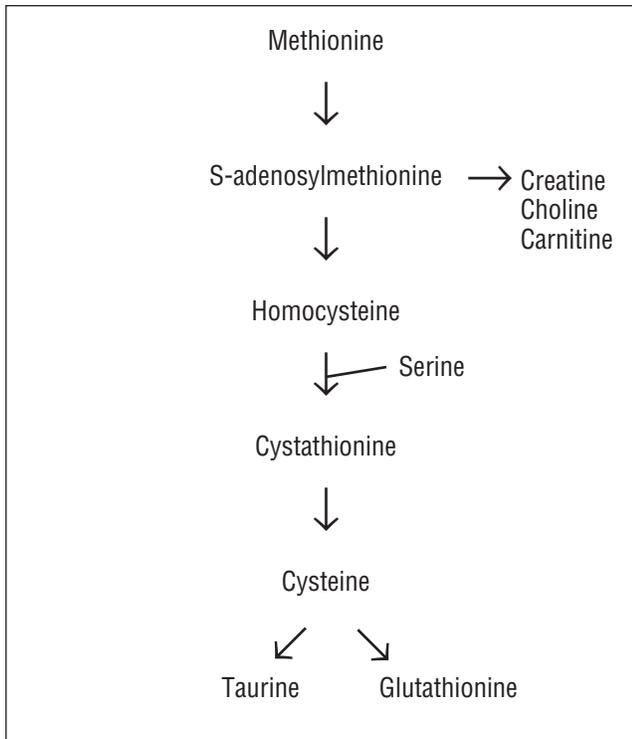


Figure 1. Transsulfuration pathway. Adapted from Chawla RK, Berry CJ, Kutner MH, Rudman D. Plasma concentrations of transsulfuration pathway products during nasoenteral and intravenous hyperalimentation of malnourished patients. *Am J Clin Nutr.* 1985;42:578.

mum of 0.5–1.0 g/kg/day of lipids (as 4%–8% daily calories) must be administered to provide sufficient linoleic acid (29). Supplementation in the form of 7.5 g intravenous or 12.6 g linoleic acid oral, such as safflower oil, has been suggested for patients receiving fat-free PN (29,30). However, to ensure efficacy of this form of supplementation, monitoring of 20:3 to 20:4 (triene:tetraene ratio) to be sure absorption is sufficient to correct the deficiency state would be beneficial (when the ratio rises above 0.1, a diagnosis of EFA deficiency can be supported).

A note of caution, excessive PN lipids may contribute to liver dysfunction and cholestasis. There is some evidence that lipid emulsions themselves cause decreased biliary flow, steatosis, and impaired endotoxin clearance from the liver (29). One report noted elevations in bilirubin and alkaline phosphatase with low dextrose PN containing increased lipid dosages of

3 g/kg/day (dextrose contributing only 22% of calories) (31). Hepatic microvacuolar steatosis and phospholipidosis have been noted in patients receiving long-term 20% lipid emulsions high in omega-6 polyunsaturated fatty acids and low in omega-3 polyunsaturated fatty acids (29). This suggests that long chain triglycerides play a key role in liver dysfunction, possibly overloading the liver and causing it to be more susceptible to infection and cholestatic injury (4). Although evidence is limited, emulsions using medium chain triglycerides lead to less long chain triglyceride deposition and may help prevent liver damage (23,32).

Limiting lipid intake to 1 g/kg/day does not significantly contribute to liver dysfunction (33). This value was validated in a prospective cohort study of 90 patients on prolonged PN in which lipid intake greater than 1 g/kg/day was strongly associated with liver disease and cholestasis (4).

Avoidance of Amino Acid Deficiencies

In the past, protein hydrolysate solutions were associated with liver dysfunction. Currently, crystalline amino acid solutions are used instead. Methionine is an important precursor to creatine, choline, carnitine, cysteine, taurine, and glutathione, and is usually the only sulfur-containing amino acid in most PN solutions (Figure 1). As a result, investigations into amino acid deficiencies have focused on pathways involving hepatic transsulfuration. Deficiencies in taurine, cysteine, choline, lecithin, and glutathione have been implicated as contributing factors in PN-associated liver dysfunction (25). Multiple biochemical pathways interlink these related amino acids, some of which are involved in bile salt conjugation and synthesis of low density lipoproteins which are required to transport fat from the liver (26).

