

Parenteral Nutrition–Associated Liver Disease and the Role for Isolated Intestine and Intestine/Liver Transplantation

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Parenteral nutrition–associated liver disease (PNALD) is the most devastating complication of long-term parenteral nutrition therapy. Because its progression is typically insidious and its long-term consequences are generally underappreciated, PNALD is often recognized too late, when liver injury is irreversible. When end-stage liver disease (ESLD) develops in these patients, most potential interventions are futile and transplantation of both an intestine and a liver becomes the only viable option, despite the relatively poor outcomes associated with this combined procedure. Although likely multifactorial in origin, the etiology of PNALD is poorly understood. Early clinical intervention with a combination of nutritional, medical, hormonal, and surgical therapies can be effective in preventing liver disease progression. If these interventions fail, intestinal transplantation should be performed expeditiously before development of ESLD mandates simultaneous inclusion of a liver graft as well. (HEPATOLOGY 2006;43:9-19.)

Long-term parenteral nutrition (PN) was introduced in the late 1960s by Stanley Dudrick, M.D., and the first patient was discharged home on PN in 1967 (Stanley Dudrick, personal communication, 2005). Although this first patient actually had carcinomatosis with intestinal obstruction from ovarian carcinoma, it was not long until the first patient with short bowel syndrome (SBS) was discharged home on PN in 1968. Her survival of 15 years on PN at home began a new era in the nutritional management of patients with intestinal failure.¹ The first report of parenteral nutrition–associated liver disease (PNALD) surfaced in 1971.² Peden described severe cholestasis in an infant who had received total parenteral nutrition (TPN) for 2.5 months before succumbing to hepatic failure. It is now commonly recognized that serum hepatic aminotransferase concentrations commonly become elevated to between 1.5 and 3

times normal levels during the initial 1 to 3 weeks of PN.³ The etiology for this transient phenomenon is probably multifactorial and may relate to cytokine release driven by the underlying illness as well as the absence of oral intake. The serum bilirubin concentration is rarely elevated during this period in adults, but is much more commonly elevated in preterm infants. It should be recognized that hepatic aminotransferase abnormalities are both insensitive and nonspecific indicators of liver pathology.⁴ Total serum bilirubin concentration may begin to increase in some adults after 10 weeks or more of PN⁵ (Fig. 1). Increases in the serum alkaline phosphatase concentration may be observed as well,⁶ although this abnormality may in part be related to the metabolic bone disease that occurs in patients who receive long-term PN.⁷

Development of Chronic Liver Disease

Although abnormalities in biochemical tests of liver function are commonly recognized in patients who receive PN, the more important concern is whether long-term PN use is associated with chronic and potentially irreversible liver disease. Numerous case reports and case series have suggested that patients with intestinal failure on PN were at increased risk of developing chronic liver disease and hepatic failure in the absence of other readily identifiable causes.⁸⁻¹⁰ Only a single case report has documented the progression of liver disease from steatosis to fibrosis and cirrhosis with serial biopsies.¹¹ This particular case was a patient with SBS secondary to Crohn's disease

Abbreviations: PN, parenteral nutrition; SBS, short bowel syndrome; PNALD, parenteral nutrition–associated liver disease; TPN, total parenteral nutrition; NEC, necrotizing enterocolitis; LPS, lipopolysaccharide; ESLD, end-stage liver disease; GLP-2, glucagon-like peptide 2.

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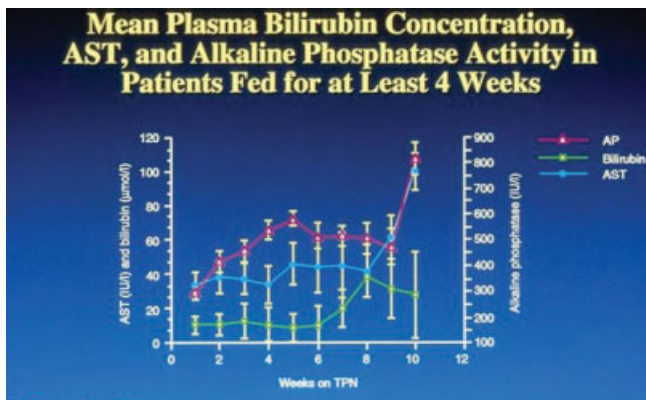


Fig. 1. The increase in serum hepatic aminotransferases in patients receiving long term TPN (reprinted with permission from Clark et al. Liver function tests in patients receiving parenteral nutrition. JPEN 1991;15:54-59.

whose hepatic aminotransferases became elevated after 11 months of PN. Liver biopsy revealed steatosis. A subsequent biopsy 8 months later showed progressive steatosis, a third biopsy 2.5 years later showed fibrosis, and a final biopsy 5 years later showed micronodular cirrhosis. Fibrotic changes on histology are generally thought to be irreversible, although there are scant human data. Progression of PNALD to fibrosis and subsequently cirrhosis with hepatocellular carcinoma has been described in an infant who had received PN for 395 days with minimal enteral intake.¹² Individuals with the least amount of residual intestine appear to be at greatest risk for eventual hepatic failure and death.¹⁰ This finding suggests the likelihood that the greater the degree of malabsorption, the greater the risk of liver disease. It may be reasonable to state that PNALD may be more a function of the underlying intestinal failure than related to the PN solution itself.

