Invited Review

Parenteral Nutrition-Associated Liver Disease in Adult and Pediatric Patients

Vanessa J. Kumpf, PharmD, BCNSP
Vanderbilt University Medical Center, Center for Human Nutrition, Nashville, Tennessee

ABSTRACT: There are essentially 3 types of hepatobiliary disorders associated with parenteral nutrition (PN) therapy: steatosis, cholestasis, and gallbladder sludge/stones. Reported prevalence rates of PN-associated liver disease (PNALD) vary greatly, and there are distinct differences between adult and pediatric patients. Various etiologic factors have been evaluated for significance in contributing to PNALD, including enteral feeding history, septic events, bacterial overgrowth, length of intestinal resection, and prematurity/low birth weight. Etiologic factors specifically related to the PN formulation or nutrient intake have also been evaluated, including excessive calorie intake, dextrose-to-lipid ratio, amino acid dose, taurine deficiency, IV fat emulsion (IVFE) dose, carnitine deficiency, choline deficiency, and continuous *vs* cyclic infusion. Minor increases in serum aminotransferase concentrations are relatively common in patients receiving PN therapy and generally require no intervention. The primary indicator of cholestasis is a serum conjugated bilirubin >2 mg/dL. When a patient receiving PN develops liver complications, it is necessary to rule out all treatable causes and minimize other risk factors. All potential hepatotoxic medications and herbal supplements should be eliminated. Modifications to the PN regimen that may be helpful include reduction of calories, reduction of IVFE dose to <1 g/kg/d, supplementation of taurine in the infant, and use of cyclic infusion. Initiation of even small amounts of enteral nutrition and use of ursodiol may be beneficial in stimulating bile flow. In the long-term PN patient with severe and progressive liver disease, intestinal or liver transplantation may be the only remaining treatment option.

Disorders of the liver and biliary system are complications commonly reported in patients receiving parenteral nutrition (PN). It remains a life-threatening complication that poses particular concern in the patient dependent on long-term support. Mechanisms explaining precisely how PN influences the development of liver disease are lacking. It was historically thought that some component of the PN formulation or missing component caused liver disease. However, that simplistic concept has been replaced with the realization that liver dysfunction can result from a complex set of risk factors present in patients receiving PN. The term *PN-induced liver disease* has therefore been replaced with the term *PN-associated liver disease* (PNALD). Strategies to minimize risk of developing PNALD should be incorporated into the care plan of all patients receiving PN, but especially in the patient requiring long-term PN because treatment options are limited when PNALD develops. It is hoped that a better understanding of etiologic factors will help prevent PNALD or lessen its severity. This article will examine the various etiologic factors thought to contribute to liver disease in both adult and pediatric patients receiving PN and address methods to prevent and manage this potentially life-threatening complication.

Correspondence: Vanessa J. Kumpf, PharmD, BCNSP, Vanderbilt University Medical Center, Center for Human Nutrition, 1211 21st Ave South, Suite 514 Medical Arts Building, Nashville, TN 37232. Electronic mail may be sent to vanessa.kumpf@vanderbilt.edu.

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Clinical Spectrum of Hepatic Disorders

The type of hepatic disorder associated with PN differs among adult and pediatric patients, although the distinction becomes less evident in the patient receiving long-term PN. There are essentially 3 types of hepatobiliary disorders associated with PN therapy: steatosis, cholestasis, and gallbladder sludge/stones; however, overlap can exist.[1,2] Steatosis, or hepatic fat accumulation, is predominant in adults and is generally benign. It typically presents as mild to moderate elevations of serum aminotransferase levels and less pronounced elevations of serum alkaline phosphatase and bilirubin concentrations. Elevations of these biochemical markers generally occur within 2 weeks of PN therapy and may return to normal even when PN is continued. Most patients are asymptomatic. Steatosis appears to be a complication of overfeeding and is therefore probably not as common now that estimates of PN calorie requirements have decreased compared with practices 10 or more years ago. Although steatosis is

generally thought to be a nonprogressive lesion, progression of hepatic steatosis to fibrosis or cirrhosis may become an issue in patients receiving long-term PN.[3,4]

Cholestasis is a condition of impaired secretion of bile or frank biliary obstruction that occurs predominantly in children but may also occur in adult patients receiving long-term PN. It typically presents as an elevation of serum concentrations of alkaline phosphatase, γ-glutamyl transpeptidase (GGT), and conjugated (direct) bilirubin concentrations with or without jaundice. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also be elevated. Although both GGT 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 is considered the prime indicator of cholestasis, typically defined as a concentration >2 mg/dL. PN-associated cholestasis (PNAC) is a serious complication because it may progress to cirrhosis and liver failure. Progressive elevation in serum conjugated bilirubin concentrations and persistent jaundice is associated with a high mortality risk.[5] If PN is stopped before irreversible hepatic damage occurs, complete liver recovery is expected, and serum conjugated bilirubin concentrations typically return to normal within 1 week to 2 months.[6]

