

Mechanisms of Disease: update on the molecular etiology and fundamentals of parenteral nutrition associated cholestasis

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SUMMARY

Since its introduction into clinical practice, parenteral nutrition has revolutionized the care of premature neonates. Serum transaminase and bilirubin levels are commonly elevated in infants on parenteral nutrition, but their normalization is typical in the setting of short-term administration of parenteral nutrition uncomplicated by sepsis. Premature infants who require long-term parenteral nutrition are, however, at severe risk for developing life-threatening hepatic complications. These complications include cirrhosis, liver failure, and the concomitant risks of sepsis, coagulopathy and death. Premature infants and those with short-bowel syndrome are most susceptible to these morbid outcomes. Although it has been more than a quarter of a century since parenteral nutrition was first introduced and its association with hepatic complications described, the precise etiology of parenteral nutrition associated cholestasis (PNAC) remains a mystery; however, our understanding of the molecular components that contribute to PNAC has improved substantially. In this Review, we summarize the fundamentals of PNAC, describe animal models of the disease, review the hepatic bile acid transporters that are crucial for bile acid homeostasis, and define the roles that endotoxin, genetics, and the components of parenteral nutrition are likely to have in the molecular pathogenesis of this life-threatening condition.

KEYWORDS cholestasis, liver, total parenteral nutrition

REVIEW CRITERIA

PubMed was searched in July 2006 for articles and abstracts using the following terms alone or in combination: "parenteral nutrition", "cholestasis", "liver disease", "TPN", "intestinal failure", "animal model", "mouse", "neonate", and "bile acid." The search was limited by considering only English-language journals published in the past 35 years. Abstracts from the American Association for the Study of Liver Disease (AASLD), the American Transplant Congress (ATC), and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) meetings also were included. The reference list was updated in September 2006.

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INTRODUCTION

The earliest attempts at intravenous nutrition infusion predate 1960 and involved a solution developed by David Drabkin that consisted of hydrolyzed proteins, including casein.¹ Although patients tolerated this intravenous infusion they developed fevers, and after a batch of the infusate became contaminated the protocol was abandoned.¹ During the 1960s, various individuals and pharmaceutical companies such as Mead Johnson (a subsidiary of Bristol-Myers Squibb, NY, USA) modified these parenteral nutrition solutions and optimized the mode of delivery to lessen the complications encountered (e.g. fever, fluid overload and pulmonary edema).¹

In 1967, Douglas Wilmore and Stanley Dudrick at the Children's Hospital of Philadelphia intravenously fed an infant who had undergone extensive bowel resection secondary to subtotal small-bowel atresia.¹⁻³ The child grew and, more importantly, was able to tolerate the intravenous nutrition for 22 months before a transition to oral feedings. This hallmark achievement marked the beginnings of parenteral nutrition as a successful therapy.

The association between parenteral alimentation and the development of cholestasis in newborn infants did not take much time to emerge. In a seminal paper published in *The Journal of Pediatrics* in 1975, Rager and Finegold reported intrahepatic cholestasis in 9 of 15 premature infants who received parenteral nutrition.⁴ They noted that these infants had several associated medical conditions, including respiratory distress, intracranial hemorrhage and infection. Interestingly, the infants who survived without developing cholestasis were those who were able to feed orally within 8 days of being born. This observation was the first indication that both prematurity and lack of enteral intake had an influence on the development of parenteral nutrition associated cholestasis (PNAC).^{4,5} Today, more than 30 years later, these factors remain important, well-established risk factors for parenteral nutrition related liver disease (Figure 1).

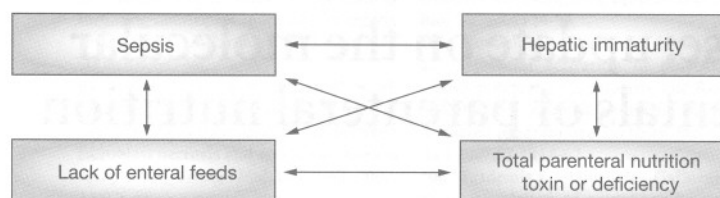


Figure 1 Factors that contribute to the development of parenteral nutrition associated cholestasis. Although the precise etiology of parenteral nutrition associated cholestasis remains unknown, it is probably a multifactorial condition, with key triggers—sepsis and/or inflammation, hepatic immaturity, lack of enteral feeds and/or hormonal triggers, and parenteral nutrition toxins and/or deficiencies—acting alone or in combination.

Unfortunately, however, during this same period of time few treatments have been developed to combat this serious medical condition.