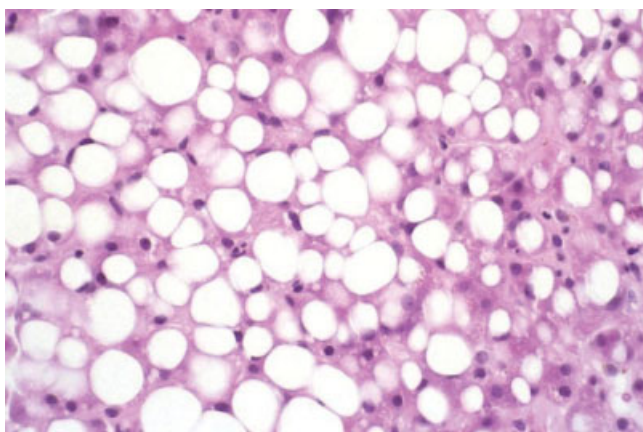


Fig. 2. Liver biopsy showing microvesicular and macrovesicular steatosis in a patient that had received home TPN for 2 years.

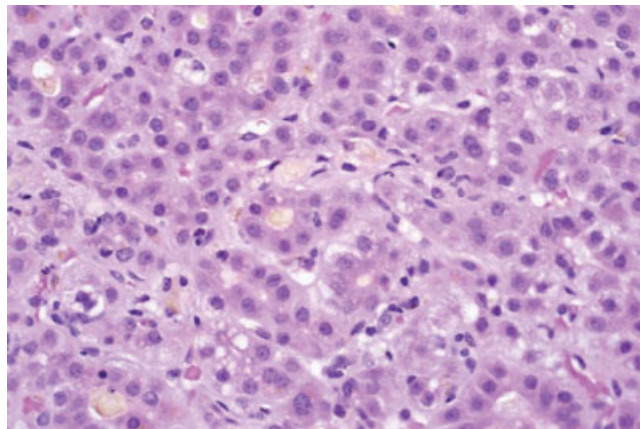


Fig. 3. Liver biopsy showing TPN-associated cholestasis in an infant.

Histology

Histologically there are two presentations of PNALD, although there is significant overlap. In adults and older children, steatosis predominates, although cholestasis may be evident as well (Fig. 2). In infants, cholestasis generally predominates (Fig. 3). There is often ballooning of hepatocytes, Kupffer cell hyperplasia, bile duct plugging, and extramedullary hematopoiesis may also be present (Fig. 4). Both macrovesicular and microvesicular steatosis are usually evident in a diffuse pattern. More ominous findings are steatohepatitis (which is initially evident with periportal lymphocyte infiltration), hepatocyte necrosis, and pericellular fibrosis. Bile duct hyperplasia and proliferation is often encountered together with the development of fibrosis.

Prevalence of PNALD

Chronic cholestasis (defined by the investigators as elevations in two of the following liver tests to $>1.5\times$ the

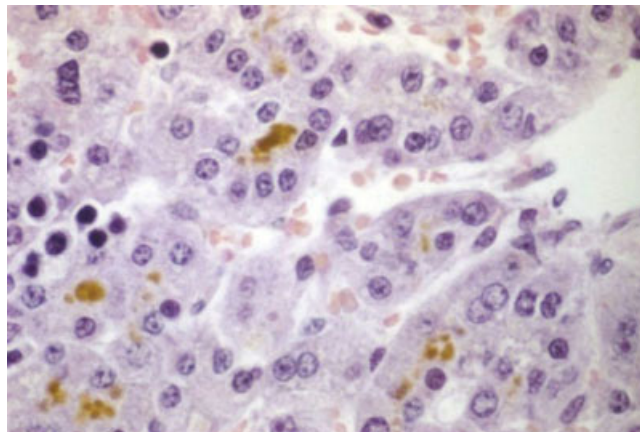


Fig. 4. Liver biopsy showing extramedullary hematopoiesis in an infant.

