Parenteral Nutrition-Associated Liver Complications in Children

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Parenteral nutrition is a life-saving therapy for patients with intestinal failure. It may be associated with transient elevations of liver enzyme concentrations, which return to normal after parenteral nutrition is discontinued. Prolonged parenteral nutrition is associated with complications affecting the hepatobiliary system, such as cholelithiasis, cholestasis, and steatosis. The most common of these is parenteral nutrition-associated cholestasis (PNAC), which may occur in children and may progress to liver failure. The pathophysiology of PNAC is poorly understood, and the etiology is multifactorial. Risk factors include prematurity, long duration of parenteral nutrition, sepsis, lack of bowel motility, and short bowel syndrome. Possible etiologies include excessive caloric administration, parenteral nutrition components, and nutritional deficiencies. Several measures can be undertaken to prevent PNAC, such as avoiding overfeeding, providing a balanced source of energy, weaning parenteral nutrition, starting enteral feeding, and avoiding sepsis.
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Parenteral nutrition is the administration of complete and balanced nutrition, given when feeding into the gastrointestinal tract is contraindicated or inadequate. A commonly reported complication of parenteral nutrition is transient elevation of liver enzyme concentrations, which return to normal after parenteral nutrition is discontinued.[1, 2] Complications affecting the liver and biliary system may occur

with prolonged parenteral nutrition and include cholelithiasis, cholestasis, and steatosis. Whereas steatosis is relatively more common in adults, cholestasis is the most common and predictable parenteral nutrition-associated hepatobiliary dysfunction in children.[3–5] In some patients it may progress to cirrhosis, liver failure, and death.[6]

Frequency

The frequency of parenteral nutrition-associated liver complications varies in studies from 7.4–84%. In follow-up studies, complications occurred in 40–60% of children who required long-term parenteral nutrition.[4] Variation in reported frequency is due to differences in study populations (premature vs term infants or older children), definition of liver dysfunction (based on biochemical or histologic values), composition of parenteral nutrition solutions, duration of parenteral nutrition administration, and underlying medical or surgical conditions in study subjects. In one study, approximately 30% of mostly premature infants had elevated liver enzyme concentrations after receiving parenteral nutrition for 2 weeks.[2] Liver enzyme concentrations were elevated in 53% of children after 4 weeks of parenteral nutrition. Patients with short bowel syndrome who require a longer duration of parenteral nutrition have a higher frequency of liver complications. Liver dysfunction occurred in 67% of children with short bowel syndrome who received parenteral nutrition for a mean duration of 16.5 weeks, compared with 30% of children with normal bowel length who received parenteral nutrition for a mean duration of 6 weeks.[7] Liver dysfunction, mainly cholestasis, was reported in 65% of parenteral nutrition-dependent infants with short bowel syndrome.[8]

The reported frequency of parenteral nutrition-associated cholestasis (PNAC) also varies among studies. In a retrospective review of medical records of neonates who received parenteral nutrition for at least 1 week, 15% of infants developed PNAC, (serum conjugated bilirubin concentrations ≥ 2 mg/dl).[9] In another study, the overall frequency of PNAC (serum conjugated bilirubin concentrations ≥ 2 mg/dl) was 43% in infants who received parenteral nutrition for 19–75 days (mean ± SEM 49.6 ± 7 days) and 67% in premature infants.[10] The disorder occurred in 23% of premature infants (serum conjugated bilirubin concentrations ≥ 1.5 mg/dl) after a mean parenteral nutrition duration of 42 days.[11]

Clinical Features

Transient elevation of liver enzyme concentrations may be observed early in the course of parenteral nutrition without denoting significant liver dysfunction.[12] However, with prolonged parenteral nutrition, liver dysfunction may be severe and may progress to liver failure.[13] As liver dysfunction progresses, patients may have hepatomegaly, splenomegaly, ascites, and varices. Cholestasis typically is associated with elevated serum bilirubin concentrations in the presence or absence of jaundice depending on the severity of the cholestasis. Progressive elevation in serum bilirubin concentrations in association with persistent jaundice usually denotes a risk for high mortality.[14, 15] Mortality was as high as 31% in surgical neonates with PNAC, compared with 3% in neonates without PNAC.[16] In a study that assessed children with PNAC for bowel and/or liver transplantation, the main risk factors for death were the presence of cirrhosis, splenomegaly, and serum bilirubin concentrations above 5.84 mg/dl.[17]

Biochemical Markers

Elevation of liver enzyme concentrations is the earliest marker of liver dysfunction. The time to onset of dysfunction after starting parenteral nutrition is difficult to predict and varies with the presence or absence of risk factors.[18] In infants with PNAC, elevations in serum alkaline phosphatase, bilirubin, and γ-glutamyl transpeptidase (GGT) are the most common biochemical abnormalities. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations also may be elevated,[2, 14, 18–20] but usually after onset of cholestasis or jaundice.[16, 21] Serum conjugated bilirubin, alkaline phosphatase, and AST concentrations were elevated after 2.2 ± 0.2, 4 ± 0.8, and 4.6 ± 0.7 weeks of parenteral nutrition therapy, respectively. The values returned to normal within 1–4 months after parenteral nutrition was discontinued.[2] Serum conjugated bilirubin concentrations typically return to normal within 1 week–2 months.[10, 11] In the absence of irreversible hepatic damage, complete liver recovery is expected,[1] although liver biopsies may show subtle abnormalities for months after parenteral nutrition is stopped.[22]

Serum bile acid concentrations were proposed to be markers that correlate with the degree of

histologic liver changes.[23–26] Elevations in these concentrations may be either the result of regurgitation of bile acids from the hepatocytes into the blood,[23, 26, 27] or a reflection of immaturity of hepatic excretory functions in premature infants.[28] Because a reference range for these concentrations in infants is difficult to establish due to changes in bile synthesis and transport,[29] and since other sensitive biochemical values are simpler to measure, monitoring serum bile acid in patients with PNAC is not a routine practice.

Serum GGT and conjugated bilirubin concentrations are considered the most sensitive indicators of cholestasis.[11, 18, 27] Both can be elevated as early as 1 week in infants with PNAC.[12]

γ-Glutamyl transpeptidase is an enzyme that is widely distributed in the body with prominent activity in the kidneys, pancreas, and liver. In the liver, it is present in periportal hepatocytes, bile canaliculi, and biliary epithelial cells. Despite GGT's sensitivity for hepatobiliary disease, serum GGT concentrations lack specificity because levels may be elevated in other diseases.[30, 31] This lack of specificity[32] makes GGT most useful as an indicator of cholestasis when measured in combination with other variables, such as to confirm the hepatobiliary origin of elevated alkaline phosphatase levels.[33] Although alkaline phosphatase is a sensitive marker for bile obstruction, its increased activity during bone formation in children[10, 21] or as a result of neonatal metabolic bone disease[34] makes it a less specific indicator of cholestasis in the growing child.