Finally, gallbladder stasis during PN therapy may lead to the development of gallstones or gallbladder sludge, with subsequent cholecystitis. It can occur in both adult and pediatric patients receiving PN and is likely related more to the lack of enteral stimulation than PN *per se*. The lack of oral intake results in decreased cholecystokinin (CCK) release and impaired bile flow and gallbladder contractility. Reduced CCK secretion has also been demonstrated in patients with severe short bowel syndrome in response to meal stimulation when compared with normal controls.[7] Impaired CCK release appears to be a primary factor in the development of biliary sludge and gallstones. As expected, the duration of PN therapy appears to correlate with the development of biliary sludge. In a group of 23 adult patients with gastrointestinal disorders who were receiving PN, serial ultrasonographic studies demonstrated a progressive increase in biliary sludge over time.[8] Documentation of biliary sludge increased from 0% at baseline, to 6% of patients within the first 3 weeks of PN, to 50% between 4 and 6 weeks, and 100% at >6 weeks. Gallstone formation was demonstrated in 6 patients. The progression of biliary sludge can also lead to acute cholecystitis in the absence or gallstones, referred to as acalculous cholecystitis. When it occurs, it is usually in a critically ill patient with bile stasis and some type of ischemic insult.[9]

Prevalence of PNALD

Reported prevalence rates of PNALD vary greatly. Determination of association is complicated by the fact that most studies have primarily relied only on elevated liver enzyme and bilirubin concentrations to define hepatic dysfunction and are not validated by biopsy. In addition, the composition of the PN formulation has changed considerably over the past 30 years and has likely influenced the occurrence of PNALD. Total calorie goals have decreased over the years, and use of IVFE as a daily caloric source has become routine.

In adult patients receiving PN, the reported incidence of abnormal enzyme elevations has varied from 25% to 100%.[1] However, few studies have correlated enzyme changes to permanent hepatic dysfunction or histologic damage. In fact, the enzyme elevations are usually mild and may normalize despite continuation of PN. In pediatric patients receiving PN, the prevalence of hepatic complications is also poorly defined and has varied from 7.4% to 84%.[1,2] The assumption is often made that abnormal enzyme or bilirubin concentrations indicate hepatic dysfunction. One aspect that does seem clear is that the prevalence of PNAC is greater in infants than in adults. The prevalence of PNAC in infants has been reported as high as 30%–70% and appears to vary according to other risk factors present, such as prematurity, low birth weight, duration of PN, and septic episodes.[10,11] One study reported 25 years of experience in surgical neonates who received at least 2 weeks of PN.[12] The 273 infants were divided into 3 groups according to the year they received PN. The prevalence of PNAC (defined as conjugated bilirubin >2 mg/dL) was 57% (1971–1982), 31% (1983–1987), and 25% (1992–1996). Of note, the total calorie intake was greater in the 1971–1982 group of neonates compared with caloric intake of groups in the more recent years. In addition, a specialized neonatal amino acid solution replaced a standard amino acid solution in 1978, and this may have also contributed to the decrease in prevalence of PNAC.

There is particular concern about the development of liver disease in both adult and pediatric patients receiving long-term PN because its occurrence and severity appears to increase with longer duration of PN usage. The prevalence of liver disease was evaluated in a group of 90 primarily adult patients receiving home PN for permanent intestinal failure in France.[4] The median age was 45 years (range, 6–77 years) and the median duration of home PN was 45 months (range, 6–198 months). Chronic cholestasis was defined as >1.5 times the upper limit of normal on at least 2 of the 3 measures (serum levels of GGT, alkaline phosphatase, and conjugated bilirubin) that persisted for at least 6 months. Chronic cholestasis was attributed to PN after extrahepatic causes were excluded and potentially hepatotoxic medications were withdrawn. The

prevalence of chronic cholestasis was 55% at 2 years, 64% at 4 years, and 72% at 6 years. The study further identified complicated liver disease if one of the following liver complications was observed, or if extensive portal fibrosis or cirrhosis was documented on liver biopsy: jaundice with a serum bilirubin ≥3.5 mg/dL for at least 1 month, ascites, variceal-related bleeding, portal hypertension, liver encephalopathy, and liver failure with a factor V level of ≤50%. The prevalence of complicated liver disease was 26% ± 9% at 2 years and 50% ± 13% at 6 years. Among the patients who developed complicated liver disease, 17 showed extensive fibrosis and 5 had cirrhosis. Six patients died of liver disease. This study demonstrates a disturbingly high prevalence of PNALD in the long-term PN patient. In another group of 42 adult patients in the United States receiving home PN for >1 year, 6 (15%) developed end-stage liver disease.[5] All 6 patients died, at an average of 10.8 ± 7.1 months after the initial elevation of bilirubin concentration.

The prevalence of PNALD in pediatric patients receiving long-term PN has also been evaluated in various retrospective studies. One study evaluated 42 neonates with intestinal resection who were dependent on PN for at least 3 months.[13] Cholestasis (defined as direct bilirubin >2 mg/dL) developed in 28 patients (67%), and 7 of these patients (17%) progressed to liver failure. Similar results were shown in the retrospective analysis of 17 neonates with intestinal failure receiving long-term PN.[14] Hepatic dysfunction, defined loosely as a serum total bilirubin level >2 mg/dL or serum transaminase concentration >80 IU/L, developed in 11 patients (61%). Of these patients, 9 developed cholestasis, 1 had steatosis, and 1 showed biliary sludge and cholelithiasis. Another study evaluating 26 pediatric patients who received PN for >2.5 years found a lower occurrence of hepatic dysfunction.[15] Episodes of hyperbilirubinemia were seen in 5 patients, whereas 4 patients had persistently elevated bilirubin levels. Liver biopsies were performed in 8 patients and showed cirrhosis in 2 patients, chronic active hepatitis with cholestasis in 1 patient, fibrosis in 2 patients, cholestasis in 1 patient, and normal results in 2 patients.