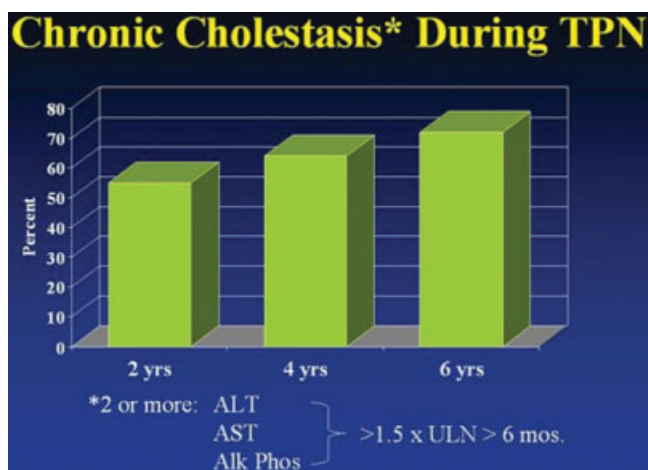


Fig. 5. Prevalence of TPN-associated cholestasis during TPN (adapted from Cavicchi et al. *Ann Intern Med* 2000;132:525-532).

upper limits of normal for >6 months: alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase) occurred in 55% of patients who received PN for at least 2 years, 64% at 4 years, and 72% at 6 years of PN (Fig. 5).¹³ One might argue that in addition to an aminotransferase abnormality, an elevation in either alkaline phosphatase or bilirubin should be required to define cholestasis. The prevalence of complicated liver disease (defined by the investigators as evidence of portal hypertension, portal fibrosis or cirrhosis on biopsy, total serum bilirubin concentration >3.5 mg/dL for at least 1 month, ascites, hepatic encephalopathy, variceal hemorrhage, or a factor V concentration <50%) was 26% at 2 years, 39% at 4 years, 50% at 6 years, and 53% at 8 years (Fig. 6). In the United States, Chan et al. reported that 22% of 42 intestinal failure patients who required home PN for more than 1 year developed chronic liver disease, with the incidence increasing over time.¹⁴ Death occurred at a median of 10.8 months following the initial increase in serum bilirubin concentration. Mortality occurred in all patients with a serum total bilirubin of >3.6 + 1.2 mg/dL, although PNALD was not necessarily more severe in those with the shortest residual intestine.

The prevalence of PNALD is much greater in infants, particularly those born prematurely. Sondheimer et al. reported that approximately 65% of their infants developed cholestasis and 13% developed hepatic failure after only 6 weeks of PN.¹⁵ Other centers have reported a prevalence ranging from 15% to 85%. In these patients it is believed that the reduced bile acid pool size with an immature enterohepatic circulation, specific underlying diseases such as necrotizing enterocolitis (NEC), frequency of infections and antibiotic use, number of surgical procedures, and number of blood transfusions may all con-

tribute to the high incidence of PNALD in this vulnerable group.¹⁶

Pathophysiology

Many etiologies have been proposed for PNALD. However, for most, there are minimal supporting data in humans.

Nutrient Deficiencies. Patients who begin TPN because of severe protein malnutrition (Kwashiorkor) may develop hepatic steatosis because of decreased very low density lipoprotein synthesis.¹⁷ Humans require linoleic acid of at least 2% to 4% of total caloric intake to avoid essential fatty acid deficiency, which may result in hepatic steatosis. Intravenous lipid emulsions are typically 50% linoleic fatty acid. Therefore, essential fatty acid deficiency is extremely rare unless lipid emulsion is completely absent from the TPN prescription.

It had been postulated that carnitine deficiency might occur during TPN because carnitine is not generally present in the TPN solution. Carnitine is essential for the transport of long chain fatty acids across the inner mitochondrial membrane for oxidation. Hepatic steatosis does develop in congenital and acquired carnitine deficiency,¹⁸ and plasma total and free carnitine concentrations are decreased in patients who receive long-term PN.^{19,20} However, carnitine concentrations decreased only to approximately 50% of normal (within 3 weeks of beginning PN) versus 10% of normal in true carnitine deficiency.¹⁸⁻²⁰ In addition, no correlation between plasma carnitine concentration and hepatic aminotransferase abnormalities has been observed and carnitine supplementation does not improve either hepatic aminotransferase abnormalities or the degree of hepatic steatosis in patients who require long-term PN.^{21,22}

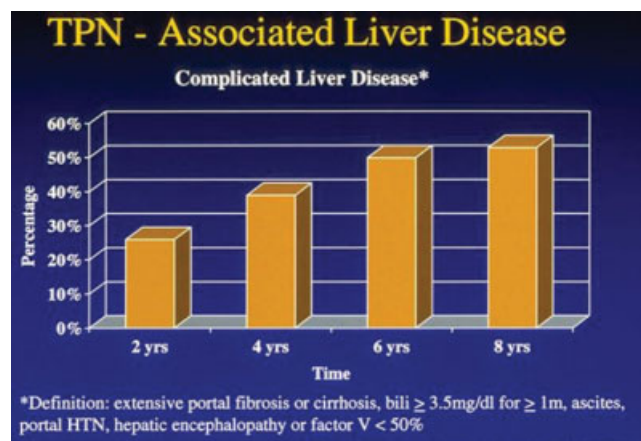


Fig. 6. Presence of complicated liver disease during TPN (adapted from Cavicchi et al. *Ann Intern Med* 2000;132:525-532).