Since elevated serum conjugated bilirubin concentrations reflect a reduction in bile flow, they are considered the prime marker for cholestasis.[21, 35] Clinical studies define PNAC as when the bilirubin concentrations are at least 1.5 mg/dl.[9–11, 16, 36–38] In clinical practice, the most established concentration is 2 mg/dl or greater. The extent and duration of elevation may predict severity and mortality in patients with parenteral nutrition-associated liver dysfunction.[13, 17, 38]

Histopathology

Histologic liver studies in patients with parenteral nutrition-associated hepatobiliary dysfunction may reveal a wide spectrum of pathologic features, including canalicular and intralobular cholestasis, periportal inflammation, bile duct proliferation, pseudoacinar formation, portal-portal bridging, steatosis, portal fibrosis, and cirrhosis.[2, 14, 18] In evaluating children with advanced PNAC for small bowel or small bowel and liver transplantation, the frequencies of specific histologic abnormalities were as follows: portal fibrosis 100%, pericellular fibrosis 95%, bile duct proliferation 90%, portal bridging 86%, pigmented Kupffer cells 81%, portal inflammation 76%, pseudoacinar formation 71%, cirrhosis 48%, and steatosis 43%.[17]

Risk Factors

The following risk factors predispose to liver complications in patients receiving parenteral nutrition: prematurity and low birthweight,[10, 11, 39] long duration of parenteral nutrition,[7, 9, 11, 16, 37, 40–42] sepsis,[23, 39] bowel rest and lack of enteral feeding,[9, 18, 41, 43] and short bowel syndrome.[15, 42, 44]

Prematurity

Premature infants are born before 38 weeks' gestational age with birthweight below 2500 g depending on degree of prematurity. They are at great risk for PNAC[11, 39] due to physiologic immaturity of their hepatic excretory systems.[10, 11, 28, 45, 46] The lower the gestational age, the higher the elevation in serum bilirubin concentrations[39] and the more rapid and severe the development of PNAC and jaundice.[40] In one study, the overall frequency of PNAC was 50% in premature infants with a birthweight below 2000 g. Fifty percent of infants weighing less than 1000 g developed PNAC compared with 7% of infants with a birthweight above 1500 g.[11] The frequency increased from 1.4% to 5.3% to 13.7% in infants who were born at over 36 weeks', between 32 and 36 weeks', and before 32 weeks' gestation, respectively.[40]

Duration of Parenteral Nutrition

The frequency of liver dysfunction and cholestasis increases with prolonged parenteral nutrition administration.[7, 9, 11, 16, 40] After mean duration of 42.6 and 115.7 days, liver dysfunction occurred in 30% and 67% of children, respectively.[7] Overall, PNAC occurred in 35% of surgical neonates who received parenteral nutrition for at least 2 weeks, and increased to 58% and 75% after parenteral nutrition was given for at least 30 and 90 days, respectively. All neonates who received parenteral nutrition for more than 180 days

developed cholestasis.[16]

In a retrospective review of the medical records of 172 neonates who received parenteral nutrition for at least 1 week, a direct correlation was seen between severity of cholestatic jaundice and duration of parenteral nutrition. Neonates who received parenteral nutrition for 1–6 weeks, 7–10 weeks, and more than 11 weeks had progressive elevations of mean serum conjugated bilirubin concentrations corresponding to 4.21 ± 1.63, 4.91 ± 1.44, and 5.56 ± 1.61 mg/dl, respectively.[9]

Because of the direct correlation between duration of parenteral nutrition and liver toxicity, parenteral nutrition should be given for the shortest possible time. In addition, oral or enteral feeding, even in partial amounts, should begin as soon as clinically feasible.[41, 42]

Sepsis

Sepsis is a common complication of the infusion of parenteral nutrition in children.[47] It may cause cholestasis, but bile stasis, in turn, may increase septic rate. In a study that included surgical neonates, sepsis was observed in 56% of infants with PNAC compared with 13% of those with normal serum bilirubin concentrations ($p<0.05$). It was reported in 78% of infants before the onset of jaundice.[16]

Sepsis as a Cause of Cholestasis

Although the source of blood infections in patients receiving parenteral nutrition is usually microbial migration along the venous catheter, bacteremia may be the result of bacterial translocation from the gut into the bloodstream.[48–50] Gram-negative bacterial infections, especially with *Escherichia coli*, were associated with hyperbilirubinemia[51] and jaundice[16] in children. Jaundice resolved and liver enzyme concentrations returned to normal after treatment with systemic antibiotics.[50, 52–55] In an analysis of risk factors leading to PNAC, surgical neonates had a 30% increase in plasma bilirubin concentrations during recurrent episodes of sepsis.[39] Other liver enzymes including AST, ALT, lactate dehydrogenase,[48, 56] and alkaline phosphatase[57] also may increase during sepsis. At the hepatocellular level, liver biopsies of infants who developed jaundice after bacterial sepsis had hepatocellular alterations, intracanalicular and intracellular cholestasis, bile stasis, and bile duct proliferation.[58]

The mechanism of sepsis-induced cholestasis is unknown, but research has focused on the possible toxic effects of endotoxins or lipopolysaccharides on the hepatobiliary system. Endotoxins are released from the outer membrane of gram-negative bacteria during systemic infections, or may translocate from the gut into the portal circulation by binding to specific sites of the intestinal membrane after their release by enteral bacteria.[59] After reaching the liver, the amount of endotoxins may exceed the ability of Kupffer cells to detoxify them,[60] thus leading to their sequestration in hepatocytes[59, 61] and causing direct hepatocellular injury. At the hepatocellular level, endotoxins may cause cholestasis by inhibiting the Na^+-K^+-adenosine triphosphatase (ATPase) pump in parenchymal liver cells.[62] Indirectly, they may mediate the formation of cytotoxic bile acids,[63] or stimulate the release of hepatotoxic inflammatory cytokines such as tumor necrosis factor (TNF) and interleukins 1 and 6,[64–66] which all are thought to be hepatotoxic mediators.

Endotoxins may alter hepatic excretory functions,[67, 68] induce giant cell transformation of the liver and hepatocyte necrosis,[69] and impair bile flow in a dose-dependent manner.[61] In an animal experiment that showed a possible role of endotoxins in cholestasis, rats injected with human serum from a patient with PNAC developed a similar cholestatic picture to the one seen in that patient. Rats had improved bile flow after they were injected with antibodies to the endotoxin isolated from sequestered *E. coli* in that patient.[68]

Tumor necrosis factor is a protein released by macrophages in response to endotoxin stimuli. Supporting evidence about its hepatotoxic effects comes from improvement in liver injury after administration of TNF antibodies to rats fed parenteral nutrition.[70] On the other hand, the administration of polymyxin B, an effective antibacterial against gram-negative bacteria, blocked endotoxin activity and consequently TNF production, and led to improvement in steatosis in rats.[71] These observations coupled with a report that TNF could stimulate hepatic lipid synthesis[72] led investigators to hypothesize that TNF is hepatotoxic and could be a cause of steatosis as well as cholestasis during sepsis.[70, 73]

Besides their effects on the liver, endotoxins may increase intestinal permeability,[74, 75] diminish immunologic defense mechanisms, and alter host response to infection.[76] Administration of endotoxins to laboratory animals increased intestinal permeability to enteric bacteria and

contributed to bacterial translocation.[77] Also, atrophy of gut-associated lymphatic tissue,[78] physical disruption of the intestinal barrier, bacterial overgrowth, and impaired gut or host defense mechanisms would facilitate bacterial translocation.[75, 79, 80]

Effects of Bile Stasis on Sepsis

Bile stasis may predispose to sepsis,[81-83] possibly by impairing cell-mediated immunity.[84] Sepsis occurred in 80% of infants with PNAC compared with 29% of infants without cholestasis (p=0.006).[82] Although a high frequency of sepsis was reported in patients with PNAC, further studies are necessary to clarify the effects of cholestasis on sepsis.

Since a strong correlation exists between cholestasis and sepsis, control measures should be undertaken to prevent infections from developing in patients receiving parenteral nutrition. Meticulous catheter care, aseptic handling of parenteral nutrition infusion, and aggressive treatment of intercurrent infections are recommended to minimize the effects of sepsis on the liver in patients who are dependent on parenteral nutrition over the long term.

Bowel Rest

Figure 1 illlustrates the possible effects of bowel rest on the pathophysiology of PNAC.

