

Liver Complications of Pediatric Parenteral Nutrition—Epidemiology

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ABSTRACT

Total parenteral nutrition (TPN)-induced liver disease develops in 40–60% of infants who require long-term TPN for intestinal failure. The clinical spectrum includes cholestasis, cholelithiasis, hepatic fibrosis with progression to biliary cirrhosis, and the development of portal hypertension and liver failure in a significant number of children who are totally parenterally fed. The pathogenesis is multifactorial and is related to prematurity, low birth weight, and duration of TPN. The degree and severity of the liver disease is related to recurrent sepsis including catheter sepsis, bacterial translocation, and cholangitis. Lack of enteral feeding leading to reduced gut hormone secretion, reduction of bile flow, and biliary stasis may be important mechanisms in the development of cholestasis, biliary sludge, and cholelithiasis. Although it is unlikely that modern TPN solutions have a major role in the etiology of TPN liver disease, manganese toxicity recently has been recognized in children with hepatic dysfunction on TPN. Although there is a definite relationship with the degree of manganese toxicity and hepatic decompensation, it is not yet clear whether this is a primary mechanism or whether the high levels are related to reduced biliary excretion of manganese. The management strategies for the prevention of TPN-induced liver disease include early enteral feeding, a multidisciplinary approach to the management of parenteral nutrition, and aseptic catheter techniques to reduce sepsis. The administration of ursodeoxycholic acid may improve bile flow and reduce gall bladder and intestinal stasis. As survival from isolated intestinal transplantation improves, this therapeutic option should be considered before TPN liver disease becomes irreversible and combined liver and small bowel transplantation is required. *Nutrition* 1998;14:153–157. ©Elsevier Science Inc. 1998

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INTRODUCTION

The successful development of total parenteral nutrition (TPN) has revolutionized the outcome for neonates and infants with intestinal failure either from congenital abnormalities or extensive gastrointestinal surgery.^{1,2} Over time, there have been major improvements in parenteral solutions as understanding of requirements for vitamins and trace elements, have made parenteral solutions safer to use. Furthermore, improvements in catheter design and placement techniques have reduced some of the septic complications of TPN.^{3,4} Hepatobiliary dysfunction remains a serious, life-threatening complication of TPN, and it is an important indication for combined liver and small bowel transplantation.

Hepatic dysfunction secondary to TPN differs in adults and children. There are essentially three clinical syndromes: cholestasis, which is more common in infants, steatosis, which is more common in adults, and biliary sludge and cholelithiasis, which occurs in both adults and children.^{5–9}

Hepatic Steatosis

Although hepatic steatosis is relatively uncommon in infants, it may be suspected by detection of hepatomegaly with transient

elevations of serum amino transferases. It is usually secondary to hepatic accumulation of lipid or glycogen from inappropriately high parenteral carbohydrate calories. Histology of the liver reveals fatty infiltration of hepatocytes, which is reversible after reduction of calories.^{10,11}

Cholestasis

The first documented case of TPN-associated liver disease was in a premature infant who developed evidence of cholestasis. Liver histology at that time showed bile duct proliferation and early cirrhosis.¹² Since then, studies of the incidence of TPN-associated liver disease have varied from 7.4% to 84%.^{13,14} Most recent studies indicate that ~40–60% of children on long-term TPN will develop hepatic dysfunction.^{15,16}

The earliest clinical sign is a rise in conjugated bilirubin, which may occur as early as within 2 wk of starting TPN and will rise during episodes of intercurrent sepsis.^{17,18} There also may be an increase in alkaline phosphatase and amino transferases within 4–6 wk in ~34% of infants. As a rise in alkaline phosphatase also may be secondary to rickets in this group of infants, it has been

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suggested that γ glutamyl transpeptidase (γ GT) may be an early marker of TPN-associated cholestasis.¹⁹

Alternatively other groups have suggested that the most sensitive indicator of early cholestatic liver disease is a rise in serum bile acid concentrations, particularly sulfated lithocholate.^{20–22}

As hypoalbuminemia has been associated with cholestasis in adult patients on TPN, the prevalence of hypoalbuminemia and its effect on outcome in parenterally fed infants has been evaluated in 56 infants receiving parenteral nutrition for gastrointestinal disease.²³ The authors found no significant difference between hypoalbuminemia and normal albumin levels on evaluation of gestational age, composition of parenteral nutrition, or weight gain.