Etiologic Factors for PNALD

Many of the studies evaluating the prevalence of PNALD have attempted to identify risk factors associated with PNALD. Various factors related to the nutrient composition of the PN formulation have been suggested to contribute to the development of liver complications. Other factors that have been evaluated for significance include enteral feeding history, septic events, bacterial overgrowth, and length of intestinal resection.[2,6,16] Gestational age and birth weight have also been evaluated for significance in the neonatal population.

Prematurity and Low Birth Weight

A relationship has been identified between the development of cholestasis in infants who are premature and of low birth weight. However, because many infants who require PN are likely to be premature and of low birth weight, it is difficult to distinguish whether these characteristics are independent or associated risk factors. Beale et al[17] reviewed 62 premature infants receiving PN and identified cholestasis in 50% of the infants with birth weight <1000 g, but only 7% if birth weight was >1500 g. The increased incidence of cholestasis in premature infants suggests that the disease may be related to the immature neonatal liver. Compared with the full-term infant, the enterohepatic circulation of the preterm infant is reduced due to both diminished hepatic uptake and diminished synthesis of bile acids.[2] It is also possible that the neonatal liver is more susceptible to damage due to reduced sulfation, which is an important step in the solubilization of toxic bile salts.[18]

Sepsis

Bacterial and fungal infections have been highly associated with cholestasis for many years.[19,20] Jaundice can occur several days after the onset of infection, and serum total bilirubin concentrations can increase to 5–10 mg/dL. Sepsis likely causes a systemic inflammation on the liver due to the release of proinflammatory cytokines that are activated by endotoxins. Cytokine release can result in altered membrane function of the bile canaliculi and reduced bile flow. There is particular concern regarding repeated insults to the liver due to recurrent septic episodes.

Short Bowel Syndrome

Massive intestinal resection has been identified as a risk factor of PNALD.[4,21–24] In one study that used multivariate analysis, a small bowel remnant <50 cm in length was significantly associated with chronic cholestasis.[4] Another study of adult long-term PN patients reported that those with the shortest residual intestine were at the greatest risk to develop eventual liver failure and death.[22] Similar results have been shown in pediatric patients with short bowel syndrome, with up to 70% developing cholestasis.[25] Because short bowel syndrome causes interruption of enterohepatic circulation and alterations in bile acid metabolism and excretion, it is considered a potential contributing factor in the development of PNALD. Unfortunately, patients with massive small bowel resection are dependent on long-term PN and options are therefore limited when liver failure develops.

Bacterial Overgrowth

Many patients receiving PN are at risk of developing small intestinal bacterial overgrowth (SIBO),

which may contribute to the development of liver disease.[16] Bacterial overgrowth occurs when large amounts of bacteria normally confined to the colon and lower small bowel populate the upper small intestine. The reduced enterohepatic circulation that results from short bowel syndrome and the intestinal stasis that occurs from motility disorders such as chronic intestinal pseudoobstruction predispose many patients receiving PN to SIBO. It has been postulated that anaerobic bacteria in the small intestine may produce hepatotoxins, such as lithocholic acid, which can lead to hepatic injury. In addition, bacterial overgrowth may contribute to cholestasis by promoting deconjugation of bile acids, which prevents their reabsorption.

Lack of Enteral Stimulation

PNALD appears more likely to develop in patients who are unable to tolerate any enteral nutrition compared with those who can tolerate even small amounts.[2] As mentioned, lack of enteral nutrition results in reduced hepatocellular bile acid and bile secretion and reduced gallbladder contractility. One mechanism may be the reduction of food-stimulated release of gastrointestinal hormones such as CCK. Biliary sludge can develop due to the reduction of gallbladder contractility and impaired bile flow. A fasting state may also reduce the size of the bile salt pool and bile formation, which can further contribute to the problem. In addition, a reduction in CCK may also lead to intestinal stasis and subsequent bacterial overgrowth, another risk factor in PNALD.

Calories

Clinical studies suggest that the development of steatosis during PN administration is primarily due to excessive calories.[1] Overfeeding either combined or individual energy substrates (dextrose, fat, amino acids) can contribute to liver complications. The administration of excessive calories is thought to promote hepatic fat deposition by stimulating insulin release, which, in turn, promotes lipogenesis and inhibits fatty acid oxidation.[1]

Dextrose

Dextrose-based PN formulations that contain little or no fat have been implicated in the development of steatosis. Not only do excess carbohydrates deposit in the liver as fat, but a dextrose-based PN formulation may result in the development of essential fatty acid deficiency (EFAD). EFAD may lead to impaired lipoprotein formation and triglyceride secretion and result in steatosis. Providing a balanced dextrose and fat source of calories appears to decrease the incidence of steatosis, possibly by decreasing hepatic triglyceride uptake, and promoting fatty acid oxidation. Now that dextrose-based PN formulations have essentially been replaced with a more balanced dextrose-fat formulation and less overall calories are provided than previously estimated, the incidence of steatosis has decreased.[1] It is recommended that a balanced PN formulation provide 70%–85% of nonprotein calories as carbohydrate and 15%–30% as fat.[26] In addition, carbohydrate content should not exceed 7 g/kg/d in adults.