BIOCHEMICAL AND CLINICAL PRESENTATION

PNAC is defined as cholestasis that is associated with a prolonged duration of parenteral nutrition administration (usually >2 weeks).⁶ The presentation of PNAC (elevated concentrations of conjugated bilirubin, serum bile acids and transaminases) is identical to that of other cholestatic liver diseases.^{7,8} PNAC is, therefore, a condition that might be accurately diagnosed only after alternative causes of cholestasis have been excluded, namely obstructive causes (e.g. extrahepatic biliary atresia), primary liver disease and metabolic liver disease (e.g. hereditary tyrosinemia).

Elevated serum transaminase and bilirubin levels are common in infants on parenteral nutrition, but in the setting of short-term administration these levels tend to normalize and jaundice tends to resolve.⁷ Unfortunately, however, premature infants who receive long-term parenteral nutrition are at severe risk of developing life-threatening hepatic complications.^{7–10} These complications include cirrhosis, end-stage liver disease, and the concomitant risk of sepsis, coagulopathy, gastrointestinal bleeding, and death.^{7,8}

Despite intravenous vitamin supplementation, children with PNAC remain at risk for malabsorption of fats and fat-soluble vitamins (e.g. vitamins A, D, E and K). Infants most susceptible to the morbid outcomes associated with PNAC are the smallest of the premature infants (<1 kg birth weight) and those with

short-bowel syndrome caused by surgical resection.^{9–11} The incidence of PNAC might be as high as 50% in infants who receive parenteral nutrition for at least 2 months.⁸ The risk of premature infants developing end-stage liver disease has been reported to be as high as 90% in those who receive parenteral nutrition for more than 3 months.^{7–9,12,13}

HISTOPATHOLOGY

The histopathological consequences of parenteral nutrition vary between patients, but certain features are common. These features include intracellular and intracanalicular cholestasis, steatosis and periportal fibrosis (Figure 2). Other features observed in some cases of PNAC include hepatocellular injury (e.g. balloon degeneration) and multinucleated giant cells. Additional histopathological consequences of parenteral nutrition include portal inflammation, acute cholangitis, extramedullary hematopoiesis, bile duct proliferation, and severe fibrosis (Figure 2).^{7,8,14–16} Steatosis is a common feature in adult recipients of parenteral nutrition. In infants and young children in particular, the histopathological features of PNAC progressively worsen with increasing time on parenteral nutrition (Table 1). Biliary cirrhosis is a late finding and is associated with death within 6 months of its onset (Figure 2D).^{8,10,13,17}

ETIOLOGY AND PATHOGENESIS

Despite the widespread use of parenteral nutrition in clinical practice for more than 30 years, and its well-documented association with cholestatic liver disease, the precise etiology of PNAC remains a mystery. What is known, however, is that there are clearly defined risk factors for PNAC. Risk factors include infant prematurity and immature hepatic function, lack of enteral feeding, repeated bouts of infection or sepsis, and various toxicities or deficiencies in the parenteral nutrition solution (Figure 1).^{7–10,12,18,19} Additional risk factors include the number of days on antibiotics (which is presumably related to infection), as well as the number of laparotomies performed on the parenteral nutrition recipient.⁶

Prematurity

Clinical experience has clearly established that PNAC is primarily a pediatric disease, with the smallest premature infants the most susceptible to this condition.^{6–8,10} There are estimates

that PNAC develops in 40–60% of infants on long-term parenteral nutrition for intestinal failure compared with 15–40% of adults on home parenteral nutrition.¹⁰ Data collected by Beale *et al.* demonstrated an inverse relationship between birth weight and the prevalence of PNAC; 50% of infants who weighed less than 1 kg at birth had clinical evidence of PNAC.¹¹ This same group reported a 23% overall incidence of cholestasis in their cohort of 62 premature infants on parenteral nutrition; the incidence increased to 80% in infants on parenteral nutrition for more than 60 days and to 90% for those who received intravenous nutrition for more than 3 months.¹¹

Why are these small, premature infants most at risk for PNAC? Over the years many investigators have attempted to answer this question. Various explanations, based on scientific findings and measurements in both humans and animal models, have been proposed. First, these small neonates have been shown to have 'immature' hepatic transport and metabolism of bile acids. Enterohepatic circulation of bile acid is dependent on the normal synthesis, conjugation, hepatic uptake and secretion, and recirculation of bile acids. Neonates have been found to have abnormalities in each one of these steps crucial for the metabolism of bile acids. Animal and human data indicate that neonates have both decreased bile acid pools and abnormal synthesis of bile acids (e.g. stereoisomers of conventional bile acids and short-chain and long-chain bile acids).^{20,21} Furthermore, additional processes in the transport and metabolism of bile acids are immature in these small infants. These processes include gallbladder contraction and reduced bile acid secretion, and intestinal and hepatic uptake of bile acids (from the portal circulation).^{22–24}