Bowel Rest and Bile Acids

Secretion of bile acids in the intestines is increased by meals and decreased by fasting. As a consequence of fasting, a decrease in canalicular bile flow causes bile acids to sequester in the gallbladder. On the other hand, hypertonicity of the parenteral nutrition solution may induce shrinkage of hepatocytes, reductions in bile volume and flow, and decreased transport of conjugated bile acids.[85] Thus, PNAC may be the result of reduced bile flow and altered bile acid metabolism.[86] As a result, accumulation of bile acids in the gallbladder will cause precipitation of cholesterol and calcium bilirubinate in bile ducts, leading to cholestasis and gallstone formation.[85] In support of this theory, hyperviscous and tenacious bile was recovered from patients during surgical biliary irrigation to relieve refractory PNAC.[87, 88] Biliary sludge or stones also were seen in many patients.[88]

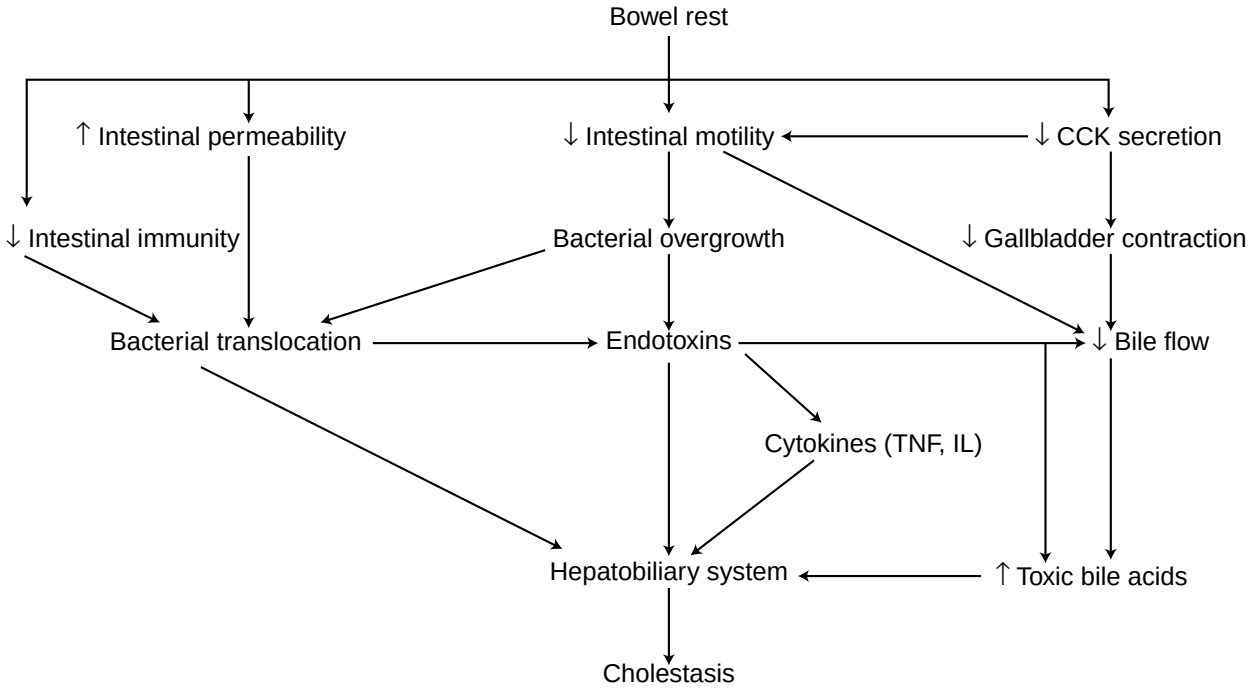

Figure 1. Suggested effects of bowel rest on the pathophysiology of parenteral nutrition-associated cholestasis. CCK = cholecystokinin; TNF = tumor necrosis factor; IL = interleukins.

The proposed effects of various bile acids in the pathophysiology of hepatobiliary complications require further elucidation. The two primary bile acids are cholic acid (CA) and chenodeoxycholic acid (CDCA). They are produced in the liver from cholesterol and then conjugated with taurine or glycine. Cholic acid and CDCA also are metabolized by intestinal bacteria to form the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. Normally, biliary bile acids in humans contain a small fraction of ursodeoxycholic acid (UDCA; < 5%) and LCA (< 5%), whereas CA, CDCA, and DCA constitute more than 90% of the overall bile acid pool.[85, 89] Contrary to LCA and CA, UDCA appears to be nonhepatotoxic due to its hydrophilicity and its lower surface activity. In animal studies LCA induced common bile duct hyperplasia and gallstones formation[90] and CA caused biliary fibrosis.[91] In addition, elevated LCA concentrations in bile and serum of patients with PNAC[24, 63] and similarities between hepatic lesions in humans with PNAC and animals that were given LCA suggest a role of LCA in causing liver injury.[63]

Administration of UDCA and enteral feeding have protective effects on the liver. Administration of UDCA improves clinical signs and symptoms of cholestasis,[92–94] possibly by displacing cytotoxic bile acids. Because bile acid secretion is proportional to oral intake,[85] early start of oral or enteral feeding restores enterohepatic circulation of bile acids and prevents accumulation of toxic bile acids in the hepatobiliary system.

Bowel Rest and Gut Hormones

The presence of food in the intestines causes stimulation and release of intestinal enzymes and hormones that help maintain physiologic balance between the gastrointestinal and hepatobiliary systems.[95] Cholecystokinin (CCK) is a peptide hormone that is secreted in the duodenum in response to food, namely, enteral fat and proteins.[96] It causes gallbladder contraction, relaxes the sphincter of Oddi, increases bile flow,[43] and stimulates intestinal motility.[97] By improving gut motility, CCK may prevent bacterial overgrowth and reduce bacterial translocation.[97]

Reduced blood concentrations of intestinal hormones and gut peptides were seen in premature infants who were parenteral nutrition dependent compared with enterally fed infants.[98] As a result of lack of CCK during bowel rest, gallbladder contractility is reduced, which could lead to bile stasis. For instance, ultrasonographic studies showed significantly more gallbladder distention in infants who received parenteral nutrition than in those who received enteral feeding (p=0.0001). Also, none of the infants in the parenteral nutrition group had gallbladder contractions.[99] On the other hand, infants with PNAC who were given exogenous intravenous CCK had a decrease in hyperbilirubinemia and improvement in clinical signs of cholestasis.[100, 101] Thus, reduced CCK secretion during bowel rest may play a role in the pathophysiology of cholestasis. As such, exogenous administration of synthetic CCK has been investigated for its possible role in preventing PNAC.

Bowel Rest and Bacterial Translocation

The gastrointestinal tract serves as a protective barrier to prevent intraluminal bacteria and toxins from reaching systemic organs.[75] This barrier may become disrupted as a consequence of bowel rest. Lack of intestinal motility leads to atrophy of the small bowel cellular lining, disrupts the normal balance of intestinal microflora,[75, 102] and promotes bacterial overgrowth that by itself may damage the intestinal barrier.[67, 103] In addition to these effects, bowel rest leads to reduced intestinal immunity,[67] decreased intestinal immunoglobulin A (IgA) levels,[104] and enhanced production of hepatotoxic cytokines.[76, 105]

As a result of increased gut permeability, bacterial translocation may occur. This describes the passage of intestinal microflora from intestines into the mesenteric lymph nodes, blood, or organs such as liver and spleen.[78, 106] Bacterial translocation has detrimental effects on the liver similar to the effects of sepsis, bacterial endotoxins, and cytokines.[107]

A few human reports focused on bacterial translocation in parenteral nutrition-dependent patients.[48, 49] A significant correlation was found between bacterial overgrowth and cholestasis[41] and between bacterial overgrowth and prolongation of parenteral nutrition dependence.[108] Intestinal microbial overgrowth was seen in 64% of infants receiving parenteral nutrition who later developed sepsis with the same microorganisms isolated from blood and gastrointestinal tract. Isolated microorganisms were *E. coli*, *Klebsiella*, enterococci, and *Candida* sp.[48]

Based on these observations, investigators

suggested that a disruption in the intestinal barrier leads to bacterial translocation to the liver with subsequent release of endotoxins that cause liver damage. Introducing enteral feeding should restore intestinal motility and prevent bacterial translocation. Bacterial overgrowth should be treated with enteral antibiotics to reduce bacterial translocation or endotoxin production by intestinal gram-negative bacteria.