Although mortality was higher in infants with hypoalbuminemia (33.3%) than in those with normal albumin (4.9%), this was unrelated to hepatic dysfunction.

Etiology of TPN Liver Disease

The etiology of TPN liver disease is unknown and is likely to be multifactorial.

Many studies have noted the close relationship among the development of TPN liver disease, prematurity, and low birth weight.^{12,21,24,25} Because many infants requiring TPN are likely to be premature with low birth weight, it is difficult to be certain whether these are independent risk factors or associated factors.^{12,21,24,25}

The development of cholestasis is related closely to birth weight and duration of TPN as demonstrated by Beale et al.¹² who reviewed 62 premature infants on TPN. The overall incidence of cholestasis was 23%, but infants receiving therapy for >60 d had an incidence of 80%, increasing to 90% in those treated for >3 mo. The incidence of cholestasis was 50% in infants with birth weight <1000 g but fell to 7% if birth weight was >1500 g.

The increased incidence of TPN liver disease in premature infants suggests that the development of disease may be related to immaturity of the neonatal liver. It is known that in premature infants the total bile salt pool is reduced. There is both diminished hepatic uptake and synthesis of bile salts and a reduced enterohepatic circulation compared with full-term infants or adults.²⁶ It is possible that other essential components of bile secretion, such as glutathione, may be reduced in the newborn, as hepatic glutathione depletion has been demonstrated in young animals on TPN.²⁷

Sulphation, which is an important step in the solubilization of toxic bile salts, such as lithocholic acid, is also deficient in the fetus and neonate.²⁸ It is therefore likely that the liver and biliary system of the premature infant is more susceptible to toxic damage of any kind.^{29,30}

A reduction in the enterohepatic circulation of bile salts may further contribute to the liver injury as intestinal stasis and bacterial overgrowth of the small intestine promotes intraluminal bile salt deconjugation and an increase in the production of lithocholic acid, which impairs bile flow and produces cholestasis in experimental animals.²⁹ There are similarities between the histologic changes secondary to TPN and lithocholate-induced liver dysfunction in animals.^{30,31}

Lack of Enteral Intake

Inability to establish enteral feeding is common in children requiring parenteral nutrition and is one of the important indications for TPN. Nevertheless, it is clear that TPN liver disease is more likely to develop in those children who are unable to tolerate any enteral feeding compared with those who have even partial enteral feeding.^{25,31,32}

From experimental studies, it is clear that short-term fasting has several metabolic and endocrine consequences on intestinal and liver function. Levels of gastrointestinal hormones in patients on TPN are reduced, which may lead not only to intestinal stasis

but to reduced gall bladder contractility.^{33,34} Intestinal stasis may lead to bacterial overgrowth, bacterial translocation, and sepsis, which may increase cholestasis,¹⁸ and to the production of lithocholic acid, which has been shown to be toxic to the liver.^{29,30}

The reduction in cholecystokinin release may influence gall bladder size and contractility and may cause the development of biliary sludge.^{35–37} It is also possible that fasting reduces the size of the bile salt pool and bile formation compounding the difficulties with gall bladder contractility and the formation of sludge.³⁸

Sepsis

TPN liver disease is more common in neonates who have recurrent episodes of sepsis, whether this is related to central line infections or bacterial translocation from bacterial overgrowth.¹⁸ Bacterial overgrowth from intestinal stasis has been related to the development of TPN liver disease, although it is not clear whether this is related to the reduction in bile flow or the production of secondary bile salts, or results from bacterial translocation leading to sepsis.³² A review of eight fatal cases of progressive liver failure in surgical neonates indicated that the hepatic failure was related closely to septic episodes and/or peritonitis.³¹

In a multivariate analysis of risk factors in 74 surgical neonates receiving TPN, the development of cholestasis was related closely to recurrent episodes of sepsis rather than to lack of enteral feeding,¹⁸ confirming an earlier study that related all cases of TPN-associated cholestasis with sepsis.³⁹ The mechanism for this is unknown but may be related to gram-negative bacterial sepsis, which has been shown to decrease bile secretion secondary to endotoxin production.⁴⁰

Components of TPN

The indications that an immature liver may be more sensitive to either bacterial or chemical toxins have led to consideration that the TPN solutions may be incriminated in the pathogenesis of cholestasis.