The developmental regulation of genes essential for bile acid transport might be responsible for the immaturity of the systems involved in enterohepatic recirculation of bile acids in premature infants compared to adults. These bile acid transporters and the nuclear receptors that regulate their expression (e.g. NR1H4 [the bile acid receptor], also known as FXR [the farnesoid X receptor]) have been discovered largely in the past decade, and their roles in various human cholestatic conditions are continuing to be elucidated.^{25,26} Such transporters are important for the enterohepatic circulation of bile acids under normal circumstances,

but especially so in settings of increased bile acid loads (Figure 3).

At present, more is known about the developmental expression of the genes that are crucial for bile acid homeostasis in animal models than in infants, but human data are beginning to emerge. Studies on the developmental expression of Ntcp (*Slc10a1*) messenger RNA (mRNA) in the rat have demonstrated that this primary bile acid importer is absent for most of gestation. In fact, immunoreactive Ntcp is first detected at embryonic day 20 in the rat, and Ntcp (*Slc10a1*) mRNA expression and basolateral Ntcp protein do not approximate adult levels until postnatal day 5.²⁷

The developmental expression of bile acid transporters in human fetal tissue was reported in 2004.²⁸ These data demonstrate that *SLC10A1*, which encodes the primary bile acid importer NTCP (located in the sinusoidal membrane of the hepatocyte) and *ABCB11*, which encodes the bile salt export pump BSEP (located on the canalicular membrane of the hepatocyte), are expressed as early as 14–15 weeks gestation in humans, with mRNA expression gradually increasing up to the 20-week gestation point (the limit of the investigators' experimental timeline).^{28,29} The expression of *SLC10A1* and of *ABCB4*, which encodes the multidrug resistance protein P-glycoprotein MDR3 (involved in biliary phospholipid excretion), was significantly lower in fetal livers than in adult livers.²⁹ Furthermore, immunofluorescent staining of tissue for BSEP revealed the subapical location of this protein in fetal hepatocytes compared with the typical sharp-linear canalicular staining pattern in adult hepatocytes.²⁹ This immaturity of key bile acid transporters in neonatal livers has led some to postulate that neonates might have a genetic susceptibility to PNAC.^{8,10} Specifically, variations in the developmental profiles of bile acid transporters might explain why one infant develops severe PNAC while another infant with a similar gestational age and feeding history avoids the condition. The immaturity of bile acid transporter expression in neonates also suggests that these bile acid transporter genes might have potential as candidates for novel therapeutic targets to counter cholestasis.

Lack of enteral feeding

The lack of intraluminal nutrients has a crucial role in the development of PNAC on various