Short Bowel Syndrome

This clinical condition is characterized by intestinal failure associated with malabsorption and metabolic abnormalities after extensive resection of the small intestine.[109] Neonates develop short bowel syndrome secondary to gastroschisis, intestinal atresia, volvolus, or severe necrotizing enterocolitis,[110] whereas in older children short bowel syndrome is a consequence of Crohn's disease, radiation enteritis, mesenteric infarction, intestinal tumor, or trauma.[109] Long-term parenteral nutrition is a life-saving therapy for patients who undergo massive intestinal resection.[110, 111] Long duration of parenteral nutrition is expected when more than 75% of small intestine is resected or less than 80–100 cm of small intestine remains.[109, 112, 113]

Parenteral nutrition-associated hepatic fibrosis, cholestasis, and liver failure are leading causes of death in patients with short bowel syndrome.[17, 38, 110, 114, 115] In a report that correlated hyperbilirubinemia with mortality, serum conjugated bilirubin concentrations greater than 4 mg/dl for at least 6 months after the development of short bowel syndrome resulted in a 78% mortality (sensitivity 70%, specificity 87%).[38]

Factors that predispose patients with short bowel syndrome to liver dysfunction include reduced intestine length,[44] bacterial overgrowth, long duration of parenteral nutrition,[108] and abnormal bile acid metabolism and excretion resulting from interruption of the enterohepatic circulation after ileal resection.[85] Of note, patients with the most severe gastrointestinal diseases require long duration of parenteral nutrition and thus are at high risk for sepsis, among other factors that cause cholestasis.[49] A significant correlation was found between remaining small bowel length of less than 50 cm and PNAC,[42] with as high as 70% of infants with short bowel syndrome eventually developing PNAC.[38] In 14 infants with mean residual jejunoileal length of 16% of normal for gestational age, PNAC and cholelithiasis developed in 57% and 21%, respectively; two infants died of liver failure.[116]

Several measures should be undertaken to prevent PNAC in children with short bowel syndrome, such as early and gradual start of enteral feeding, treatment of bacterial overgrowth, and prevention and treatment of sepsis.[117] In addition to maintaining gut integrity, enteral feeding promotes intestinal adaptation and minimizes dependence on parenteral nutrition.[109, 118] Unfortunately, patients with massive small bowel resection require long-term supplemental or full parenteral nutrition support and are likely to develop liver failure. The only life-saving alternative to indefinite parenteral nutrition in patients with short bowel syndrome and advanced liver disease is intestine or combined intestine-liver transplantation.[13, 119, 120]

Possible Etiologies

Excessive Calories

Excessive calorie administration (overfeeding) from combined or individual energy substrates (amino acids, dextrose, lipids) or an imbalanced source of energy can contribute to liver dysfunction. Jaundice and the histologic features of PNAC were improved by reducing the total amount of calories from parenteral nutrition.[121]

Excessive Dextrose

Although excessive dextrose infusion may lead to steatosis but not to cholestasis, both conditions may coexist in patients with parenteral nutrition-associated liver dysfunction.[122] Presumably, the abnormalities are the result of altered insulin: glucagon ratio in portal circulation and resultant hyperinsulinemia that causes glucose to convert to fat in the liver.[123] Although parenteral nutrition-associated steatosis is reported primarily in adults and is uncommon in infants, it should be suspected when hepatomegaly and elevated serum aminotransferases are present.[4] Since excess carbohydrates deposit in the liver as fat,[124] reducing the carbohydrate load should prevent steatosis.[20, 125] In children, carbohydrates should provide no more than 65% of total calories,[125] and dextrose infusions in infants should be limited to a rate not exceeding 14 mg/kg/minute, which corresponds to infants' maximum glucose oxidative capacity.[124] Also, providing a balanced source of calories avoids liver dysfunction. Liver steatosis occurred in 53% of patients who received only dextrose

infusions, compared with 17% of those who received mixed dextrose and lipid emulsions (70:30 ratio, respectively, p=0.05).[126] Therefore, a safe and balanced parenteral nutrition regimen should provide 25–30% of calories from lipids and 50–60% of calories from dextrose.[56, 127-129]

Amino Acids

Protein hydrolysates of casein and fibrin were early sources of parenteral amino acids. Such formulations had large amounts of dipeptides, tripeptides, and ammonia, and variable amounts of nonessential amino acids.[130] These solutions were associated with hyperammonemia, acidemia, allergic reactions, and liver dysfunction.[131] Later, standard as well as disease- and age-specific formulations of crystalline amino acids were introduced to replace protein hydrolysates.[132] Of these, the specialized pediatric crystalline amino acid formulation was developed to try and reproduce a plasma amino acid profile consistent with that of breastfed infants and to contain a balanced source of essential and nonessential amino acids.[133] These formulations were better tolerated and resulted in satisfactory weight gain and nitrogen retention in children.[133–135]

Amounts and Types of Amino Acids

The development of PNAC in children may be linked to both excessive[136, 137] and cumulative amounts of amino acids.[138] The disorder also may be related to the toxicity or deficiency of certain amino acids, specifically methionine excess,[139] cysteine deficiency,[140] and tryptophan and its degradation products[137, 141] that were suggested as causes of cholestasis. Several mechanisms are proposed to explain the mechanism of amino acid-induced cholestasis, such as possible alteration in canalicular flow and membrane permeability[142] by a direct effect of amino acids on the canalicular membrane,[27] leading to accumulation of hepatotoxic bile acids,[142, 143] dissipation of the transmembrane sodium gradient by uptake of sodium-dependent amino acids that decrease the driving force for bile acid transport,[144] or depletion of hepatic adenosine triphosphate (ATP) by excess methionine.[145]

The notion that amino acids have a tendency to suppress bile flow and bile salt secretion is supported by animal studies.[142] In studies of rat liver perfusion, amino acids caused a concentration-dependent inhibition of bile flow with high amino acid perfusate concentrations, causing great reduction in bile flow.[146–148] When parenteral nutrition was given to rabbits intravenously or orally, bile flow and hepatic secretory functions became clearly suppressed compared with rabbits that had chow feeding. Histologic studies showed that liver injury in animals was similar to that in humans with PNAC.[149]

Although some studies did not support a link between amino acids and cholestasis,[16, 40] others did.[27, 136, 137, 150] Premature infants who received amino acid-free parenteral nutrition with enteral whey protein supplementation 2.5–3 g/kg/day had no signs of PNAC, compared with 58% of infants who developed PNAC after 3 weeks of standard parenteral nutrition with amino acids. However, the investigators were unable to conclude whether the reduction in cholestasis in the enterally fed group was due to enteral feeding or avoidance of parenteral amino acids.[151] In a study that reported two levels of amino acid intake, infants who received 16% (5.0 ± 0.2 g/kg/day) of calories from amino acids had a substantial increase in serum alkaline phosphatase concentrations during the fourth week of the study compared with infants in whom amino acids provided 8% (2.7 ± 0.1 g/kg/day) of total calories. Cholestasis developed in two of five infants with the higher amino acid intake.[137]