Choline Deficiency

Choline, a precursor used for phospholipids and cell membranes, is necessary for very low-density lipoproteins (VLDL) synthesis. Under normal circumstances, it can be synthesized de novo from methionine using the intrahepatic transsulfuration pathway (34,35) (Fig-

ure 1). Choline will substitute for vitamin B₁₂ in states of vitamin deficiency and as a result, exacerbate choline deficiency. This underscores the need for adequate supplementation of vitamin B₁₂ and folate to prevent liver dysfunction in long-term PN patients (36).

Lecithin (phosphatidylcholine), a component of VLDL, contains 13% choline by weight and is the main source of choline in the diet. Foods rich in choline include egg yolks, organ meats, beef, leafy greens, nuts, legumes, seed oils, grain germs, and dairy products (35). Choline may serve as a precursor to lecithin, which can be produced de novo via sequential methylation using S-adenosylmethionine (SAM) as a methyl donor (34).

Normal plasma choline levels vary depending on the reference laboratory, but a recommended level is 11.4 ± 3.7 nmol/mL (36). Buchman, et al have published extensively concerning choline deficiency among long-term PN patients (1,36–39). Lipid emulsions provide minimal amounts of choline in the form of lecithin. Although oral lecithin supplementation can increase free plasma choline levels, this does not raise choline levels to normal. Despite this data, authors observed that lecithin supplementation, given in 20 g oral suspension twice a day, decreased hepatic fat density in long-term PN patients when evaluated by computed tomography (CT).

In malnourished and cirrhotic patients, the conversion of methionine to SAM is impaired by medications, such as methotrexate, or underlying liver disease. The impaired production of SAM may be the rate limiting step in choline biosynthesis. For this reason, choline is considered a conditional essential nutrient among long-term PN patients (34,35). Several studies correlated low free plasma choline levels with abnormal AST and ALT levels and an increased degree of hepatic steatosis (1,36).

Buchman, et al have also published multiple studies concerning the use of choline supplementation. This group noted improved liver function tests using a standardized 2 g IV choline chloride dose. After the cessation of choline supplementation, hepatic steatosis occurred within ten weeks (36). In another study, this group documented normalization of free plasma choline levels and resolution of CT documented hepatic steatosis in choline-deficient, long-term PN

patients after four weeks of intravenous choline supplementation (39).

Intravenous choline chloride is currently under clinical investigation and not available except in the research setting. An intravenous 2 g choline chloride dose provides 1.1 g of choline (38). Oral formulation of lecithin (active components of lecithin are the phospholipids, primarily phosphatidyl choline 12%, phosphatidylethanolamine 10%, phosphatidylinositol 7%) or choline, are alternatives, however patient tolerance, gastrointestinal comfort, and absorption may be poor. Lecithin is available in an oral soybean suspension. Patients suffering from liver failure, cirrhosis, malnutrition or those receiving hypercaloric feeds may also require additional choline (35,36).

Although there have been promising data regarding intravenous choline supplementation, choline is not commercially available for general use. Lecithin is included in fat emulsion solutions for PN. In cases of PN-associated liver dysfunction, a trial of oral lecithin may be beneficial, however gastrointestinal tolerance to this supplement may be a limiting factor (Table 3).

Carnitine Deficiency

Carnitine, produced in the liver and kidneys via a combination of lysine, cysteine and methionine, has the main function of transporting long-chain fatty acids into cell mitochondria for oxidation. Carnitine biosynthesis requires the addition of chemical moieties from the essential amino acids methionine and lysine. Although carnitine can be synthesized endogenously, it is also readily found in a diet containing foods of animal origin (40). In the absence of carnitine from oral or enteral nutrition, endogenous production of carnitine may be inadequate (40,41). Decreased carnitine metabolism results in lowered fatty acid oxidation and then ultimately hepatic steatosis. Steatosis has been reported in patients with carnitine deficiency on long-term PN, however, low plasma concentrations may not reflect tissue stores or correlate with the severity of hepatic dysfunction (42). Normal carnitine levels are as follows: plasma carnitine 30–60 μ mol/L, free carnitine 20 μ mol/L, and plasma acylcarnitine:free (A/F)