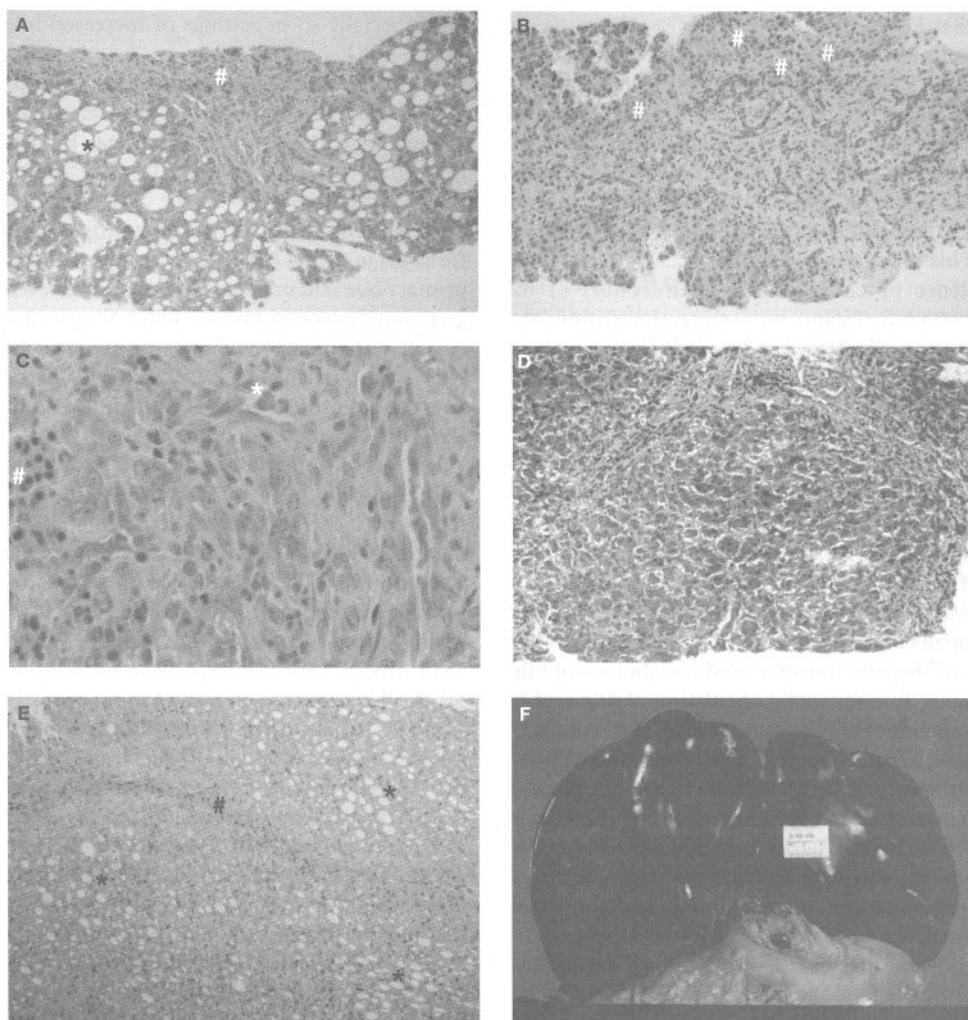


Figure 2 Pathological features of parenteral nutrition associated liver injury. (A) Classical early parenteral nutrition induced liver injury with steatosis (indicated by *) and ductal proliferation (indicated by #). (B) Acute cholestatic response with ductal proliferation (indicated by #). (C) Immature liver with extramedullary hematopoiesis (indicated by #), cholestasis (indicated by *), and ductal proliferation. (D) Biliary cirrhosis (poor prognosis in patients with parenteral nutrition related cholestasis). (E) Steatosis (indicated by *) and fine fibrosis (indicated by #) without cholestasis (typical of parenteral nutrition related liver injury in an adult recipient). (F) Dilated gallbladder and grossly normal liver (the latter is not a typical pathological finding after long-term parenteral nutrition associated cholestasis in neonates). All images generously provided by Milton J Finegold, Department of Pathology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA.

levels. Enteral feeding stimulates bile flow. Biliary stasis, reflected by the ultrasonographic finding of biliary sludge in the gallbladder, is common in infants with PNAC.³⁰ Presumably, this biliary stasis is caused, at least in part, by a lack of enterally stimulated cholecystokinin release. The levels of cholecystokinin and other hormones, such as glucagon, gastrin,

and enteroglucagon, are markedly different when enterally fed and parenterally fed neonates are compared.^{31,32} These hormones are instrumental in stimulating bile flow and contraction of the gallbladder. Lack of enteral feeding can, therefore, result in gallbladder dilatation (Figure 2F). Enteral starvation also contributes to intestinal hypomotility, which in turn has the capacity to

promote overgrowth of bacteria in the small intestine.³³ This bacterial overgrowth, in turn, might contribute to infections and endotoxin-associated downregulation of bile acid transport (see following section). Finally, this increased intraluminal bacterial load has the ability to convert chenodeoxycholic acid into the more-hydrophobic and more-hepatotoxic bile acid, lithocholic acid.³⁴

Endotoxin

No review of PNAC is complete without mentioning the crucial roles of infection and sepsis in the development of this condition. First and foremost, the administration of parenteral nutrition requires an intravenous line (usually a central venous catheter) to be in place. This intravenous line, along with conditions associated with parenteral nutrition, such as intubation, previous surgery, or short-bowel syndrome, increases the risk of repeated bouts of sepsis.