In another study that correlated the severity of PNAC with amount of parenteral amino acids and duration of parenteral nutrition, preterm infants who received amino acids (mean ± SEM) 4.2 ± 1.1 g/kg/day developed PNAC, whereas PNAC was not seen in infants who received amino acids 1.7 ± 0.5 g/kg/day. Infants who received more than 2.5 g/kg/day for more than 4 weeks developed cholestatic jaundice. As a result, the investigators suggested that the amino acid dosage in preterm infants should not exceed 2.5 g/kg/day.[150] Similarly, infants who received parenteral amino acids 3.6 g/kg/day had significantly higher serum conjugated bilirubin concentrations than infants who received 2.3 g/kg/day. The higher dosage was associated with more severe and earlier onset of cholestatic jaundice.[136]

A definite relationship between plasma amino acid concentrations and liver dysfunction has not been established. However, results of available studies may lead one to conclude that liver abnormalities with amino acid infusions suggest possible dose-related toxicity. Amino acid dosages that were associated with liver toxicity[136,

[137, 150] exceeded the usually recommended maximum dosage of 3 g/kg/day for parenteral amino acids in infants.[152] Thus, since dosages of 2.5–3 g/kg/day would achieve a positive nitrogen balance in most infants,[152–154] it seems prudent not to exceed that limit so as to avoid liver toxicity.

Methionine Toxicity

Animal studies implicated certain free amino acids, namely methionine, in causing cholestasis[149, 155] and steatosis.[145] Methionine is an essential sulfur-containing amino acid that is metabolized by transsulfuration and transmethylation pathways, leading to the formation of cysteine, taurine, and glutathione. Cystathionase is the rate-limiting enzyme in the formation of cysteine from cystathionine, an intermediate in the metabolism of methionine (Figure 2).[139, 156]

In animal studies, plasma methionine concentrations were higher in rabbits that received parenteral nutrition than in rabbits that had chow feeding.[149] Intravenous methionine repressed bile flow and reproduced histologic liver injury in rabbits similar to that observed with parenteral nutrition.[155] A direct correlation was found between methionine perfusate concentrations and inhibition of bile flow in perfused rat liver.[146]

In humans, blood methionine concentrations were high in infants receiving parenteral nutrition[135, 140] and in those who died of PNAC and cirrhosis.[157] To date, no human data have correlated cholestasis to methionine in parenteral nutrition or to methionine blood concentrations.

Several theories are proposed to explain the mechanisms behind the potential hepatotoxic effects of methionine in infants. Premature infants are born with a low cystathionase activity, which reduces their ability to metabolize methionine to taurine and glutathione efficiently.[45, 158] They also may be unable to synthesize adequately S-adenosylmethionine,[151] a methyl donor derived from methionine and ATP (Figure 2).[139] Since taurine plays a role in bile acid conjugation, a deficiency may predispose these infants to cholestasis.[159] In addition, research focused on the possible role of free radicals in causing liver injury and the protective role of the antioxidant glutathione. Since premature infants may have low levels of glutathione as a result of low cystathionase activity and S-adenosylmethionine deficiency, they may be at increased risk for liver damage from free radicals, especially during oxidative stress.[139] On the other hand, S-adenosylmethionine deficiency in these patients may predispose to cholestasis. In a preliminary study in rats, S-adenosylmethionine increased bile acid secretion and maintained bile flow possibly by maintaining a normal Na^+-K^+-ATPase plasma membrane activity.[160]

Strong human data correlating cholestasis to methionine in parenteral nutrition are lacking. Nevertheless, some investigators suggested lowering methionine concentrations in crystalline amino acid solutions and providing alternative substrates for the transsulfuration pathway to minimize possible toxic effects of methionine on the liver.[139]

Lipid Emulsions and Plant Sterols

Lipid Emulsions

Lipid emulsions are a source of calories and essential fatty acids. Accumulated evidence shows that liver dysfunction may occur only with high dosages of lipid emulsions, and in rare cases

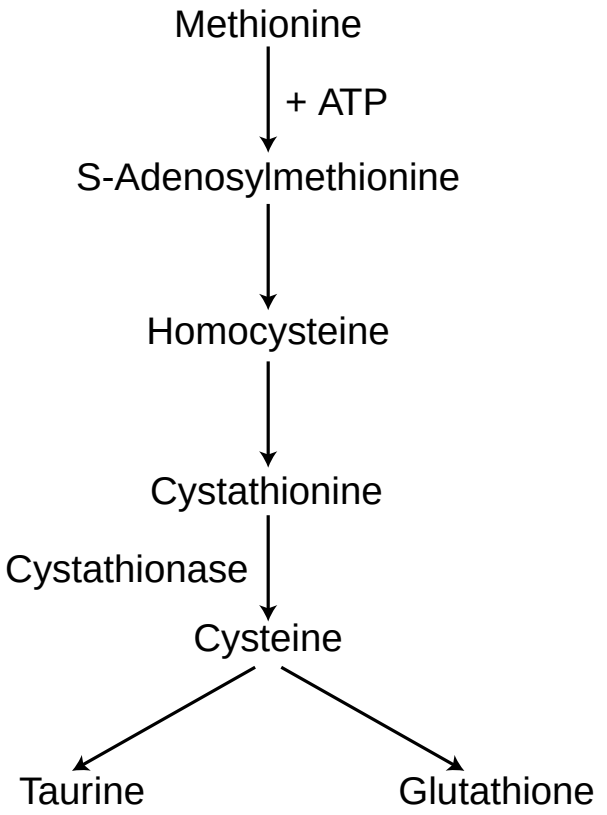

Figure 2. Methionine metabolism via the transsulfuration pathway (some intermediates and pathways are omitted for clarity). ATP = adenosine triphosphate.

of essential fatty acid deficiency. The exact mechanism of such toxicity is unknown.

A report of patients who developed cholestasis and hepatic cytolysis after a change in lipid emulsion formula raised the hypothetical question whether liver dysfunction could be related to the size of lipid particles in that emulsion, lecithin purification process, or sodium oleate content.[161] Based on an in vitro study, lipid emulsions induce dose-dependent inhibition of cholesterol uptake by cultured hepatic cells. It thus is proposed that reduced cholesterol availability for bile formation by hepatocytes would result in decreased bile volume and reduced bile secretion and flow that lead to cholestasis.[162] Similarly, animal studies showed that lipid emulsions may cause a reduction in bile flow[163, 164] but without an effect on serum bile acid concentrations[138] or on GGT levels.[164] Also, parenteral nutrition regimens that incorporated lipid emulsions caused further exacerbation of hepatic steatosis in rats.[164, 165]

In humans, the association between lipid emulsions and liver dysfunction was reported in adults[166] and children.[167] In adults, a significant elevation in serum bilirubin and alkaline phosphatase concentrations occurred with high dosages of lipids when dextrose only provided 22% of total calories. Patients who received a lower lipid dosage with a balanced calorie regimen (65% of calories from dextrose, 35% from lipids) did not show signs of liver abnormalities.[166] In a retrospective review of 10 children with PNAC receiving home parenteral nutrition, a relationship was suggested between lipid emulsions and cholestasis. This led investigators to suggest giving lipid emulsions 5 days/week at a dosage not exceeding 2–2.5 g/kg/day, with a lipid:energy ratio not exceeding 25%.[167]

Conversely, other human studies showed a protective effect of lipid emulsions on the liver when a balanced nutritional regimen was provided. Patients who received lipid-free parenteral nutrition later developed steatosis as a result of essential fatty acid deficiency that resolved with fatty acid supplementation.[168, 169] Hepatic accumulation of fat was seen in patients who received amino acid and carbohydrate mixture but not in those who received a balanced parenteral nutrition that provided lipid emulsions.[170] When one-third of carbohydrate calories was replaced with lipid calories, the elevation of liver enzyme concentrations was lower than that with lipid-free parenteral nutrition.[129]