Amino Acids

Early sources of amino acids for parenteral use included protein hydrolysates that had significant amounts of aluminum contamination. Animal studies have suggested that high levels of aluminum contamination may lead to the development of cholestasis. Five pediatric patients who developed cholestasis and were receiving PN that contained casein hydrolysate as the protein source demonstrated markedly elevated hepatic aluminum content on biopsy.[27] However, the replacement of protein hydrolysates with crystalline amino acids has significantly reduced the overall aluminum contamination in PN formulations and is no longer considered a significant risk factor for the development of liver complications.[28]

In children, the development of PNAC may be related to the toxicity or deficiency of certain amino acids. Cysteine and taurine, which are amino acids synthesized from methionine in older infants and adults, are diminished in the premature infant due to immature enzyme systems necessary for amino acid formation. Because they are not a component of standard crystalline amino acid preparations, premature infants may be at risk of deficiency states. Taurine deficiency has been shown to occur in the premature infant as well as both pediatric and adult patients receiving long-term PN.[29] Taurine serves to solubilize bile salts and is therefore necessary for adequate biliary secretion and ileal reabsorption. It has also been shown to protect against lithocholate toxicity. Therefore, taurine deficiency may play a role in the development of PNAC.[30] In 3 children with short bowel syndrome due to necrotizing enterocolitis and receiving PN who died with liver failure, serial plasma aminograms demonstrated markedly elevated levels of methionine, low levels of cysteine, and undetectable levels of taurine.[31] In a large prospective multicenter study conducted between 1996 and 2001, the presence or absence of taurine in PN formulations was analyzed by multivariate analysis.[32] The choice of taurine supplementation in these patients was based on the individual hospital formulary that provided either the standardized adult crystalline amino acid solution or the specialized neonatal amino acid solution supplemented with taurine. Because the study period occurred during the transition between these preparations, the investigators were provided a unique opportunity to obtain data that would be difficult to repeat because the use of the specialized neonatal amino acid solution is now essentially considered

the standard care in the neonatal population. Among the 236 neonates receiving PN, use of the taurine-supplemented PN was associated with a significant reduction of PNAC in infants with necrotizing enterocolitis and approached significance in premature infants. The investigators concluded that these subgroups of neonatal patients are most likely to benefit from taurine supplementation.

High cumulative amino acid doses may also be associated with development of PNAC in pediatric patients, although a definitive relationship has not been established. One study compared infants receiving 3.6 g/kg/d to those receiving 2.3 g/kg/d and found more severe and earlier onset of cholestatic jaundice with the higher dose.[33] Another study in preterm infants compared those who developed PNAC with those who did not and found that those who developed PNAC received 4.2 ± 1.1 g/kg/d amino acids and those who did not received 1.7 ± 0.5 g/kg/d.[34] It has therefore been suggested that protein intake in the infant not exceed 2.5–3 g/kg/d.[6,26,34] It is not clear what role the type and dose of amino acids play in the development of PNALD in the older child and adult, but it does not seem to be as significant as it is in the infant.

IV Fat Emulsion (IVFE)

There are various concerns regarding the role of IVFE in the development of liver complications, including the fat source, the phytosterol content, and the dose. The source of IVFE may play a role in risk of developing liver complications. In the United States, IVFE is composed of long-chain triglycerides (LCT). Medium-chain triglycerides (MCT) are oxidized in the liver at a faster rate than LCT, and data suggest that an MCT-LCT mixture may be less likely to cause hepatic complications than LCT alone. One short-term study in 14 patients receiving PN compared an LCT emulsion with a MCT-LCT mixture and found changes suggestive of fatty infiltration of the liver in the LCT group when compared with baseline.[35] No change of hepatic morphology was seen in the MCT/LCT group. Although available in Europe, an MCT-LCT mixture is not yet available in the United States.

Another factor that may contribute to risk of liver complications is the phytosterol content of IVFE. Phytosterols are found in vegetable oils and are present in significant quantities in IVFE. Adult patients with short bowel syndrome receiving IVFE-containing PN have been shown to have much higher serum phytosterol levels than other short bowel syndrome patients or healthy controls.[36] Phytosterols are inefficiently metabolized to bile acids by the liver, and it has been postulated that phytosterols may impair bile flow and cause biliary sludge and stones. Case reports are available which report high serum phytosterol levels in children with PN-related cholestasis.[6] However, further studies are required to determine if phytosterols in IVFE actually contribute to the development of cholestasis.