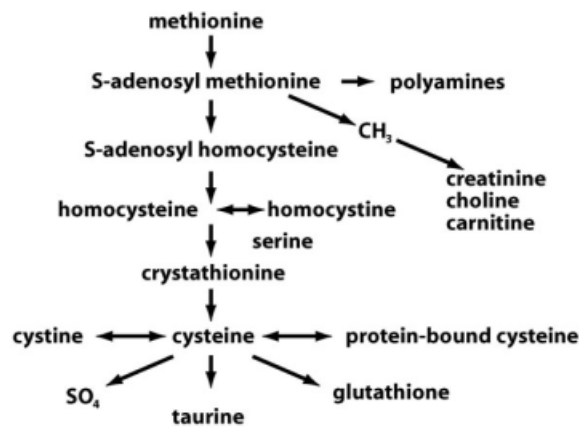


Fig. 7. Diagram of the Hepatic Transsulfuration Pathway. Adapted from Chawla et al. *Am J Clin Nutr* 1985;42:577-584.

Taurine is often supplemented in neonatal PN, although not routinely in adults. In guinea pigs, oral supplementation increases bile flow and the taurine:glycine ratio of conjugate bile acids.²³ It had been widely believed that taurine supplementation was responsible for the decreased incidence observed in neonatal PNALD,^{24,25} although more recent data have suggested that it does not lead to a lower incidence of cholestasis.²⁶⁻²⁸ It is more likely that overall improvements in neonatal critical care, including treatment of sepsis, hypoxia, hypotension, and early enteral feeding, have contributed to the decline in the incidence of PNALD in this population.²⁹

Plasma-free choline, like carnitine and taurine, another product of the hepatic transsulfuration pathway (Fig. 7), is low in more than 90% of patients who require long-term TPN.⁶ Choline deficiency results in hepatic steatosis because of impaired very low density lipoprotein synthesis, which results in hepatic triglyceride accumulation. Studies in humans have found a significant negative correlation between hepatic aminotransferase abnormalities and plasma-free choline concentration.³⁰⁻³² Initial human trials have shown that hepatic steatosis resolves and hepatic aminotransferase abnormalities significantly improve with intravenous choline supplementation.³⁰⁻³² (Fig. 8A-E) TPN does not currently include choline and intravenous choline is not currently commercially available, although there is an ongoing multicenter trial.

Intravenous nutrient requirements may differ from orally consumed nutrients because metabolism may differ. Normally, with oral intake, digestion begins in the oropharynx with the secretion of lingual lipase and salivary amylase. In addition, epidermal growth factor released from the esophageal mucosa is stimulated by oral food intake.³³ Nutrient metabolism following portal absorption differs from that received intravenously. Following hepatic first-pass metabolism, nutrient remnants are

transported to systemic circulation via the right side of the heart and eventually to the kidneys, where some nutrients are reabsorbed and others are excreted as waste materials. This process differs for intravenously infused nutrients in which case nutrients bypass the portal circulation and are first transported to the heart and later to the liver via the hepatic artery. Methionine, a sulfur amino acid that is the substrate for choline synthesis, is normally metabolized to cysteine and other metabolites via the hepatic transsulfuration pathway. Stegink and Besten showed that when methionine was infused intravenously in normal volunteers, cysteine was nearly undetectable in blood, as opposed to when methionine had been consumed in the diet or administered via a nasogastric tube.³⁴ It is likely that plasma free choline concentration is low in patients who receive TPN because the methionine contained in the TPN solution is not metabolized to choline to any significant extent and choline likely becomes an essential nutrient for humans who receive PN.³⁵ Although choline is ubiquitous in the diet, patients with malabsorption that is significant enough to require PN will malabsorb choline as well.³⁰ Some choline is present in lipid emulsion, but the amount is insufficient to prevent choline deficiency.^{6,36}

Although it appears that choline deficiency is a necessary condition for developing PN-associated hepatic steatosis, it is not clear whether choline deficiency alone is sufficient to result in the eventual development of fibrosis, cirrhosis, and hepatic failure. It is possible, although conjecture, that a second hit is necessary to trigger the rapidly progressive steatohepatitis that may be observed in patients who require long-term PN. For example, Eastin et al. found that choline-deficient rats treated with endotoxin lipopolysaccharide (LPS) exhibited substantially increased serum hepatic aminotransferase concentrations and steatosis and steatonecrosis on liver histology when compared with choline-sufficient rats treated with LPS, which had very minor increases in liver tests and no histological changes.³⁷ Experimental evidence suggests that progression of steatosis to fibrosis may also be related to lipid peroxidation, particularly in zone 3.³⁸ Lipid peroxidation may be increased during PN,³⁹ although this observation has not been a universal one,^{40,41} as the multivitamin preparations used in TPN may be a protectant factor.^{40,42} During TPN use, methionine concentration in the blood increases as it is not metabolized via the hepatic transsulfuration pathway to choline and other metabolites.³⁵ Experimental data in a rabbit model of TPN suggest that this build-up of excessive methionine may itself induce cholestasis.⁴³

Premature infants may be at particular risk in developing TPN-associated liver disease because the hepatic transsulfuration pathway may not be fully developed.^{44,45}