The occurrence of small-bowel bacterial overgrowth and translocation of intestinal bacteria is also worth addressing, especially since neonates with short-bowel syndrome are particularly susceptible to both bacterial translocation and parenteral nutrition induced hepatic injury.⁸ In 1990, Lichtman *et al.* used jejunal self-filling blind loops to create small-bowel bacterial overgrowth in a rat model.³⁵ Dependent on the inflammatory background of the particular rat strain used, these animals developed weight loss, hepatomegaly and hepatic inflammation as early as 4 weeks after the creation of the self-filling bowel loops.³⁵ This study group subsequently reported that there was also evidence of biliary tract injury in these rat strains (decreased bile flow rates, dilatation of bile ducts, and beaded appearance of the bile ducts on cholangiogram).³⁶ Reduction in inflammation-induced liver injury in rats after initiation of oral metronidazole and/or tetracycline has also been reported by multiple investigators, which indirectly suggests that bacteria have a role in the development or exacerbation of PNAC.^{37,38} In addition to abdominal surgery and short-bowel syndrome, other inflammatory or sepsis-related conditions (such as IBD and hematological malignancies) have been associated with the development of parenteral nutrition related liver injury.^{39,40}

The role of cytokines in the development of PNAC has been observed both clinically and

Table 1 Histopathological findings of parenteral nutrition associated liver disease over time.^a

Duration of parenteral nutrition (weeks)	Histopathology
<2	Cholestasis; aggregates of macrophages
2–6	Marked cholestasis (zone 3 > zone 1)
8–12	Fibrosis
>12	Cirrhosis

^aAdapted from Mullick *et al.*¹⁵ Nature Publishing Group © Mullick *et al.* (1994) *Mod Pathol* 7: 190–194.

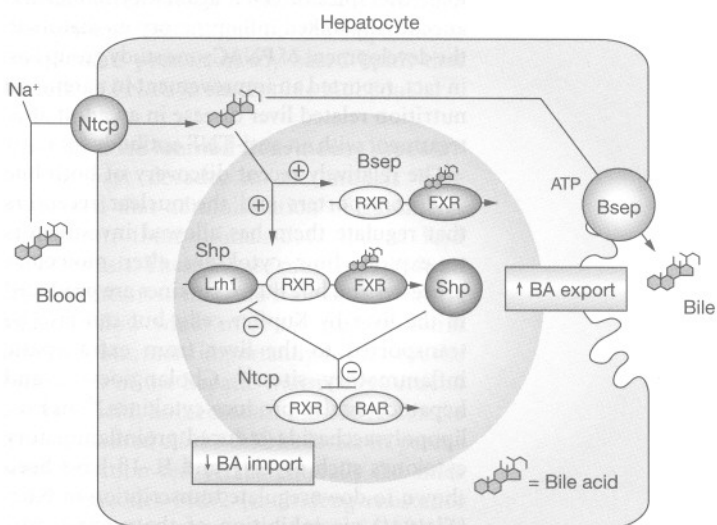


Figure 3 Hepatocyte transporters and nuclear receptors involved in bile acid homeostasis. Representative bile acid transporters and associated nuclear receptor mediated regulatory mechanisms are illustrated in this schematic of a normal hepatocyte. Primary bile acids, cholic acid and chenodeoxycholic acid, are potent agonists of the nuclear receptor FXR and directly activate an FXR response element in Bsep (*Abcb11*). Bile acids likewise activate the Shp (*Nr0b2*) promoter, which, in turn, interferes with LRH-1 and RXR-RAR transactivation of the Ntcp (*Slc10a1*) gene promoter. The net effect under normal circumstances, but especially in the presence of increased intrahepatic bile acid loads, is decreased bile acid import (via Shp-mediated Ntcp downregulation) and increased bile acid export (via FXR-mediated upregulation of Bsep). Abbreviations: *Abcb11*, ATP-binding cassette, sub-family B, member 11; BA, bile acid; Bsep, bile salt export pump; FXR, farnesoid X receptor; LRH1, liver receptor homolog 1; *Nr0b2*, nuclear receptor subfamily 0, group B, member 2; Ntcp, Na⁺ taurocholate cotransporting polypeptide, sodium/bile acid cotransporter; RXR-RAR, retinoid X receptor-retinoic acid receptor heterodimer; Shp, small heterodimer partner; *Slc10a1*, solute carrier family 10, member 1.

in animal models. Cruccetti *et al.* noted that the percentage of monocytes that produce tumor necrosis factor (TNF; previously known as TNF- α) and interleukin-6 (IL-6) after a

microbial challenge was lower in infants who received parenteral nutrition than in enterally fed infants and adults, which suggests that the inflammatory response is impaired in infants who receive parenteral nutrition.⁴¹ Zheng *et al.*, however, found significantly higher levels of TNF and IL-6 in rats that received parenteral nutrition than in a control group of rats that received normal chow plus saline infusion.⁴² They postulated that these elevated cytokine levels occurred in response to bacterial translocation. Finally, the emergence of pharmacologic therapies directed against cytokines has anecdotally linked inflammatory mediators to the development of PNAC; one study group has, in fact, reported an improvement in parenteral nutrition related liver disease in an adult after treatment with an anti-TNF antibody.⁴³