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Table 3
Suggested Guidelines for the Prevention and Treatment of Parenteral Nutrition-Associated Liver Dysfunction

Trial of enteral nutrition	<ul style="list-style-type: none">• Use the enteral route as soon as possible• Provide as much enteral nutrition as tolerated• Even small volumes of enteral feeds are beneficial• If liver function does not improve within 3 weeks of discontinuing PN and initiating full enteral feeds, then consider other therapies
Prevent sepsis	<ul style="list-style-type: none">• Minimize catheter-related sepsis risks• Aggressively treat bacterial and fungal infections
Prevent bacterial translocation Treat small bowel bacterial overgrowth	<ul style="list-style-type: none">• Provide as much enteral nutrition as tolerated<ul style="list-style-type: none">– Metronidazole 500 mg twice a day orally– May require cycled antibiotics in some cases such as those with chronic intestinal pseudoobstruction• Alternatives to oral metronidazole include intravenous and rectal forms
Avoid overfeeding	<ul style="list-style-type: none">• Limit total daily calories from dextrose to 65% or less• Adults: 4 g/kg/day• Other studies suggest limiting glucose infusion rate to 4 mg/kg/min to avoid respiratory quotient (RQ) >1.0
Optimize lipid emulsions	<ul style="list-style-type: none">• Prevent essential fatty acid deficiency by avoiding prolonged lipid-free PN<ul style="list-style-type: none">– Check triene:tetraene ratio—a ratio above 0.1 is diagnostic of EFA deficiency• Use lipid emulsions with a low proportion of polyunsaturated fatty acids that contain medium triglycerides• Limit lipid to total daily calories ratio to 30%• Adults: 1.0 g/kg/day lipid supplementation• At the onset of liver dysfunction, consider reducing or suspending lipids such as limiting lipid infusions to 5 per week
Optimize amino acid infusions	<ul style="list-style-type: none">• Avoid excess amino acid infusions• Avoid amino acid deficiencies• Adults: 0.8–1.5 g/kg/day
Prevent choline deficiency	<ul style="list-style-type: none">• May be conditionally essential among long-term PN patients and those with certain medical conditions• Maintain normal plasma levels: 11.4 ± 3.7 nmol/ml• Consider choline supplementation<ul style="list-style-type: none">– 6 g oral choline bitartrate or choline chloride daily (not available commercially)– 2 g IV choline chloride daily (goal of 1.1 g choline supplementation)• Consider oral lecithin supplementation<ul style="list-style-type: none">– 20 g twice a day oral suspension in a soybean oil based liquid– Available as PhosChol from <i>Advanced Nutritional Technology, Inc.</i>, (P.O. Box 2130, 6988 Sierra Court, Dublin, California 94568. Phone (800) 624-6543, (925) 828-2128).• May have poor patient tolerance due to gastrointestinal discomfort and poor oral absorption• Maintain adequate vitamin B₁₂ and folate supplementation

Table 3 (continued)

Suggested Guidelines for the Prevention and Treatment of Parenteral Nutrition-Associated Liver Dysfunction