Animal studies have implicated amino acids in the production of cholestasis, whereas studies in the human neonate suggested a direct effect of amino acid infusions on the hepatocyte canalicular membrane.^{19,38} Clinical support for this mechanism came from studies in which the incidence of cholestasis was related directly to the volume of amino acid infused or the cumulative amino acid intake.^{12,41,42}

Alternatively, the hepatotoxicity may relate to a deficiency of an essential amino acid not available in a commercial preparation (e.g., tyrosine or cysteine), which may be limited due to their relative insolubility.⁴⁴ In older infants and adults, cysteine and taurine are synthesized from methionine but this production is diminished in premature infants.⁴⁵ Not only is taurine one of the main bile acid conjugates in the neonate, but it has been shown to increase bile flow and protect against lithocholate toxicity. Thus taurine deficiency has been postulated as a mechanism in TPN cholestasis although the benefits of taurine supplementation are uncertain.^{46–48}

Some studies have indicated that it is the infusion of amino acids rather than the components that may be toxic as infusion of amino acid into experimental animals reduces bile flow in the animal.⁴⁹

An alternative possibility is that TPN may impair intestinal mucosal immunity and promote translocation of bacteria across the gut wall. In animal studies, bacterial translocation was stimulated by both oral and intravenous administration of TPN solutions possibly by encouraging small intestinal overgrowth.^{50,51}

There is no evidence that lipid emulsions induce cholestasis, although excess lipid calories may lead to hepatic steatosis. In neonates with hepatic dysfunction, close monitoring of triacylglycerol levels is necessary to monitor lipaemia.^{52,53}

Toxic Components of TPN

Historically the degradation of tryptophan in TPN solutions contaminated by sodium bisulphate was thought to produce cholestatic metabolites,⁵⁴ but this is irrelevant with modern solutions. Although aluminium toxicity is well recognized in TPN and may lead to bone disease, there is no evidence that it is implicated in TPN liver disease.^{55,56}

Chromium toxicity, secondary to TPN, has been reported in animals. Both serum and urine chromium levels are higher in children on long-term TPN than in control subjects, although there was no correlation with liver disease.⁵⁷

Manganese Toxicity

The realization that manganese was an essential trace element led to its recent addition to parenteral nutrition solutions.⁵⁸ A number of recent studies have reported the effects of manganese toxicity in children on long-term TPN.^{59,60}

Fifty-seven children receiving long-term TPN including the multi-trace element solutions of Pedel or Addamel (Pharmacia and Upjohn, England) were studied.⁶⁰ Forty-five children (79%) had whole blood manganese concentrations above the reference range. Children with impaired liver function had the highest manganese levels, and there was a significant correlation between whole blood manganese levels, aspartate aminotransferase ($r = 0.63$, $P = <0.001$), and total plasma bilirubin ($r = 0.64$, $P = <0.001$). Eleven children had both hypermanganesemia and cholestasis and four of these died. In the seven survivors whole blood manganese declined when manganese supplements were reduced or withdrawn.⁶⁰

Although it is known that manganese is toxic to both the brain and the liver,⁶¹ it is not clear whether the high magnesium levels lead to cholestasis or are a secondary effect, because manganese is excreted in bile. Nevertheless it is likely that manganese toxicity exacerbates cholestasis in children with established liver disease, and monitoring of manganese levels is particularly important in patients with TPN cholestasis.^{60,62}

Biliary Sludge and Gall Stones

Acalculous cholecystitis, biliary sludge, gall bladder distention, and gall stones have been reported in infants and children on long-term TPN.^{5,7,8,35-37} The incidence of biliary sludge increases with duration of TPN, increasing from 6% at 3 wk to 100% at 6-13 wk⁶³ as does the incidence of gallstone formation,³⁶ particularly in children who have had ileal resection or disease.³⁶ It is presumed that the increase in gallbladder size, noted in parenterally fed infants when compared with enterally fed infants,³⁷ is related to the reduction in cholecystokinin production and other gut hormones.³⁴ Of potential relevance to the pathogenesis of cholestasis and cholelithiasis in infants on long-term TPN is the effect of TPN on bile flow and composition in which impaired bile flow has been a constant finding,^{64,65} although there is no evidence that bile is supersaturated.⁶⁶ In addition to impaired bile flow, gall bladder stasis and impaired gallbladder emptying may be important in the development of gallstones.^{5,67}

Gallbladder stasis may be prevented by administration of cholecystokinin or by stimulating endogenous release of cholecystokinin through pulsed infusions of large volumes of amino acids or by small amounts of enteral nutrition.^{69,70} Because the development of gallstones may be related to biliary and gallbladder stasis secondary to lack of enteral stimulation, it is possible that TPN-related cholestasis may have a similar etiologic basis.