The relatively recent discovery of both bile acid transporters and the nuclear receptors that regulate them has allowed investigators to explore how cytokines alter molecular processes and bile flux. Cytokines are produced in the liver by Kupffer cells, but can also be transported to the liver from extrahepatic inflammatory sites.⁴⁴ Cholangiocytes and hepatocytes also produce cytokines.⁴⁵ In rats, lipopolysaccharide-induced proinflammatory cytokines such as TNF and IL-1 β have been shown to downregulate transcription of Ntcp (*Slc10a1*) via inhibition of the nuclear retinoic acid and retinoid X receptor heterodimer RXR:RAR.⁴⁶ Similarly, intraperitoneal lipopolysaccharide administration to mice reduces expression of the mRNAs of crucial bile acid transporters, including Ntcp (*Slc10a1*) and Bsep (*Abcb11*).⁴⁷ The cytokine-mediated effects on nuclear receptors and the downstream genes involved in bile acid homeostasis that they regulate is rather complex and probably also involves other signaling pathways. For example, Li *et al.* reported that, in rats, IL-1 β -mediated suppression of RXR:RAR transactivation of the Ntcp (*Slc10a1*) promoter is dependent on c-Jun N-terminal kinase (JNK).⁴⁸

In summary, investigators have found that treatment of animals with endotoxin, or cytokine treatment of cells, leads to downregulation of bile acid transporters at multiple levels, including transport function, mRNA levels, initiation of transcription, and promoter activity.^{46,48–50} Parenteral nutrition recipients are inherently susceptible to infection because they have catheters in place and often have a history of

abdominal surgery. The *in vivo* and *in vitro* studies described link such infection-induced inflammation to the dysregulation of critical bile acid transporters and the development of cholestasis.

Toxicity or nutrient deficiency

Over the years, toxicity or deficiencies of various components present in parenteral nutrition have been implicated in the pathogenesis of PNAC. The implicated components include taurine, chromium, aluminum, oxidants and lipids.^{7,8,10,51}

Taurine deficiency

Taurine deficiency could have a role in the development of PNAC in neonates. Premature infants have a decreased ability to synthesize taurine and cysteine from methionine compared with full-term infants, which is secondary to low hepatic cystathionase levels.⁵² This taurine deficiency leads to the inability to form taurine-conjugated bile acids efficiently and, unfortunately, favors the formation of hydrophobic and toxic glycine-conjugated bile acids. Taurine supplementation has been shown to improve bile flow and the bile acid secretion rate in a guinea pig model of parenteral nutrition and could be beneficial in the prevention of PNAC in specific neonatal subpopulations (e.g. severely premature infants or those with necrotizing enterocolitis).^{53–55}

Aluminum and manganese toxicity

Aluminum has been shown to be related to bone disease and in parenteral nutrition aluminum has been recognized as toxic, but a clear causative role for aluminum in the pathogenesis of PNAC remains to be proven.^{56,57} Similarly, chromium can intrahepatically accumulate in parenteral nutrition recipients but does not seem to be associated with liver disease.^{58,59} By contrast, infants and children on long-term parenteral nutrition are at risk for manganese retention, which results in manganese deposition in the liver and brain.⁶⁰ The elimination of manganese from the parenteral nutrition has been shown to reduce deposition of manganese in the basal ganglia and might help avert future development of manganese-associated hepatotoxicity.⁶⁰

Oxidant imbalance

Bile flow was reported to be decreased in a guinea pig model of parenteral nutrition; however, the

resultant cholestasis did not seem to be the result of an oxidant–antioxidant imbalance.⁵¹

Caloric loads

Caloric loads in parenteral nutrition, in the form of either dextrose or amino acids, have been associated with hepatic pathological and biochemical changes. For example, in both animals and humans, caloric excess is associated with elevated transaminase levels and hepatic steatosis.^{61,62} In addition, amino acid infusions have been associated with cholestatic liver disease in humans and animals.^{63,64} Vileisis *et al.* demonstrated that premature infants who received daily amino acids of 3.6 g/kg had a more rapid rise in bilirubin levels than those who received 2.5 g/kg daily.⁶³

Neonates, unlike their adult counterparts, have immature metabolic pathways that limit the conversion of lysine and methionine to carnitine.⁶⁵ Carnitine is required for mitochondrial fatty acid oxidation, but, although a deficiency in carnitine has been demonstrated in both infants and adults who received parenteral nutrition, the biochemical features of PNAC do not improve with normalization of serum carnitine levels.⁶⁶ By contrast, a randomized trial in adults has demonstrated that choline supplementation results in normalization of elevated transaminase levels and improvement in hepatic steatosis.⁶⁷ Serum bilirubin levels were normal in these patients and did not change with choline supplementation.⁶⁷