The dose of IVFE is another concern. As previously mentioned, the development of EFAD may contribute to liver dysfunction, but this is relatively uncommon. A more likely complication is what can occur when the IVFE dose is too high. When the rate of IVFE infusion exceeds the liver's ability to clear the phospholipids and fatty acids, it can lead to direct deposition in the liver and result in steatosis. In addition, cholestasis may be associated with high doses of IVFE, especially with long-term use. In patients receiving long-term PN, multivariate analysis demonstrated that chronic cholestasis and severe PNALD was strongly associated with IVFE intake >1 g/kg/d.[4] It was not associated with nonprotein calorie or dextrose intake, so did not seem to be related to overfeeding itself. In fact, the nonprotein calorie intake was only 88% ± 13% of the basal energy expenditure in the patients studied. Another study evaluated 10 children receiving long-term PN who presented with 23 episodes of cholestasis; the researchers retrospectively identified an association with IVFE administration.[37] Fifteen episodes of cholestasis occurred after an increase in IVFE frequency or increase in daily IVFE dose was made due to concern of slowing weight gain. In addition, IVFE was stopped in 20 of the 23 episodes of cholestasis and bilirubin concentration improved in 17 cases. In most cases, the improvement in bilirubin concentration was rapid and reached a normal concentration by 3.2 ± 2 months. It is recommended that IVFE content not exceed 2.5 g/kg/d in adults and children and not exceed 3 g/kg/d in the preterm infant.[26] However, it may be further beneficial to limit IVFE to <1 g/kg/d or temporarily remove IVFE in patients who develop PNAC.

Carnitine

Carnitine plays an important role in fat metabolism, and primary carnitine deficiency has been associated with the development of steatosis. Because carnitine is not routinely added to PN, 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.[6] However, low serum carnitine concentrations do not necessarily correlate with hepatic dysfunction in adults. In adult home PN patients with elevated serum liver enzymes and low serum carnitine concentrations, no improvement was shown in liver enzymes when carnitine was supplemented for 1 month and serum carnitine concentrations normalized.[38] The role of carnitine in the prevention and treatment of PN-associated liver complications remains to be established.

Table 1
Suggested laboratory monitoring parameters for parenteral nutrition-associated liver disease (PNALD)

Parameter	Comment
Aspartate aminotransferase (AST)	Insensitive and nonspecific marker of hepatocellular injury
Alanine aminotransferase (ALT)	Insensitive and nonspecific marker of hepatocellular injury
γ-Glutamyl transpeptidase (GGT)	Sensitive marker of cholestasis, but nonspecific
Alkaline phosphatase	Sensitive marker of cholestasis, but nonspecific
Bilirubin	
Conjugated (direct)	Considered the primary marker of cholestasis (generally defined as >2 mg/dL)
Unconjugated (indirect)	Isolated elevation rarely due to liver disease; primarily associated with hemolytic disorders
Total	Includes both conjugated and unconjugated fractions; both fractions may be elevated in liver disease
Bile acids	Proposed marker of cholestasis, but not routinely used in practice

Choline

Choline is a nutrient found in many foods but is not considered essential. 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 effective when methionine is given parenterally than when it enters the liver *via* the portal vein.[39] Free choline is one of the pathway products of choline synthesis, and low plasma free choline concentrations have been reported in patients receiving long-term PN. In addition, low concentrations have been associated with elevated serum hepatic aminotransferase concentrations and steatosis that resolves with choline supplementation.[40–43] A group of 15 adult patients receiving long-term PN with hepatic steatosis confirmed by CT were randomized to receive their usual PN formulation, or one supplemented with 2 g choline chloride daily for 24 weeks.[43] Only 9 patients completed the study, but steatosis resolved in the 4 patients who received choline and none of the 5 patients who did not receive choline as determined by liver/spleen CT scanning. In addition, 2 of the choline-supplemented patients who returned for follow-up 10 weeks after choline had been discontinued had recurrence of steatosis. In a pediatric population, 21 children receiving long-term PN were compared with 31 normal controls.[44] The mean plasma free choline concentrations were significantly lower in the long-term PN patients than the control group and showed a steady and significant decline with increased age. In addition, a significant negative correlation was shown between plasma free choline concentration and serum hepatic aminotransferase concentrations. Additional studies are under way to further evaluate the role of choline in the prevention and treatment of PNALD. At present, there is no injectable choline preparation commercially available.

Cyclic Infusion

Cyclic infusion of PN refers to the infusion of a daily supply of PN components over a <24-hour period (generally 8–12 hours), allowing a period of time off PN. A continuous infusion of PN can result in hyperinsulinemia and fat deposition in the liver and thereby potentially increase risk of liver complications. Cyclic infusion of PN has been shown to result in a reduction of serum liver enzyme concentrations and conjugated bilirubin concentrations in adult and pediatric patients when compared with continuous infusion.[6,45] Allowing a period of time each day off PN may reduce the risk of liver complications, especially in patients requiring long-term use.

Monitoring

Careful monitoring of patients for identification of PNALD is warranted and should include an evaluation of the biochemical parameters as outlined in Table 1. Frequency of monitoring is generally at least once per week in the adult and pediatric hospitalized patient receiving PN and monthly in the long-term PN patient. In the patient receiving short-term PN therapy, minor increases in serum concentrations of aminotransferases (less than twice the upper limit of the normal reference range) without an elevation of bilirubin are relatively common and generally require no intervention. In this situation, it is sufficient to reevaluate caloric intake to minimize the possibility of overfeeding and follow up with weekly laboratory monitoring. If there is an increase in serum levels of bilirubin or a progressive increase in aminotransferases, alkaline phosphatase, or GGT, then further evaluation is warranted to exclude reversible causes. Because no single laboratory or even histologic finding is definitive for identification of PNALD, it should be based on clinical presentation and exclusion of other diseases.