Prevent carnitine deficiency	<ul style="list-style-type: none"> • Conditionally essential in premature infants • Patients with liver dysfunction and choline deficiency may require more carnitine • Maintain normal plasma levels: <ul style="list-style-type: none"> – Plasma: 30–60 $\mu\text{mol/L}$ – Free: 20 $\mu\text{mol/L}$ • Check the plasma:free ratio (A/F); <ul style="list-style-type: none"> – A/F ratio > 0.4 may indicate carnitine insufficiency • Consider carnitine supplementation • Maintenance supplementation in adult long-term PN patients (controversial) <ul style="list-style-type: none"> – 40 mg/day or 2–15 mg/kg/day IV solution carnitine • Lower doses may provide adequate supplementation • Correction of low plasma carnitine levels may be safely corrected with a loading dose regimen <ul style="list-style-type: none"> – 400 mg/day IV carnitine solution for seven days and then 60 mg/day maintenance dose – Levocarnitine (L-carnitine hydrochloride) IV formulation is available from <i>Sigma Tau Pharmaceuticals, Inc.</i> (800 South Frederick Avenue, Suite 300, Gaithersburg, MD 20877. Phone (800) 447-016)
Prevent taurine deficiency	<ul style="list-style-type: none"> • Conditionally essential for premature infants • Maintain normal plasma levels • Consider taurine supplementation <ul style="list-style-type: none"> – Adults: 1.5–2.5 g/day; 40 $\mu\text{mol/kg/day}$ taurine supplementation
Supplement with glutamine	<ul style="list-style-type: none"> • Non-essential amino acid that is traditionally not added into PN • Difficult to store and maintain within solution • New formulations, such as dipeptide formulations, are more stable • No specific dosing or regimens recommended within the literature for PN-associated liver dysfunction • Consider trial of alanyl-glutamine dipeptide 0.5 g/kg/day mixed into PN solution (not available in U.S.) • Other formulations of glutamine may be available in future
Trial of cyclic infusion of PN	<ul style="list-style-type: none"> • Cycle PN feeding schedules in 8–16 hour periods • When prolonged PN therapy is expected, start PN cycling as soon as possible • Stop PN completely one day per week <ul style="list-style-type: none"> – Give patient one night off/week if possible; compound their nutrient requirements in 6 days if necessary; hydration fluids only can be given on the 7th night if need be • Consider using a dextrose-free PN cycle to avoid disturbing the post-absorptive state • Cycling may not be effective in lowering severely elevated liver function test
Trial of Ursodeoxycholic acid (ursodial, UDCA) therapy	<ul style="list-style-type: none"> • Available as oral capsules; absorption will be a challenge for patients with malabsorption processes <ul style="list-style-type: none"> – In short bowel syndrome, may need to give higher doses and more often to achieve efficacy • Adults: 10–15 mg/kg/day

Table 3 (continued)

Suggested Guidelines for the Prevention and Treatment of Parenteral Nutrition-Associated Liver Dysfunction

Trial of infusion of IV cholecystokinin-octapeptide (CCK-OP)	<ul style="list-style-type: none"> • Prophylaxis of gallbladder and biliary sludge formation • Daily intravenous CCK-OP 50 ng/kg over 10 minutes • Consider adding thyrotropin-releasing hormone (TRH) 0.4 mg intravenous over 1 minute
Prophylactic Cholecystectomy	<ul style="list-style-type: none"> • May not be a viable option due to underlying disease and operative morbidity and mortality risks

ratio 0.25. An A/F ratio greater than 0.4 may indicate carnitine deficiency (43).

Clinical data supporting the efficacy of carnitine supplementation in the resolution hepatic dysfunction have been inconclusive. Worthley, et al reported on a single case of hyperbilirubinemia normalization with improved free plasma carnitine levels (44). In contrast, Bowyer, et al observed increased free plasma carnitine concentrations with supplementation, but no change in hepatic steatosis or hepatic enzyme levels (42).

The literature is controversial regarding the optimal dose of carnitine for deficiency and maintenance therapy. An intravenous form of L-carnitine is available and can be added directly to PN solutions. When correcting carnitine deficiency, Worthley, et al administered L-carnitine 400 mg/day for seven days and then 60 mg/day continuously (44). A maintenance daily dose of 40 mg continuous intravenous carnitine infusion has been suggested for all long-term PN patients (41). In a recent publication, Shatsky and Borum presented differing views regarding carnitine supplementation. Borum advises a carnitine dose similar to dietary provisions, such as 2–5 mg/kg/day and insists that pharmacological doses may not be beneficial except in the case of an inborn error of metabolism (43). Alternatively, Shatsky advocates a maintenance carnitine supplement of 15 mg/kg/day (43).

In the treatment or prevention of PN-associated liver dysfunction, carnitine supplementation dose can only be more reliably recommended after further investigation.

Taurine Deficiency

Taurine, a sulfur-containing β -amino acid derived from cysteine, promotes bile flow and biliary conjuga-

tion. Taurine deficiency may occur in patients with liver disease due to insufficient conversion of methionine to cysteine. Neonates primarily use taurine for bile acid conjugation, however as a person ages, glycine is used preferentially over taurine. Taurine supplementation may improve bile flow and secretion and thus prevent cholestasis induced by hepatotoxic sulfated lithocholate. Wang, et al gave 40 μ mol/kg/day of taurine supplementation to post-operative patients with hepatobiliary disease (45). The percentage of bile acid conjugated by taurine in the treated group was increased compared to controls, suggesting improved bile acid conjugation. However, total volume of biliary excretion was unaffected. A dose of 1.5–2.25 g/day of taurine in PN solution restored normal plasma concentration in six weeks (46). This treatment may be more efficacious in neonates given that the majority of bile is conjugated with taurine. However, there is no strong correlation found between low taurine levels and cholestasis in adults.