Lipids

Lipids have been implicated in the pathogenesis of both hepatic steatosis and PNAC, and there is some clinical evidence to support such a role. For example, Cavicchi *et al.* reported that cholestasis in adults is associated with increased lipid loads (>1 g/kg body weight daily).⁶⁸ Similarly, Colomb *et al.* correlated 23 cholestatic episodes in 10 infants with increases in lipid administration.⁶⁹

A molecular mechanism that underlies this lipid-induced cholestasis has now been described.^{68,69} It seems that in both primary mouse hepatocytes and human liver cell lines, stigmaterol, a soy lipid-derived phytosterol present in the lipid fraction of parenteral nutrition, antagonizes the expression of the mRNAs of the crucial bile acid homeostatic proteins (i.e. BSEP and the organic solute transporter OST α –OST β) that are involved in protecting

hepatocytes from increased bile acid loads.^{70,71}

Extremely high serum levels of phytosterols have previously been reported in children for whom there is biochemical evidence of PNAC, but the reported effect of a phytosterol on bile acid homeostatic genes such as the gene encoding BSEP (*ABCB11*) is a novel molecular explanation for the progressive cholestasis that occurs in parenteral nutrition recipients.^{70–72} A report of complete resolution of PNAC in two children given a fish-oil-derived (rather than soy-derived) intravenous lipid emulsion provides additional indirect clinical evidence that phytosterols might be the hepatotoxic components present in soy-based lipids that exacerbate PNAC in susceptible individuals.⁷³

What have we learned from mouse models?

In the past decade, mouse models have confirmed that administration of parenteral nutrition to these animals does, indeed, lead to cholestasis. These mouse models provide an efficient means to measure transaminase levels and bile flow while mice receive parenteral nutrition, but, more importantly, to measure the expression of the hepatic transporters crucial for bile acid homeostasis. In 2004, Tazuke *et al.* measured *Abcb4* mRNA levels in parenteral nutrition fed versus enterally fed mice (*Abcb4* encodes Mdr2 [multidrug resistance protein 2], the mouse homolog of human MDR3). Although the livers of the parenteral nutrition fed mice showed no histological injury, *Abcb4* expression was decreased by 66% and serum bile acid levels were elevated in these animals compared with the enterally fed controls.⁷⁴ The authors concluded that decreased *Abcb4* expression and the resultant loss of a hepatobiliary adaptive mechanism could be one of the causative factors in the development of PNAC. In the same mouse model of parenteral nutrition, these investigators also showed that Fas-mediated apoptotic signaling and histological manifestations of apoptosis are increased in animals administered parenteral nutrition that included lipids.⁷⁵ Finally, more recently, Javid *et al.* demonstrated that transaminase levels and hepatic steatosis are increased in mice that received an intravenous lipid emulsion rather than enteral lipids. Javid and colleagues, therefore, concluded that lipids administered through the enteral route protect against parenteral nutrition associated liver injury in this animal model.⁷⁶

TREATMENT

Pharmacologic therapy

Although the effects of parenteral nutrition on the liver were first observed more than a quarter of a century ago, there are still very few pharmacologic options for the treatment of this condition. The dihydroxy bile acid ursodeoxycholic acid (UDCA) is the only pharmacologic therapy that has been approved for use in a cholestatic condition. Although UDCA has proven most effective for the treatment of primary biliary cirrhosis, its beneficial effects have been studied and observed in patients with primary sclerosing cholangitis, cholestasis in pregnancy, graft versus host disease with hepatic involvement, and in various pediatric cholestatic conditions.⁷⁷ UDCA is beneficial in cholestatic conditions because it has multiple mechanisms of action within the hepatobiliary system. Specifically, UDCA promotes both hepatobiliary and cholangiocyte secretion, inhibits bile acid induced hepatocyte apoptosis, and diminishes bile acid cytotoxicity.⁷⁷