Elevated serum conjugated bilirubin and GGT concentrations are considered the most sensitive indicators of cholestasis. However, GGT is an enzyme with activity in the kidneys and pancreas, as well as liver, and therefore lacks specificity to liver disease. The same limitation applies to alkaline phosphatase. It is a sensitive marker for biliary obstruction but is also active in bone and will there-

Table 2
Strategies to manage parenteral nutrition-associated liver complications

1. Rule out other causes	Hepatotoxic medications Herbal supplements Biliary obstruction Hepatitis Sepsis
2. Consider modifications to parenteral nutrition	Decrease dextrose Decrease IV fat emulsion (IVFE) to <1 g/kg/d Provide a balance of dextrose and IVFE Cyclic infusion Specialized amino acid formulation in infants
3. Maximize enteral intake	Encourage oral diet Tube feeding, even at slow rate
4. Prevent/treat bacterial overgrowth	Enteral antibiotics, such as Metronidazole Gentamicin Neomycin Doxycycline Ciprofloxacin In CIPO patients, consider agents to enhance motility Metoclopramide Erythromycin Tegaserod Octreotide
5. Pharmacotherapy	Aggressive treatment of infection Ursodeoxycholic acid (ursodiol) Treatment of pruritus Cholestyramine Rifampin Phenobarbital
6. Intestinal transplantation	Consider for patients with parenteral nutrition failure

CIPO, chronic intestinal pseudoobstruction; IVFE, intravenous fat emulsion.

fore also be increased during bone formation in children. Serum bile acid concentrations have also been proposed as a marker of cholestasis in infants. However, bile acid concentrations have been demonstrated to have no diagnostic advantage to conjugated bilirubin in at least 1 study done in neonates.[46] Also, because bile synthesis and transport are variable in the infant, a serum bile acid reference range is difficult to establish. Its routine use as a marker for cholestasis is therefore not recommended at this time. The primary marker for cholestasis is conjugated bilirubin because elevated levels reflect a reduction in bile flow. A conjugated bilirubin >2 mg/dL is generally considered a significant indicator of cholestasis.

Progressive and sustained elevations of conjugated bilirubin concentrations have been used to predict severity and mortality in patients with PNALD.[2,4,10] Liver enzyme elevations have been shown to be of limited predictive value because enzyme release can be blunted when there is little liver parenchyma left to damage. Bilirubin monitoring can serve as a useful indicator to guide when referral to an intestinal transplant center may be warranted. It has been suggested that a total serum bilirubin >3 mg/dL for >3 months despite some enteral nutrition should indicate a need to refer the patient to a transplant center.[47] Late-stage indicators of reduced hepatic function include hypoalbuminemia, coagulopathy, and hypoglycemia occurring during PN cycling.

Strategies to Manage Complications

When a patient receiving PN develops liver complications, it is necessary to review all aspects of care to identify and eliminate or treat other factors that may be contributing. It is also important to review the PN formulation and consider modifications that may improve outcome. Unfortunately, there are only limited pharmacotherapeutic options available to consider when cholestasis develops. Transplantation of the intestine or of both liver and intestine may be the only remaining treatment option for some patients. Table 2 outlines strategies to consider when a patient receiving PN develops liver complications.

Drug-Induced Liver Disease

A thorough medication and herbal supplement history and review is an important step to take whenever evidence of liver disease presents. Drug-induced hepatotoxicity is a potential complication of

Table 3
List of drugs associated with cholestatic injury[49]

Antimicrobials	Amoxicillin-clavulanate
	Cephalosporins
	Erythromycin and other macrolides
	Nafcillin
	Nitrofurantoin
	Quinolones
	Rifampin
	Tetracycline
	Trimethoprim-sulfamethoxazole
Estrogens and anabolic steroids	Estradiol
	Tamoxifen
	Danazol
Psychotropic agents	Chlorpromazine
	Haloperidol
	Prochlorperazine
	Carbamazepine
	Phenytoin
	Tricyclic antidepressants
	Sertraline
	Fluoxetine
Nonsteroidal antiinflammatory agents	Sulindac
	Diclofenac
	Ibuprofen
	COX-2 inhibitors
Immunosuppressive agents	Cyclosporine
	Azathioprine
	6-Mercaptopurine
Miscellaneous	Terbinafine
	H2-receptor antagonists
	Sulfonylureas
	Rosiglitazone
	Pioglitazone
	Terfenadine
	Antiretroviral therapy to treat HIV
	Warfarin
	Captopril
	Mesalamine
	Infliximab
	Gold compounds

nearly every medication because the liver is responsible for their metabolism. Injury to hepatocytes may occur either directly or indirectly due to various reactions. Acetaminophen is an example of an agent that causes a direct toxic reaction to the liver and is the leading cause of drug-induced acute liver failure.[48] It accounts for nearly 50% of cases reported from the US Acute Liver Failure Study Group and is the most common drug or toxin leading to liver transplantation for acute hepatic failure. Another drug-induced mechanism for liver damage is alteration of bile flow. Table 3 provides a list of medications that can contribute to cholestatic injury by affecting bile formation or flow.[49] Patients who develop cholestasis while receiving PN should eliminate medications on this list if at all possible. It is also important to identify and eliminate any herbal supplements that may cause hepatotoxicity, as listed in Table 4[50] (see also Hanje et al in this issue[51]). Because herbal supplements do not require a prescription and are assumed by many to be nontoxic, their use is often not revealed by the patient and requires specific probing by the clinician.