Glutamine Deficiency

Glutamine is a nonessential amino acid and major fuel source for the gut that is not traditionally included in PN solutions and has not been readily available in intravenous form. However, in several animal studies, glutamine supplementation has been implicated in the prevention of hepatic dysfunction via multiple pathways. In rat models, glutamine-enriched PN feeding prevents hepatic steatosis (47).

Glutamine supplementation may prevent hepatic steatosis by its glucagon-stimulating activity and by increasing hepatic lipid exportation. Li, et al observed increased portal glucagon levels in glutamine-enriched

hypertonic dextrose PN fed rats (48). These rats also had no increased portal insulin:glucagon ratio or development of hepatic steatosis in comparison to enterally-fed control rats.

Glutamine supplementation may prevent bacterial translocation from the intestinal tract by preventing gut mucosa atrophy and improving immune responsiveness (47,49). Improved immunoglobulin A (IgA) and interleukin (IL)-4 and IL-10 levels are observed in PN-reliant animals with glutamine supplementation (50).

Glutamine supplementation has been difficult to implement due to its instability when mixed within PN solutions and while undergoing the sterilization process. In hospitalized patients, frequent mixing of PN solutions prevents separation. In a glutamine-enriched (0.285 g/kg) four-week home PN trial, Hornsby-Lewis, et al witnessed solution stability with a cold sterilization process, but ironically observed elevations in hepatic transaminase and alkaline phosphatase levels in three out of seven patients and caused early trial cessation (51). Yu, et al suggested the use of alanyl-glutamine dipeptide as a more stable form of glutamine supplementation in PN; 3% alanyl-glutamine dipeptide solution is equivalent to a 2% glutamine preparation (52). In a human study, 0.23 g/kg/day glutamine (formulated as alanyl-glutamine dipeptide or glycyl-L-glutamine) was safely added to a PN solution and prevented gut mucosal atrophy (53). In a recent study of critically-ill patients, those who were PN supplemented with alanyl-glutamine dipeptide 0.5 g/kg/day had a reduced rate of infections and hyperglycemia (54).

Glutamine appears to be a promising agent to improve gut immunity and glucose and lipid metabolism. Currently, there is limited data regarding appropriate clinical use (and dose) of glutamine. IV glutamine is not yet available commercially.

Cyclic Infusion of Parenteral Nutrition

In theory, constant feeding may be detrimental to liver function due to prolonged hyperinsulinemia. Continuous dextrose infusions may cause a constant state of elevated blood sugar which in turn elicits higher insulin levels. Insulin promotes further lipogenesis and inhibits lipolysis; this may result in increased hepatic

lipid deposition. Another potential complication of hyperinsulinemia is the decreased mobilization of free fatty acids from adipose tissue leading to deficiencies of essential fatty acids in those not receiving lipid emulsions (24).

Cyclic PN has been recommended to achieve metabolic objectives and patient comfort. Cyclic PN has been well tolerated in stable patients requiring prolonged PN by improving patient mobility and psychological well-being (55). Cycling regimens usually range from 10 to 16 hours (23,56,57). Steiger, et al recommended the initiation of a cyclic PN schedule as soon as PN therapy is expected to be prolonged in addition to the provision of a "PN vacation" one day per week (23). Maini, et al used a daily 12-hour dextrose-free infusion break (58); fat and protein may be given during a longer cycle because there is less disturbance of the post-absorptive state (32). Hwang, et al used a 12-hour infusion cycle that was effective in preventing further liver enzyme elevation for patients with total bilirubin levels ≤ 10 mg/dL (56). In patients with severely elevated bilirubin (≥ 20 mg/dl), improvement in liver enzymes was not appreciated.