Accumulated evidence in humans makes it unlikely that lipid emulsions in recommended amounts are a major factor in causing direct hepatocellular toxicity.[18, 171, 172] No statistically significant differences were found in elevations from baseline of serum alkaline phosphatase and AST concentrations when a high lipid (30% calories as lipid) and low lipid (2.5% calories as lipid) parenteral nutrition were compared.[173] The emulsions appear safe when given to children at dosages not exceeding 3 g/kg/day. In case of hypertriglyceridemia, the dosage should be reduced to 0.5–1 g/kg/day to provide enough linoleic acid to prevent essential fatty acid deficiency.[174] A lipid:energy ratio of 25–30% is appropriate to provide balanced caloric intake.[167, 173]

Lipid emulsions in the United States are made of long-chain triglycerides (LCT) derived from soybean or soybean-safflower oil. Considering the faster oxidation rate of medium-chain triglycerides (MCT) compared with LCT, early animal and human data suggest that the MCT-LCT mixture may be better tolerated and may be less likely to cause hepatic dysfunction.[175] Such a mixture is available in Europe but is still investigational in the U.S.

Plant Sterols

Interest in the role of plant sterols in the pathogenesis of cholestasis increased after high plasma concentrations of phytosterols were detected in a 3-year-old boy with PNAC.[176] Phytosterols form major plant sterols and are contaminants of lipid emulsions. Unlike cholesterol, they are inefficiently metabolized to bile acids by the liver.[177]

It is postulated that phytosterols may impair the hepatocyte canalicular secretory activity,[178] bind to membrane proteins and affect membrane fluidity and transporters, reduce bile synthesis and flow, and precipitate in the bile causing formation of biliary sludge and stones.[176] In an experimental neonatal piglet model, daily injection of plant sterols for 14 days resulted in phytosterolemia and decreased bile acid excretion. No histologic or clinical signs of cholestasis were detected.

In a human study of 29 children who had received lipid emulsions over 2 months, 5 children with severe PNAC (bilirubin > 5.84 mg/dl, AST > 200 U/L) had high plasma concentrations of phytosterols (campesterol,

stigmasterol, sitosterol, isofucosterol, sitostanol, cholestanol) similar to that seen in hereditary phytosterolemia.[179] Children with less severe PNAC had lower concentrations. All plant sterols in the plasma were present in the lipid emulsion. All five patients had decreased plasma phytosterol concentrations with reduction or discontinuation of lipid emulsions; however, only three had improvement in liver function tests. Of note, lipid dosages were higher in the group with severe PNAC than in the group with mild PNAC.

Based on available studies, no convincing data allow a definite correlation between phytosterols and cholestasis in patients receiving lipid emulsions. Further studies are required to explain whether an association exists between plasma phytosterol concentrations and liver dysfunction.

Manganese Toxicity

Manganese is a trace mineral that is supplemented daily to parenteral nutrition solutions in accordance with recommendations of the American Medical Association and the American Society for Clinical Nutrition. It is primarily eliminated in the bile and may accumulate in patients with cholestasis. High plasma manganese concentrations were reported in patients who had cholestasis while receiving parenteral nutrition.[180] Neurotoxicity is the most frequent toxicity with hypermanganesemia that was reported in patients receiving long-term parenteral nutrition[7, 181–184] and in those with cholestasis.[185]

In a group of 57 children receiving parenteral nutrition for longer than 2 weeks, 11 had both cholestasis and hypermanganesemia.[186] A significant correlation was found among whole blood manganese concentrations, plasma AST ($r=0.63$, $p<0.001$), and bilirubin ($r=0.64$, $p<0.001$) concentrations. Manganese and bilirubin concentrations declined after manganese supplements were reduced or withdrawn. Results of this study support the association between cholestasis and hypermanganesemia but do not provide evidence that the latter causes the former. A comparison of two groups of infants who received either high or low manganese dosage in parenteral nutrition solutions found no significant difference in the frequency of cholestasis.[187] Unfortunately, plasma manganese concentrations were not measured in all infants.

Manganese and bilirubin may have additive toxic effects on the biliary canalicular membrane.[188, 189] Although an association was found between elevated whole blood manganese concentrations and plasma alkaline phosphatase and GGT concentrations, no conclusion could be drawn as to whether hypermanganesemia caused cholestasis.[190, 191] It is also unclear whether blood manganese concentrations reflect liver and tissue manganese stores.[180] Nevertheless, monitoring manganese concentrations is particularly important in patients with PNAC, and restriction of manganese is necessary to avoid its accumulation.

Nutritional Deficiencies

Taurine Deficiency

Taurine is a sulfur-containing β-amino acid derived from cysteine. One of the many physiologic functions of taurine is in bile acid conjugation.[159] Animal studies suggest that taurine improves bile flow and protects against sulfolithocholate- and LCA-induced liver injury.[192, 193] It prevented parenteral nutrition-associated liver membrane damage and maintained bile flow in guinea pigs.[194]

Taurine becomes a conditionally essential amino acid in premature infants[159, 195] who are at risk for a deficiency due to decreased hepatic cystathionase activity[159] and increased taurine losses in the kidneys.[196] The deficiency may be aggravated in patients with advanced liver disease due to decreased liver ability to convert methionine to cysteine.[156] Low plasma taurine concentrations were reported in children receiving long-term parenteral nutrition without taurine supplementation.[197–199] Taurine 1.5–2.25 g/day in parenteral nutrition solutions returned plasma concentrations to normal after 6 weeks.[197]

Some reports did not support taurine supplementation's protective effect on the liver. Short-term supplementation to parenteral nutrition of 20 premature infants at 10.8 mg/kg/day for 10 days did not result in a different effect on hepatic function.[200] In children dependent on home parenteral nutrition who developed cholestasis, supplementation did not improve liver function tests despite a significant increase in blood taurine concentrations.[201] In a retrospective review of the frequency of cholestasis in infants who received two different commercial parenteral amino acid formulations supplemented with taurine (25 and 70 mg/100 ml bulk solution), PNAC occurred in 21.4% of subjects (15/70 patients) in equal numbers of those who received either formulation for at least

14 days.[37] This frequency fell within the range reported for PNAC in infants receiving parenteral nutrition without taurine supplementation. However, limitations to this study included its retrospective nature, small sample, and various underlying medical and surgical conditions in subjects that may have affected the results.

In summary, taurine supplementation improves bile flow and enhances bile acid conjugation.[202] Low taurine and high methionine plasma concentrations in infants with PNAC led investigators to suggest that taurine deficiency may impair bile acid conjugation, resulting in cholestasis.[157] Accordingly, the formulation of some neonatal parenteral amino acids was changed to include taurine in amounts to maintain normal plasma concentrations.[37, 203, 204] However, no correlation has been found between low plasma taurine concentrations and cholestasis, and no strong evidence suggests that returning plasma taurine concentrations to normal would prevent PNAC.