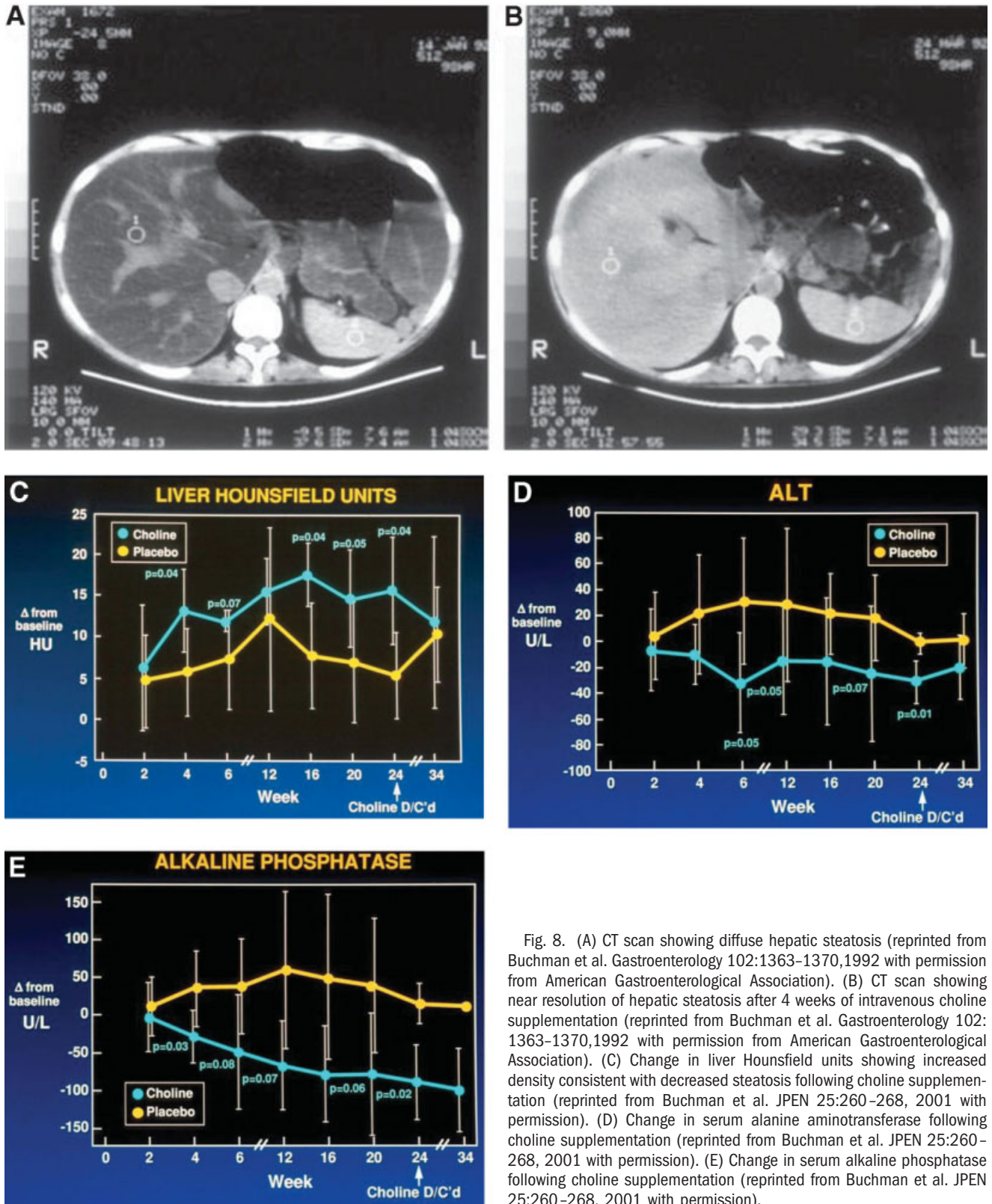


Fig. 8. (A) CT scan showing diffuse hepatic steatosis (reprinted from Buchman et al. *Gastroenterology* 102:1363-1370,1992 with permission from American Gastroenterological Association). (B) CT scan showing near resolution of hepatic steatosis after 4 weeks of intravenous choline supplementation (reprinted from Buchman et al. *Gastroenterology* 102: 1363-1370,1992 with permission from American Gastroenterological Association). (C) Change in liver Hounsfield units showing increased density consistent with decreased steatosis following choline supplementation (reprinted from Buchman et al. *JPEN* 25:260-268, 2001 with permission). (D) Change in serum alanine aminotransferase following choline supplementation (reprinted from Buchman et al. *JPEN* 25:260-268, 2001 with permission). (E) Change in serum alkaline phosphatase following choline supplementation (reprinted from Buchman et al. *JPEN* 25:260-268, 2001 with permission).

This disease may also put such infants at particular risk for choline deficiency. Plasma-free choline concentration is also lower in infants who require TPN than in those who do not,⁴⁶ and further investigation in this area is ongoing.