Gramlich and Bistran caution against the use of cyclic PN in the acute setting due to the risk of excessive dextrose infusion per hour infused (24). Furthermore, theoretical disadvantages of cycling lipids include lowered immune function when administering high lipid content over a short infusion period.

Despite several studies promoting the use of cyclic PN to prevent further PN-associated cholestasis, evidence is not yet available to suggest a definitive regimen.

Prevent Bacterial Translocation

Increased bacterial translocation occurs with disruption of small bowel bacteria balance, impaired immune response, and physical interference of the intestinal mucosal barrier (59). PN-reliant animals have lowered levels of IgA, IL-4, and IL 10. These animal models also have increased bacterial translocation into mesenteric lymph nodes (21). Release of hepatotoxins, such as TNF or endotoxins, have been implicated as the source of liver damage in PN-associated liver dysfunction. Animal studies by Alverdy, et al suggest that the lack of enteral stimulation reduces intestinal mucosal

immunity, allowing bacterial translocation across gut walls (21,60). In addition to bacterial translocation, small bowel overgrowth of anaerobic intestinal bacteria has been postulated to be a source of liver damaging endotoxins and lithocholic acid (5,20).

To reduce bacterial translocation and small bowel bacterial overgrowth, treatment with antibiotics, such as metronidazole, have been suggested. In a short five-day study involving PN-reliant rats, Freund, et al observed decreased hepatic lipid content in rats treated the metronidazole 15 mg/kg/day compared to non-treated rats (61). In a retrospective study, Lambert, et al examined PN-reliant patients who received metronidazole during their PN course compared to non-treated PN-reliant controls. In comparison to the metronidazole-treated patients, the control patients had increased alkaline phosphatase, gamma glutamyl transpeptidase, and aspartate aminotransferase following their PN course (average 13 days) compared to controls (62). Metronidazole had been given in intravenous, oral or rectal forms with a dose range of 750 to 3000 mg.

In a 30-day trial, Capron, et al used prophylactic metronidazole, 500 mg twice a day, throughout the duration of PN in patients with Crohn's disease (63). Those within the metronidazole-treated PN group had improvement or maintained normal serum levels of alkaline phosphatase and gamma glutamyl transpeptidase. These findings suggest that metronidazole may prevent the development of PN-associated liver dysfunction.

Data regarding metronidazole use in the prevention of PN-associated liver dysfunction has been sparse. Optimal dose for metronidazole in this setting has not been studied. With the available data, we recommend metronidazole 500 mg twice a day orally. Adverse effects to metronidazole, such as metallic taste in the mouth and peripheral neuropathy, should be monitored.

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA, ursodiol) is a natural hydrophilic bile acid formed in the liver and small bowel. UDCA has multiple effects that include stimulating bile production, reducing cholesterol absorption and hepatic cholesterol synthesis, and the enhancing of

cholesterol gallstone dissolution. UDCA is passively absorbed in the small intestines prior to being conjugated with glycine and taurine and then excreted into bile. It then is actively reabsorbed at the terminal ileum (64). UDCA may be a promising treatment for PN-associated cholestasis, as it may improve liver function by promoting bile flow, displacing toxic bile acids, providing chemoprotective effects on hepatocytes, reducing intestinal translocation of endotoxins and bacteria, and enhancing endotoxin biliary excretion (65,66). While receiving total PN, UDCA-treated animals had improved transaminases, alkaline phosphatase, total cholesterol, total bilirubin, triglycerides, and free bile acids; significantly, there was also a decreased incidence of hepatic steatosis (67). Beau, et al observed normalization of gamma glutamyl transpeptidase in three out of nine patients and ALT in four out of five patients when employing UDCA 10–15 mg/kg/day over a two month period (68). In a single case study, Lindnor, et al noted the resolution of hyperbilirubinemia after two months of UDCA 600 mg/day (69). At doses of 10–15 mg/kg/day, UDCA becomes the predominant bile acid in patients in cholestasis (64).

UDCA is available in an oral capsule as a protonated acid. As the efficacy of UDCA may be dose-dependent, patients with malabsorption syndromes may require higher doses and should use extemporaneously prepared solutions instead of capsules.