Carnitine Deficiency

Carnitine is a quaternary amine synthesized in the liver and kidneys from lysine and methionine. Its primary function is to transport long-chain fatty acids across the mitochondrial membrane for oxidation and generation of ATP.[205] Carnitine becomes essential in premature infants who are at risk for deficiency due to their limited reserves and reduced capacity for carnitine biosynthesis.[206, 207]

Based on reports of hepatic steatosis in carnitine-deficient patients and results of animal studies, the deficiency may be a factor in the pathogenesis of parenteral nutrition-associated liver dysfunction.[208, 209] A patient with systemic carnitine deficiency also had elevated liver enzyme concentrations, hepatomegaly, and steatosis.[210] In animal studies, carnitine supplementation reduced liver fat deposition that was induced with hypercaloric parenteral nutrition[211] and prevented alcohol-induced hepatic steatosis.[212]

In children, low serum carnitine concentrations[213–216] and depletion of tissue stores were associated with carnitine-free parenteral nutrition.[217] In other human reports, adding carnitine to parenteral nutrition returned plasma carnitine concentrations to normal, enhanced ketogenesis and fat metabolism,[218–220] reduced hepatocyte fatty infiltration,[208] and reversed the hyperbilirubinemia.[209] As a result, the improvement in fat metabolism led to the suggestion that carnitine supplementation mobilizes hepatic lipid stores and prevents steatosis in parenteral nutrition-dependent patients. However, supplementation for 1 month in four adults receiving parenteral nutrition returned plasma and liver carnitine levels to normal but did not improve steatosis.[221]

Carnitine is not routinely added to parenteral nutrition. L-Carnitine for intravenous administration is stable and compatible with parenteral nutrition solutions.[222, 223] The optimal dosage to prevent deficiency is not well defined, but 3–10 mg/kg/day added to neonatal parenteral nutrition is suggested when the duration of parenteral nutrition administration exceeds 2 weeks.[224]

Low plasma carnitine concentrations may not necessarily reflect tissue stores and may have no correlation with hepatic dysfunction associated with parenteral nutrition.[216] It remains to be established whether routine carnitine supplementation in children prevents liver dysfunction associated with parenteral nutrition.

Nonpharmacologic Management

Enteral Feeding

Enteral feeding reverses the intestinal mucosal hypoplasia induced by starvation,[102] preserves immunologic integrity of gut-associated lymphatic tissue,[78] prevents bacterial translocation,[139] and protects against PNAC.[106] In animal studies, parenteral nutrition-fed rats had significantly higher bacterial translocation from the intestines into mesenteric lymph nodes than enterally fed rats ($p<0.014$). No bacteria were cultured from the liver, spleen, or blood of rats in either group. Translocating bacteria were *E. coli* and *Proteus mirabilis.* The parenteral nutrition-fed rats also had higher cecal bacterial overgrowth and decreased intestinal IgA levels than enterally fed rats.[79]

Despite accumulated evidence of the protective effects of enteral feeding, a recent study in animals raised doubts about the efficacy of commercial liquid enteral feeding formulas in preventing bacterial translocation. Mice fed with such formulas had a significant increase in intestinal bacterial overgrowth ($p<0.01$) and bacterial translocation to the mesenteric lymph nodes ($p<0.05$) compared with chow-fed controls.[225] The clinical significance of these results and the effect of enteral formulas on bacterial translocation in humans is unknown.

In humans, PNAC is more common in children

who do not receive enteral feeding than in those who do.[18, 41] Lower serum levels of interleukins and endotoxins were found in stressed patients who received enteral feeding compared with those who received parenteral nutrition, suggesting a protective effect of enteral feeding.[226] Even small amounts of trophic feeding reduce intestinal stasis, diminish bacterial translocation, and improve bile flow.[98] Infants who waited for a mean of 34 days before starting enteral feeding developed PNAC; however, none of those who received enteral feeding after a mean fast of 14 days had PNAC.[9]

Starting enteral feeding early delays the appearance of liver dysfunction[18] and leads to resolution of jaundice.[43] Considering the benefits of maintaining the functional and structural integrity of the gut, early enteral feeding, even in small amounts, is the most established means to prevent parenteral nutrition-associated liver dysfunction.

Cyclic Parenteral Nutrition Infusion

Standard administration of parenteral nutrition for hospitalized patients is by continuous infusion over 24 hours. Cyclic parenteral nutrition refers to infusion over less than 24 hours, usually at night, to provide the patient with time off the intravenous and pump apparatus.

Cyclic or intermittent parenteral nutrition reduces hepatic complications associated with continuous infusion. Because continuous dextrose infusion results in hyperinsulinemia and fat deposition in the liver,[227, 228] cyclic parenteral nutrition may avoid compulsive overloading of the liver with dextrose and other nutrients.[117, 229–232] Cyclic infusion over 16 hours led to a decrease in liver enzyme concentrations, improvement in hepatomegaly, and resolution of jaundice.[232] Serum conjugated bilirubin concentrations decreased or stabilized after parenteral nutrition cycling in infants.[229] Liver enzyme concentrations were reduced and hepatomegaly improved after cycling for 2–3 weeks over 14–16 hours with 8–10 hours of dextrose-free infusions.[230]

When patients are expected to receive long-term parenteral nutrition, early cycling is recommended, with the usual goal over 10–14 hours. However, premature infants may experience fluctuations in blood glucose concentrations with short cycles. This is primarily due to their limited glycogen stores and immaturity of their glucose-regulatory mechanisms.[233] For instance, hyperglycemia may occur at high dextrose infusion rates, whereas rebound hypoglycemia may occur after abrupt discontinuation of parenteral nutrition.[234] To avoid short-term changes in blood glucose and insulin concentrations, the parenteral nutrition cycle usually is advanced over 2 hours and tapered off over 2 hours. Blood glucose concentrations are monitored at peak infusion rate and 30 minutes after parenteral nutrition is discontinued.

Pharmacologic Management

Ursodeoxycholic Acid

Ursodeoxycholic acid (urosodiol) is a naturally occurring hydrophilic bile acid formed in the liver and intestines. It plays a role in stimulating bile production and reducing cholesterol absorption and hepatic cholesterol synthesis,[235] allowing cholesterol gallstone dissolution.[89] It is passively absorbed from the intestines. Approximately 50–70% of UDCA undergoes first-pass hepatic metabolism.[89, 236] In the liver, it is conjugated with glycine and taurine and secreted in bile. The pharmacology of UDCA is reviewed elsewhere.[89]

The exact mechanisms by which UDCA exerts its protective effects on the liver are unknown. It is proposed that UDCA protects the liver by improving bile flow, displacing toxic bile acids, exerting immunoprotective effects on hepatocytes,[237] and protecting against endotoxemia by reducing intestinal endotoxin translocation[238] and enhancing endotoxin biliary excretion.[239]

Since UDCA is a minor bile acid in humans, it is suggested that low bile concentrations allow retention of toxic bile acids. Accumulation of toxic bile acids may lead to precipitation of cholesterol and calcium bilirubinate in form of gallstones or may even lead to cholestasis. Therefore, exogenous administration would enrich the bile with UDCA to displace toxic bile acids.[85, 240]

In addition to its benefits in improving PNAC,[92–94, 241, 242] UDCA relieves pruritus.[243] In children with intrahepatic cholestasis, dosages of 15–20 mg/kg/day improved pruritus and reduced serum ALT and GGT concentrations.[94] In children with PNAC, serum bilirubin concentrations decreased after 2 weeks of treatment with UDCA 15–30 mg/kg/day.[92] Similarly, UDCA 30 mg/kg/day resulted in resolution of hepatomegaly and jaundice within

1–2 weeks and normal liver enzyme concentrations within 4–8 weeks in children with PNAC.[93] A rebound increase in liver enzyme concentrations occurred after discontinuation of UDCA.[93, 94, 241] In adults with PNAC, UDCA improved serum GGT, ALT,[241] and bilirubin concentrations.[242] However, results in adults may not be extrapolated to children since the pathophysiologic changes of parenteral nutrition-associated liver dysfunction differ in the two populations.[244]