It has also been suggested that vitamin E deficiency may play a role in the development of PNALD. Vitamin E may mitigate lipid peroxidation; however, vitamin E deficiency in patients who require PN is very rare,⁴² at

least in patients who routinely receive lipid emulsion,⁴⁷ and has not been shown to result in liver disease.⁴⁸ Selenium, a cofactor of glutathione peroxidase, may be deficient in patients with cirrhosis,⁴⁹ but there is no evidence that selenium deficiency plays a role in the development of PNALD.

In a rodent PN model, depletion of plasma glutamine was associated with the development of hepatic steatosis, and glutamine supplementation resulted in decreased steatosis.^{50,51} However, rodent glutamine requirements are quite different from those of humans; in fact, glutamine supplementation for long-term PN patients resulted in hepatic abnormalities in one study.⁵² In addition, not all studies have indicated a role for glutamine deficiency in the development of hepatic steatosis.⁵³

Nutrient Toxicities. Overfeeding patients with either carbohydrate or lipid may be associated with developing hepatic steatosis and/or cholestasis. Infusion of >50 kcal/kg/day as dextrose leads to an increase in the portal insulin:glucagon ratio,^{54,55} which subsequently leads to the development of hepatic steatosis.⁴⁵ The increased insulin concentration inhibits mitochondrial carnitine acyltransferase, the rate-limiting factor in fatty acid oxidation.⁵⁶ Excessive carbohydrate infusion also results in increased hepatic acetyl-coenzyme A concentration, and induction of acetyl CoA carboxylase, which in turn stimulate fatty acid synthesis.^{57,58} Cycling PN to an overnight infusion, although increasing blood glucose and insulin concentration during the infusion, is associated with a decreased risk of hepatic dysfunction.⁵⁹ This outcome may be because increases in portal insulin concentration occur only intermittently. However, the references in this review to PNALD were virtually entirely in patients who received long-term, overnight PN infusion.

Lipid overload syndrome (even >2.5-3.0 g/kg/day) may result in development of cholestasis in addition to hypoxia, thrombocytopenia, disseminated intravascular coagulation, and death.^{60,61} Although it is quite rare that adult patients receive such massive doses of lipid emulsion infusion, such doses are often used in the premature neonate, in whom growth is a critical priority. Two retrospective studies have suggested that serum hepatic aminotransferase abnormalities may be associated with even more conventional doses (>1.0 g/kg/day),^{13,14} although a randomized, controlled trial comparing doses of intravenous lipid emulsion is required for more definitive association of cause and effect. One hypothesis for the role of lipid emulsion in the pathogenesis of PNALD involves the role of plant sterols (phytosterols). These are contained in large concentrations in commercially available lipid emulsions, and blood concentrations are correspondingly increased in patients

who receive PN with lipid emulsion.⁶² The development of PN-associated phytosterolemia appeared to correlate with the onset and severity of PNALD and with the dose of commercial lipid emulsion used. Despite the striking temporal association, a causal relation was not established. *In vitro* and *in vivo* animal investigations have indicated that parenteral phytosterol supplementation was associated with decreased bile acid secretion and decreased secretory function in isolated rat hepatocyte couplets.⁶³ However, no specific correlation with hepatic abnormalities in humans has been demonstrated and reduction of the volume of lipid infusion is not invariably associated with improvement or resolution of liver abnormalities.⁶² The recent characterization of the sterol transporters, ABC-G5 and G8 has led to renewed interest in the potential role of phytosterols in the development of PNALD, perhaps through alterations in bile acid transporter expression.⁶⁴

Manganese is contained in PN both as a contaminant and as an additive.⁶⁵ Nearly all manganese excretion is via the biliary tract. Several case reports describe increased serum manganese concentration in patients with PN-associated cholestasis.⁶⁶⁻⁶⁸ It is probably more likely that manganese retention occurs because of decreased biliary flow rather than as a primary cause of decreased biliary flow.⁶⁹ Another metal, aluminum, has been associated with the development of cholestasis in rodent TPN models.^{70,71} Prior to mid-1985, the amino acid component in TPN was derived from casein hydrolysate, rather than synthesized as individual amino acids to form the balanced free amino acid solutions used today. Current amino acid solutions have little aluminum contamination, although there is some contamination present in some of the potassium, phosphate, sodium, and calcium additives. The overall contribution of these additives to PN aluminum contamination is minimal, and aluminum contamination is <2% of pre-1985 levels.⁷² Copper is excreted via the biliary route. Although the copper contained in the multitrace metal formulation used in PN does not lead to hepatotoxicity, copper should be removed from the PN solutions in patients with significant cholestasis because of the potential for developing copper toxicity.⁷³

Bacterial Overgrowth and Altered Bile Salt Metabolism

Bacterial overgrowth is another hypothesized cause of PNALD. However, hepatic dysfunction as a direct result of bacterial overgrowth, bacterial translocation, or endotoxemia has never been described in humans; in fact, there is evidence to the contrary.⁷⁴ Lithocholic acid, a second-