Table 4
List of hepatotoxic herbs and supplements[50]

DHEA/androstenedione	Inositol nicotinate
Boldo	Kava
Chaparral	Pennyroyal oil
Coenzyme Q-10	Red Yeast
Comfrey	Scullcap
Germander	Valerian root

Sepsis

Sepsis is a common complication in patients receiving PN, primarily related to the central venous access device. Infection should be aggressively treated and measures should be taken to minimize recurrence. Strict catheter care procedures should be followed in both the hospital and home setting, including minimizing manipulation of the catheter, using proper hand hygiene and aseptic technique when accessing the catheter, using proper site care, and ensuring proper education of catheter care to the patient or caregiver.[52] Although removal and replacement of a long-term tunneled or implanted central venous access device should be avoided whenever possible, it is also important to recognize those situations when removal is necessary for successful treatment of infection. Efforts to prevent recurrent catheter-related bloodstream infections (CRBSI) rely on identifying those situations when successful treatment with antibiotic or antifungal therapy alone is limited. Catheter removal and 7–10 days of antimicrobial therapy is recommended for patients with a tunnel infection or port abscess.[53] In addition, patients with fungal infections or CRBSI complicated by septic thrombosis, endocarditis, or osteomyelitis require removal of the catheter and appropriate antimicrobial therapy.

Bacterial Overgrowth

Treatment of bacterial overgrowth appears to play an important role in preventing and managing PNALD. Identification of SIBO is generally not difficult due to hallmark symptoms that are present, including complaints of postprandial bloating, gas, cramps, foul-smelling stool or ostomy output, and diarrhea. In addition, serum enzymes or bilirubin concentrations may be elevated. When treating SIBO, the enteral administration of antibiotic therapy appears to be more effective than the IV route because the intestine is the targeted site for activity. Because anaerobic bacteria normally found in the colon are primarily associated with overgrowth in

the intestine, antibiotic agents that target these organisms have been used and include metronidazole, oral gentamicin, oral neomycin, ciprofloxacin, doxycycline, and others.[54–57] Although the choice of antibiotic is empiric, metronidazole is generally considered the agent of first choice due to its anaerobic coverage. A typical adult dose of metronidazole is 250 mg orally 3 times daily for 10–14 days. In addition to improvement of liver enzyme and bilirubin concentrations, clinical response may be dramatic from the patient perspective due to resolution of the uncomfortable and embarrassing symptoms noted above. For patients that do not respond to a course of metronidazole, switching to another antibiotic may be beneficial. Measures that may be helpful in preventing recurrence of SIBO include avoidance of simple sugars in the diet, avoidance of gastric acid–suppressing agents, and use of probiotic therapy. In addition, for patients with intestinal stasis due to chronic intestinal pseudoobstruction, agents used to enhance motility may be useful in minimizing recurrence of SIBO.[58] Trials of prokinetic agents such as metoclopramide, erythromycin, tegaserod, and octreotide may be beneficial in improving motility. Octreotide stimulates small intestinal motility and has been shown to be beneficial in patients with chronic intestinal-pseudoobstruction and SIBO.[59] Due to octreotide's ability to also inhibit gastric emptying, combination therapy with erythromycin may be beneficial in mitigating this effect.[60]

Modification of PN

A critical review of the PN formulation should be done whenever liver complications develop. Even if the PN therapy did not initiate the complication, it may contribute to or exacerbate the problem. Overfeeding should be avoided, and a trial of decreasing calories may be warranted when energy requirements are unclear. Providing a balanced energy source by adjusting the carbohydrate-to-fat ratio to give more IVFE may improve serum liver enzymes that are elevated due to steatosis. In the patient receiving long-term PN who develops cholestasis, specifically limiting IVFE dose may be beneficial. Although standard guidelines suggest keeping IVFE <2.5 g/kg/d in adults and children,[26] there is evidence that an IVFE dose >1 g/kg/d is associated with development of PNAC.[4] Therefore, at least a short-term trial of stopping IVFE or limiting to <1 g/kg/d appears reasonable.

Although the role amino acids play in the development of PNALD in the adult and older child is unclear, it does seem to influence the development of cholestasis in the infant. Using specialty neonatal amino acid formulations that are supplemented with taurine may be beneficial in reducing PNAC in the infant, particularly in the premature infant and in those with NEC.[32] In addition, avoiding high-protein doses (>2.5–3 g/kg/d) in the infant may also be beneficial in minimizing risk of developing PNAC. Carnitine deficiency has been suggested as a cause for steatosis, but the benefits of supplementing the PN formulation with carnitine is yet to be established. Finally, infusing PN over a cyclic period rather than a continuous, 24-hour infusion rate may be beneficial in reducing the risk of PNALD.