Rabbits given parenteral nutrition plus UDCA for 8 days have been shown to have more favorable liver biochemical and histological parameters than a control group of animals that received parenteral nutrition alone.⁷⁸ Although studies of UDCA efficacy in children and adults with PNAC have thus far been conducted retrospectively and/or with small patient populations, there remains some scant evidence that this therapy might also be helpful in reversing biochemical manifestations of PNAC in humans.^{79,80} In 1991, Lindor and Burnes described a case of a patient with PNAC that improved during the period UDCA was administered. The patient relapsed with jaundice while this therapeutic bile acid was ceased, and biochemically improved, once again, after oral UDCA was reinstituted.⁸¹ In 1996, Spagnuolo and colleagues described seven children who experienced biochemical resolution of PNAC while on UDCA.⁸² In a 2006 study, 12 children with intestinal failure and PNAC were treated with UDCA for at least 6 months, and cholestasis improved in 11 of the 12 children, with the one case of treatment failure attributed to poor plasma levels of UDCA secondary to suboptimal intestinal absorption.⁷⁹ Similarly, nine adults with short-bowel syndrome and PNAC demonstrated significant improvements in γ -glutamyl transpeptidase and alanine aminotransferase

levels while on UDCA compared with periods of no treatment.⁸⁰ The pediatric dosing of oral UDCA for cholestatic diseases is 15–45 mg/kg body weight daily, given in two or three doses. A typical adult dose for oral UDCA is 8–10 mg/kg body weight daily given in two or three doses.

Alternatives to UDCA have largely been ineffective for the treatment of PNAC. For example, cholecystokinin-octapeptide administration to infants on parenteral nutrition for a prolonged period of time failed to resolve PNAC, did not significantly improve conjugated bilirubin levels, and was ineffective at preventing parenteral nutrition associated gallstone disease.^{83,84} Likewise, tauroursodeoxycholic acid was tested as a potential treatment for PNAC in 22 infants, but failed to either prevent or treat the condition when assessed against controls ($n=30$).⁸⁵

Yet another strategy for treating or preventing PNAC is empiric treatment for small-bowel bacterial overgrowth. The potential role for oral antibiotics such as metronidazole in inflammation-induced cholestasis has been described earlier in this Review, but, importantly, such oral decontamination has never been stringently tested in humans with PNAC in prospective, randomized trials.^{37,38}

Transplantation

Since its discovery and implementation, parenteral nutrition has been life-saving but, unfortunately, has also been associated with the development of end-stage liver disease, especially in the smallest premature infants on a prolonged course of parenteral nutrition.^{3,7–10,12} In severe cases of end-stage liver disease, liver transplantation or combined liver–bowel transplantation often remain the only life-preserving options. The 1-year and 5-year survival rates for pediatric patients who received isolated liver transplants in the US for the indication of PNAC in the years 1988–2004 have been reported to be 73% and 64%, respectively.⁸⁶

CONCLUSIONS

PNAC is a serious clinical condition that can rapidly progress to cirrhosis, end-stage liver disease, and the need for liver transplantation, especially in premature neonates who have received parenteral nutrition for a prolonged period of time (i.e. months to years). The

pathogenesis of this primarily pediatric condition is probably multifactorial, with prematurity, bouts of sepsis, lack of enteral feeds, and the presence or absence of specific components in parenteral nutrition solutions most certainly contributing to the disease mechanism. The discovery of crucial nuclear receptor mediated bile acid transporters in the past decade and the development of animal (especially mouse) models of PNAC are proving invaluable, and allow investigators to unravel the molecular mechanisms that lead to PNAC. These advances are encouraging and it is tempting to speculate that further elucidation of the molecular mechanisms that exacerbate PNAC might lead to the development of novel anticholestatic therapeutics that abrogate the end-stage liver disease that is so often seen in neonates on long-term parenteral nutrition.

KEY POINTS

- Parenteral nutrition provides valuable life-sustaining nutrients to patients unable to tolerate enteral nutrition, but prolonged administration is associated with severe, life-threatening liver disease, especially in premature neonates
- The precise etiology of parenteral nutrition associated cholestasis (PNAC) is probably multifactorial, with risk factors including prematurity, history of bowel resection and/or lack of enteral feeds, catheter infections and/or sepsis, and a lack of or presence of specific components in the parenteral nutrition itself
- Older children and adults are less prone to severe cases of PNAC than are neonates, and animal models suggest that there is a developmental component to bile acid transporter gene expression; these factors indicate that the expression of critical hepatic protective genes might be involved in susceptibility to PNAC
- Animal models of parenteral nutrition administration suggest that parenteral nutrition itself and/or particular components of parenteral nutrition might affect key hepatic bile acid transporters, apoptotic signaling, and other detoxification mechanisms at the gene level, thereby promoting cholestasis and hepatocellular injury
- Few therapeutic options are available for PNAC, with severe cases necessitating liver or combined liver–bowel transplantation

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Competing interests

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