Table 1. Potential Therapies for TPN-Associated Liver Disease

Decrease dextrose infusion
Decrease lipid infusion
Provide sufficient lipid emulsion
Cycle TPN infusion
Encourage oral intake
Ursodeoxycholic acid
Metronidazole
Choline (investigational)
Isolated intestine transplant
Combined liver/small intestine transplant

ary bile acid, is formed by bacterial 7- α dehydroxylation of chenodeoxycholic acid, and has been postulated to have hepatotoxicity in infants. However, the neonatal animal is actually more resistant to the effects of lithocholic acid-induced cholestasis than the adult⁷⁵ and there is no corroborative evidence from human investigation. Ursodeoxycholic acid is also metabolized to lithocholic acid, albeit to a lesser extent than with chenodeoxycholic acid. It has been used to treat TPN-associated cholestasis. Data in adults are limited to a single case report⁷⁶ and a case series of 9 patients.⁷⁷ The data in neonates consist of one retrospective review and two open-label studies.⁷⁸⁻⁸⁰ Cocjin et al. observed a significant decline in serum total bilirubin concentration when a dose of ursodeoxycholic acid of 15 to 45 mg/kg/day was used, although cholestasis was not eliminated.⁷⁸ A retrospective human study suggested that there were minimal effects on liver test abnormalities in patients who had received metronidazole.⁸¹ Another study indicated that metronidazole use was associated with improvements in liver test abnormalities, but the patients all had active Crohn's disease and were overfed, which are both factors that may lead to hepatic derangements.⁸²

Notwithstanding the previous section, sepsis appears to be an independent risk factor for liver disease. The frequent clinical observation of acute worsening of biochemical tests of liver function in patients during episodes of catheter-related or other sepsis supports the belief that recurrent sepsis is an important risk factor for the development of PNALD. A detailed postmortem histopathological study of livers of 19 patients who died of clinical sepsis reported a moderate to marked degree of midzonal and periportal necrosis in 11 patients.⁸³ Moderate to severe acute inflammation was seen in 7 of the 19 patients and moderate to severe cholestasis was seen in 5. Manginello and Javitt first suggested that the development of PNAC in infants was related to the presence of sepsis rather than the duration of PN or the composition of the administered solutions.⁸⁴ Utili et al. reported the cholestatic effects of *E. coli* endotoxin on the isolated perfused rat liver and pointed out the similarity of light and elec-

tron microscopic appearances of PNAC to those associated with endotoxin.⁸⁵ Against this increasing body of evidence for a major role of sepsis in the development of PNAC, at least one recent histopathological study in rats demonstrated that the light and electron microscopic appearances of cholestasis from intraperitoneal sepsis and from PN administration were sufficiently different.⁸⁶ In rats that developed cholestasis from intraperitoneal sepsis, degenerative changes were observed in the intermediate and external zones of the hepatic lobule with electron microscopic appearances of dilated bile canaliculi and altered microvilli. In contrast, liver specimens from rats with PN-induced cholestasis showed dilated central veins and sinusoids with proliferation of Kupffer cells and prominent phagocytosis. Electron microscopy in this group showed many highly electron dense particles in the cytoplasm and numerous secondary lysosomes near dilated bile canaliculi.

PNALD may develop on top of pre-existing liver disease such as hepatitis C. It is unknown whether and to what degree the additional insults from the described pathophysiology may stimulate more rapid progression to end-stage liver disease (ESLD).

The Role of Intestinal Transplantation in PN-Associated Hepatobiliary Disease

In patients with intestinal failure, who are PN-dependent, impending or overt liver failure is considered an indication for intestinal transplantation (Table 2).⁸⁷ Impending PN-associated liver failure has been defined rather loosely by the development of any of the following clinical manifestations: elevations in serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, peristomal bleeding, or hepatic fibrosis/cirrhosis. Although many patients with mild or transient elevations in bilirubin or liver enzymes will not require a transplant, those with persistent or progressive liver abnormalities should be considered for transplantation. Earlier stages of liver injury are reversible following "intestinal rehabilitation," by which oral intake and fluid/nutrient ab-

Table 2. Medicare-Approved Criteria for Small Intestinal Transplantation

- 1. Impending or overt liver failure** (ie, elevated serum bilirubin and/or liver enzymes, splenomegaly, thrombocytopenia, gastroesophageal varices, coagulopathy, stomal bleeding or hepatic fibrosis/cirrhosis)
- 2. Thrombosis of major central venous channels** (ie, ≥ 2 thromboses in subclavian, jugular, or femoral veins)
- 3. Frequent central line related sepsis** (ie, ≥ 2 episodes of systemic sepsis secondary to line infection per year, ≥ 1 episode of line-related fungemia, septic shock, or ARDS)
- 4. Frequent severe dehydration**

sorption are optimized^{87,88} and, if necessary, by transplantation of an isolated intestine;⁸⁹ however, the development of cirrhosis and/or overt portal hypertension signifies progression to ESLD and leaves combined intestine and liver transplantation as the only option for survival.