Enteral Nutrition

Because even small amounts of enteral intake may be beneficial in promoting enterohepatic circulation of bile acids, all measures to optimize the enteral route for feeding should be taken. For example, in the patient with chronic intestinal pseudoobstruction receiving continuous gastric decompression, a trial of jejunal feeding at a slow rate during the night may be beneficial. Medications to enhance motility may be necessary to aid success, and multiple attempts may be required before tolerance is achieved. During periods of acute illness, enteral tolerance may be more difficult to achieve and setbacks can be expected, but attempts should be made to restart enteral feeding as soon as possible once the condition has stabilized. Patients with short bowel syndrome should be encouraged to maximize oral intake because at least some of their intake will be absorbed. These patients may even require a reduction in PN calories in order to prevent unwanted weight gain, but fluid requirements generally remain high because stool output tends to increase when oral intake increases.

Other Pharmacotherapeutic Options

In addition to enteral intake, medications can also be used to help stimulate bile flow and maintain gallbladder contractility. Ursodiol (ursodeoxycholic acid) is a form of bile acid that has been used widely in the treatment of various chronic cholestatic liver diseases and has been shown to improve biochemical markers of cholestasis.[61] When given orally at therapeutic doses, it becomes the predominant biliary bile acid and is thought to displace potentially hepatotoxic bile salts. It may also protect against hepatobiliary injury by exerting a hepatocyte membrane-stabilizing or immunomodulatory effect. Experience using ursodiol to treat PNAC is limited but somewhat encouraging. In adults receiving long-term PN who developed cholestasis, ursodiol 600 mg/d was associated with normalization of biochemical markers and resolution of pruritus.[62] Retrospective studies done evaluating the use of ursodiol therapy with doses of 10–30 mg/kg/d in neonates with PNAC demonstrated a reduction in serum bilirubin concentrations.[63,64] In children with PNAC receiving long-term PN, ursodiol 30 mg/kg/d resulted in resolution of hepatomegaly and jaundice within 1–2 weeks and normal liver enzyme concentrations within 4–8 weeks.[65] Although ursodiol may improve biochemical markers and symptoms of pruritus, there is no

evidence that it alters the progression of disease. In addition, because ursodiol is only available for oral administration, it has limited usage in patients who cannot absorb oral medications. Extemporaneous preparation of an oral suspension from ursodiol capsules may enhance absorption, but it may not be enough for some patients.

CCK-octapeptide (CCK-OP) is a synthetic fragment of CCK that produces the biologic activities of CCK and is available in injectable forms for IV and intramuscular administration. In studies that were nonrandomized or retrospective, its use was reported to have some benefit in reducing serum conjugated bilirubin concentrations in patients with PNAC[66,67] and in preventing elevated conjugated bilirubin concentrations in infants receiving long-term PN.[68] However, a more recent multicenter, double-blind, randomized, controlled trial conducted between 1996 and 2001 did not support these results.[69] The study enrolled 243 neonates considered at risk for developing PNAC and randomized them to receive CCK-OP at a dose of 0.04 mcg/kg twice/day or placebo. According to conjugated bilirubin concentrations, the CCK-OP failed to significantly reduce PNAC and it had no effect on secondary measures such as incidence of sepsis, time to achieve enteral intake goals, incidence of biliary sludge and cholelithiasis, and hospital days. The investigators concluded that CCK-OP should not be recommended for the prevention of PNAC.

Phenobarbital has been used in the treatment of other types of cholestatic liver disease, but any benefits in treating PNAC have not been established. Available case reports demonstrate inconsistent results.[6] In a retrospective review of 31 noninfected neonates receiving PN, there were 14 infants in the group who were also receiving phenobarbital for neurologic indications.[70] More patients in the phenobarbital group actually developed cholestasis (defined as a total bilirubin >3 mg/dL) compared with the nonphenobarbital group. Phenobarbital has also been used in relieving pruritus in patients with cholestasis. Other medications that have been used in treating symptoms of pruritus include ursodiol, rifampin, cholestyramine, and antihistamines.

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 remaining treatment option.[71] Medicare has approved payment for intestinal transplantation in patients who fail PN therapy, and one of the criteria used by Medicare to define PN failure is the development of impending or overt liver failure. The choice of isolated small bowel *vs* combined small bowel and liver transplantation depends on the extent of liver disease. Although many patients are able to stop PN after receiving intestinal transplantation, there are other life-threatening complications and quality-of-life issues that must be considered before deciding on this option. In addition, isolated liver transplantation may be an option for selected pediatric patients with liver failure associated with short bowel syndrome in whom more time will allow for enteral adaptation and anticipated complete enteral autonomy.[72]

Summary

The association between PN and liver disease is well established, but understanding how to prevent and manage the complication remains a difficult clinical problem. The etiology is multifactorial, and therefore a thorough approach is required to minimize risk of PNALD in all patients receiving PN, but especially in patients dependent on long-term support. The PN formulation should be evaluated for appropriateness because nutrient excess or deficiency can contribute to PNALD. It is important to aggressively treat sepsis and take measures to avoid recurrence, as well as to manage SIBO. Efforts should be taken to promote tolerance of even small amounts of enteral feeding in patients with motility disorders and encourage oral intake in patients with short bowel syndrome. Pharmacotherapeutic options are limited when severe and progressive PNALD develops and these patients may be candidates for intestinal or liver transplantation.

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