Cholecystokinin Infusion

Cholecystokinin (CCK) is a hormone that promotes gallbladder contraction and bile flow release following proximal small bowel stimulation by enteral nutrients, primarily fats. The hypothesis surrounding CCK infusions stems from its potential to prevent biliary stasis during prolonged PN. A synthetic form, CCK-octapeptide (CCK-OP) is available in intravenous and intramuscular formulations. Side effects are likely dose-related and include abdominal cramping, nausea, and leucopenia. Kalfarentzos, et al used CCK, 3 ng/kg/min over 15 minutes, in combination with thyrotropin-releasing hormone (intravenous TRH 0.4 mg given over 1 minute) to increase gallbladder contraction in adults on PN over a two week period (70). In a

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preliminary human study, Sitzmann, et al noted that daily CCK-OP infusions, 50 ng/kg over 10 minutes, prevented the formation of biliary sludge in adults on long-term PN (71).

Large studies evaluating the effectiveness of CCK-OP in cholelithiasis prophylaxis have not been completed. Only preliminary studies have been completed regarding the use of CCK-OP to prevent biliary complications in PN-reliant patients. Optimal CCK-OP dosing parameters have not been studied.

Prophylactic Cholecystectomy

Several studies have noted the high incidence of cholelithiasis and the eventual need for cholecystectomy in some long-term PN patients (12). About 25% of short-bowel patients will eventually develop gallstones and require cholecystectomy (25). Given the incidence, prophylactic cholecystectomy has been suggested. Multiple reasons, such as underlying disease and surgical morbidity, prevent prophylactic cholecystectomy from becoming a widespread viable option.

Addition of Enteral Feedings

Enteral feedings may prevent PN-associated steatosis for various reasons. Several mechanisms of action have been proposed such as the enteral addition of an, as yet unidentified, specific nutrient (essential fatty acid or protein), prevention of gut atrophy and loss of gut mucosal immunity, and avoidance of gut flora imbalance with endotoxin formation or alterations in gut bacteria (21,59,60). Abad-Lacruz, et al compared incidences of liver test abnormalities between patients with inflammatory bowel disease on PN and those on enteral nutrition (72). In this randomized, controlled trial, 61.5% PN patients had elevated levels of liver enzymes or bilirubin in comparison to 6.2% of patients who received only enteral nutrition. Both groups were similar in age, sex, diagnosis, disease activity, nutritional status, daily nutrient supply, and days on artificial nutrition; however, disease etiology, ulcerative colitis versus Crohn's disease, was different between the two groups.

In an animal study by Zamir, et al, there was reduced hepatic lipid accumulation in rats allowed enteral feedings in addition to PN (73). These results

are echoed in human studies, however, are difficult to interpret due to the different underlying diseases, bowel length, infection rates, and length of PN administration between the PN-only and the PN with enteral feeding groups (74).

Enteral feedings may also prevent extra-hepatic cholestasis. In patients with ultrasound-documented cholestasis, Messing, et al observed complete sonographic resolution of biliary sludge within four weeks of restarting enteral/oral feeding (12).

CONCLUSION

Upon review of available published data concerning the treatment of PN-associated liver dysfunction, general consensus has been lacking. Multiple hypotheses have been postulated as to the etiology behind this process; however, there have been no reproducible or definitive studies. Comparison of treatment and incidence studies are difficult due to a wide variation of PN solutions and patient populations. While many associations exist, clear cause and effect relationships are hard to come by. Given the complexity of these patients and the frequent need to continue PN for life, recommendations are derived from tentative associations and the fact that many of these patients have no other options. In rare cases, small bowel transplantation may be the option of last resort; however, rarely is this procedure available.

After review of the available evidence, suggested guidelines to aid the medical practitioner in the treatment of PN-associated liver dysfunction have been proposed (Table 3). Previous studies support the initiation of enteral feedings, the aggressive treatment and prevention of sepsis, and the avoidance of overfeeding in the management of PN-associated liver dysfunction. Amino acid supplementation, prophylactic metronidazole, UDCA use, and other interventions have limited data, and subsequently, incomplete dosing and safety parameters. As with any medical intervention, the risks and benefits of the proposed treatment must be weighed.

The goal of this review is to summarize available data for PN-associated liver dysfunction; however, there are no definitive guidelines in the treatment of this disease process. Before such guidelines can be fully developed, standardization of study variables,

such as patient population or PN solution, is needed and subsequent studies conducted. ■

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