Because the progression to ESLD is often insidious and has not been clearly defined with discrete incremental stages, any persistent liver abnormalities detected by laboratory tests (elevations in serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin or INR and/or a falling platelet count) or histology (steatosis, cholestasis, fibrosis, steatohepatitis) should raise concerns and prompt an aggressive investigation of all potential causative factors at centers with expertise in PNALD. One might argue that all long-term PN patients should be seen in specialized centers, as survival is better when compared with survival in community-treated patients.⁹⁰ Once other causes of liver disease are excluded, conservative medical and surgical strategies should be attempted before proceeding with transplantation.

The optimal timing of intestinal transplantation in patients that develop PN-associated liver injury has been controversial; thus far the majority of patients are not referred for transplant evaluation until they have already developed advanced liver disease. In the United States, 74% of all patients who have been listed for an intestine transplant have also needed to be listed for a liver transplant either simultaneously (52%), previously (10%), or subsequently (12%) (unpublished data from UNOS database, 2005). Although the reasons for these late transplant referrals have not been clearly defined, they likely reflect an uncertainty about the role of transplantation in preventing ESLD and its relationship to other potentially hepatoprotective therapies (see Table 1).

Unfortunately, most (55%) patients who require combined liver/intestine transplants do not survive to transplant because their waiting list mortality is higher than that for any other transplant candidate population.^{89,91} Although this high waiting list mortality is primarily attributable to the fact that this patient subset is extremely sick,¹⁴ it also reflects the more limited availability of donor livers. Furthermore, posttransplant outcomes in liver/intestine transplant candidates who do survive to transplant are also inferior to those seen with recipients of intestine transplants who do not need livers (Table 3).⁹² Although recent modifications to UNOS allocation policies regarding prioritization of candidates needing combined liver/intestine transplants may help reduce waiting list mortality, the influence of these policies on overall outcomes and their impact on the liver transplant waiting list remains to be seen.

Table 3. Post-Transplant Pretreatment Graft Survival for Isolated Intestine on Liver/Intestine Transplants

Organs	Survival	1 year	3 years
Intestine only	Patient	79.1 %	73.1 %
Liver/intestine	Patient	60.0 %	39.2 %
Intestine only	Graft	71.8 %	43.6 %
Liver/intestine	Graft	56.1 %	39.2 %

Because the options for intestinal failure patients who develop PNALD are limited and associated with dismal outcomes, early and aggressive interventions to prevent development of ESLD should be implemented, including, if necessary, isolated intestinal transplantation. Such program, which should include not only transplantation but “rehabilitation” of the intestine using dietary, surgical, medical and hormonal therapy, should include patients with <100 cm of residual intestine because these patients are at greatest risk for development of ESLD.^{10,93}

Not all high-risk intestinal failure patients will need an intestinal transplant. While the current Medicare criteria (Table 2) suggest that patients with intestinal failure and abnormal liver enzymes or elevated bilirubin are candidates for intestinal transplantation, without additional information such transplantation is difficult to justify because these abnormalities may be transient, benign, or unrelated to the patients’ intestinal failure/TPN. The contributions of other factors, including gallstones, medications, sepsis, bacterial overgrowth, alcohol abuse, and hepatitis must be excluded. Furthermore, these liver abnormalities may be reversible following other interventions. As previously discussed, conservative measures such as optimizing enteric feeds, minimizing TPN, and controlling the toxic effects of enteric bacteria and sepsis can often be effective in stabilizing or reversing the TPN-associated liver injury. Growth factors, such as recombinant human growth hormone^{94,95} and glucagon-like peptide 2 (GLP-2),^{96,97} which may augment gut adaptation and may reduce TPN dependence in patients with, may be considered if liver abnormalities persist despite optimal use of conservative measures. Additionally, non-transplant surgical modifications, including gut-lengthening procedures, provide significant benefit in selected patients.^{98,99} If these interventions fail to reverse the progression of liver injury, intestinal transplantation must be considered to restore gastrointestinal function, allow PN discontinuation, and halt the progression to ESLD, thereby obviating the need for a liver/intestine transplant.

Intestine transplant candidates who do not also need livers have significantly better outcomes both on the waiting list (9% mortality) and after transplantation (Table 3).^{91,92} These patients are generally less sick going into the

transplant and are also more salvageable post-transplant if severe complications develop, because graft removal with discontinuation of immunosuppressive drugs and resumption of TPN may be an option, at least in some cases. Although no randomized controlled trials exist, recent results suggest that mortality in high-risk intestinal failure patients who do not receive a transplant may exceed that of those who receive intestine-only transplants.^{91,92}

The available data clearly indicate that waiting for the progression to ESLD before attempting to salvage with a combined liver/intestine transplant has not been an effective management strategy for patients with PNALD. Intestinal transplantation should therefore be considered before ESLD develops. However, there are currently no widely accepted criteria to define earlier stages in liver disease progression that should automatically mandate intestine transplantation. Greater efforts are needed to develop a clinical-pathological staging system that will help elucidate this decision process.

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