Histology

The histopathologic changes of TPN cholestasis were described in the early 1970s.³¹ The earliest changes are related to

centrilobular cholestasis with little evidence of inflammation and necrosis and no fatty infiltration. More advanced liver disease has been described in a study of 21 children who were being evaluated for combined liver and small bowel transplantation.⁷¹ The most common histologic changes in children with or without cholestasis consisted of portal fibrosis (100%), pericellular fibrosis (95%), and bile ductular proliferation (90%). Pigmented Kupffer cells (81%) and portal bridging (86%) also were prominent features. Biliary cirrhosis was a late development that was associated with death within 6 mo.

Clinical Features

Clinical jaundice is an obvious sign of TPN cholestasis, and fluctuations in serum bilirubin may be related to septic episodes.¹⁸ However, persistent elevation of serum bilirubin ($>200 \mu\text{mol/L}$) suggests an adverse prognosis.^{18,71,72} In 22 children who were evaluated for combined liver and small bowel transplantation, a raised plasma bilirubin concentration ($>200 \mu\text{mol/L}$) predicted death from liver failure within 6 mo in the 11 children who subsequently died of liver failure.⁷²

Even in children without obvious cholestasis, hepatic dysfunction with portal fibrosis and splenomegaly may be present. In 37 children referred for small bowel and liver transplantation, splenomegaly was a constant feature in 75% of this group, irrespective of cholestasis. Despite fairly extensive hepatic fibrosis and splenomegaly, esophageal varices are infrequent in these children.⁷¹⁻⁷³

Management

TPN-induced hepatic dysfunction and structural changes seen are potentially reversible if the TPN can be discontinued before the development of severe fibrosis or cirrhosis.^{74,75}

In many children, however, it may be impossible to discontinue TPN for a considerable period of time, and it is important to reduce the development of hepatic dysfunction. It is clear that the introduction of some enteral feeding is important as even a small amount of feeding will encourage normal biliary dynamics, decrease gall bladder size, improve bile flow, and reduce intestinal stasis and bacterial overgrowth.

The next important strategy is the prevention of sepsis. There was a marked difference between the incidence and the age of development of liver disease in children whose central line catheter care was managed by units with nutrition care teams with experience in parenteral nutrition.⁷² In this study, 22 children were evaluated for small bowel transplantation, 11 of whom were not managed by a multidisciplinary nutrition care team. These 11 children had more complications with intravenous feeding catheters, were less well nourished, and developed liver disease within 1 y, which was associated with early mortality.⁷² Thus strict catheter care and reduction of central line infections is an important preventative mechanism in the development of TPN liver disease.

Other strategies to prevent sepsis include the addition of fiber to enteral feedings if tolerated as this reduces bacterial translocation.^{50,76} Addition of glutamine to TPN solutions is thought to improve gut immunity as it may prevent TPN-related depletion of immunoglobulin A,⁷⁷ while also improving intestinal adaptation.⁷⁸

To improve bile flow and reduce the formation of biliary sludge, oral ursodeoxycholic acid may be advantageous.⁷⁹ Alternatively *Saccharomyces boulardii*, which is a nonpathogenic yeast, may have a trophic effect on the gut and reduce bacterial translocation.⁸⁰

Small Bowel Transplantation

As more than 200 small bowel operations have been carried out worldwide with a 5-y survival of $>50\%$, it is important to consider this therapeutic option in children with intestinal

failure.⁸¹ Current results suggest that isolated small bowel transplantation has more favorable long-term results than combined small bowel and liver transplantation, which has important implications for children with intestinal failure.⁸² As the hepatic complications of TPN are potentially reversible, if TPN

is discontinued soon enough, it is important to consider children with early TPN cholestasis and persistent intestinal failure for isolated intestinal transplantation before liver disease becomes irreversible and a combined transplant is required.⁸⁰⁻⁸²

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