The agent is available as the protonated acid in capsule forms for oral administration. Although intestinal absorption may be slow and incomplete, in patients with chronic liver dysfunction, UDCA 8–12 mg/kg/day increases biliary concentrations by 30–60%.[89] The problem with absorption remains in patients with short bowel syndrome, in whom absorption is unreliable due to significant intestinal resection, chronic diarrhea, and gastric acid hypersecretion.[85, 109] In such patients, an extemporaneously prepared UDCA solution would be better absorbed than the capsule form.[85] Since UDCA is a weak acid, its solubility increases at alkaline intestinal pH above 8 unless it is solubilized with micelles. This alkaline pH is achieved only after meals, assuming sustained pancreatic secretions. An enteric-coated capsule in a pH-sensitive polymer was formulated to bypass poor intestinal absorption of protonated form, although it is not available in the U.S. It releases UDCA in the small intestines at pH 5.5 or greater, making it better absorbed than the regular capsule.[245]

Although UDCA is not approved for pediatric use,[246] it has been given in dosages of 10–20 mg/kg/day in children with cholestasis.[247] Up to 30 mg/kg/day divided in three doses was given to children with PNAC.[92, 93, 248] Gastrointestinal side effects include diarrhea, nausea, and abdominal pain.[241, 248] Although UDCA may improve clinical signs and symptoms of cholestasis, it does not alter disease progression. Thus, the effects of prolonged therapy on the course and prognosis of cholestasis are unknown.[94] Prospective, controlled studies are necessary to assess the agent's effects on morbidity and mortality in children with PNAC.

Cholecystokinin-Octapeptide

Cholecystokinin-octapeptide (CCK-OP, Sincalide) is the synthetic C-terminal octapeptide fragment of CCK that produces the biologic activities of CCK. In a preliminary human study, prophylactic CCK-OP prevented biliary sludge in adults receiving long-term parenteral nutrition.[249] Eight infants with PNAC had improvements in serum conjugated bilirubin concentrations and resolution of jaundice after intravenous administration of lyophilized porcine CCK. Although the authors advocated that CCK may reverse PNAC, seven patients were weaned from parenteral nutrition before CCK administration, one patient did not respond to repeated CCK, and a control group was absent.[100] In a pilot study of 11 infants with PNAC, CCK-OP caused reductions in serum conjugated bilirubin concentrations without significant effects on AST, ALT, and alkaline phosphatase levels.[101] However, five patients were receiving enteral feeding and two no longer were receiving parenteral nutrition. Enteral feeding and parenteral nutrition cessation may have led to the reduction in bilirubin. Also, a statistically significant decrease in hyperbilirubinemia was achieved only after three patients with liver failure were excluded. If these three patients had PNAC, this raises the question of whether CCK-OP has a role in advanced liver disease.

In a subsequent study, CCK-OP was administered to 21 neonates with PNAC who had received parenteral nutrition over 14 days.[250] The starting dosage was 0.02 µg/kg twice/day and increased to 0.04 µg/kg 3 times/day if parenteral nutrition was continued over 14 days. The control group consisted of infants with PNAC who were matched with the experimental group. Although CCK-OP slightly lowered serum conjugated bilirubin concentrations, the frequency of PNAC at concentrations greater than 2 mg/dl was not statistically significant between groups. Patients were allowed enteral feeding, which could have improved cholestasis independently.

Although in early animal studies CCK-OP prevented bile stasis associated with parenteral nutrition,[251, 252] the same benefits were not reproduced in later studies.[253, 254] The agent did not improve bile flow or bile acid secretion despite slight improvements in liver fibrosis and portal inflammation.[253] Also, it did not prevent gallstone formation and did not return the bile salt profile to normal despite improvements in bile acid synthesis and output.[254]

Currently, CCK-OP is not approved for prevention or treatment of cholestasis. It is available in injectable forms for intravenous and intramuscular administration. At dosages used in studies, it appears safe but with a commonly reported side effect of abdominal cramping[100, 101,

[249] that is likely dose related.[250] From study reports, CCK-OP appears to improve the clinical signs of cholestasis, but its long-term effects in preventing PNAC are unknown.

Enteral Antibiotics

Bacterial overgrowth is a common complication in children with short bowel syndrome.[255] Treatment is crucial to reduce intestinal bacterial overload and minimize bacterial and endotoxin toxic effects on the liver. Improvements in liver enzyme concentrations after treatment with antibiotics that target intestinal bacteria suggest a role of these bacteria in the pathogenesis of parenteral nutrition-associated liver dysfunction. Although different antibiotics are administered to treat bacterial overgrowth in patients with PNAC, no clear consensus on the choice of drug exists. Metronidazole[256–260] and oral nonabsorbable antibiotics such as gentamicin,[261] kanamycin,[68] neomycin,[79] and polymyxin B[65, 71] are effective.

Metronidazole

The ability of metronidazole to prevent liver injury in rats suggests a role of anaerobic bacteria, particularly *Bacteroides* sp, in the pathogenesis of hepatic injury associated with bacterial overgrowth.[256, 258, 260] In animals, reduction of intestinal anaerobic flora by the agent was associated with a reduction in hepatic lipid content.[259] In humans, the drug prevented steatosis in obese patients with jejunoileal bypass.[262] This effect possibly was mediated through inhibition of jejunal bacterial overgrowth and intestinal deconjugation of bile acids, a known complication of jejunoileal bypass surgery.[263] In a retrospective review of adults who received parenteral nutrition, metronidazole given intravenously, orally, or rectally prevented elevations of serum alkaline phosphatase, GGT, and AST concentrations.[258] Reductions in liver enzyme concentrations were similarly reported after oral[256] or intravenous[264] administration to adults with parenteral nutrition-associated liver dysfunction.

Metronidazole does not improve liver enzyme concentrations in advanced liver disease.[114] Intravenous administration in infants receiving parenteral nutrition did not have a significant effect on the frequency of hyperbilirubinemia. Only infants who received metronidazole 50 mg/kg/day had significantly lower serum AST and ALT concentrations compared with infants in the control group ($p<0.05$).[257]

Gentamicin

Very low-birthweight infants who were given oral gentamicin for prophylaxis of necrotizing enterocolitis while receiving parenteral nutrition had less significant increases in serum conjugated bilirubin concentrations than infants with significantly higher serum bilirubin concentrations who did not receive the drug. The frequency of cholestasis was 8% and 42%, respectively. Also, patients receiving gentamicin had no significant rise in serum conjugated bilirubin concentrations from baseline after starting parenteral nutrition.[261]

Neomycin

Oral neomycin given to rats reduced the frequency of bacterial translocation and the number of cecal gram-negative bacteria.[79] The drug protected against fibrosis, cirrhosis, and fatty infiltration of the liver. Since oral administration of endotoxins reversed these protective effects, it was concluded that neomycin protects against liver injury by suppressing intraluminal bacterial growth.[265]

Polymyxin B

Oral polymyxin B decreased cecal flora, TNF production, and hepatic steatosis in rats given parenteral nutrition.[65, 71] In vitro experiments showed polymyxin B binds and inactivates the lipid A-core region of the lipopolysaccharide portion of endotoxins.[266] Besides its bactericidal effect on enteral gram-negative bacteria, the agent may prevent release of TNF by macrophages in response to lipopolysaccharides and protect against lipopolysaccharide-induced liver toxicity and steatosis.[65, 71]

Enzyme Inducers

Phenobarbital

Phenobarbital may improve cholestasis possibly by enhancing conjugation of bilirubin.[267, 268] Results of the effects of phenobarbital in cholestasis are inconsistent. In a premature infant with PNAC, 5 mg/kg/day improved hyperbilirubinemia that did not respond to discontinuation of parenteral nutrition; hyperbilirubinemia recurred after phenobarbital was discontinued.[266] However, in two other case reports, the same dosage did not improve hyperbilirubinemia in infants with PNAC.[140] In a retrospective review of medical

records of 31 infants who were treated with phenobarbital for neurologic conditions while receiving parenteral nutrition, 60% developed cholestasis, compared with 33% of untreated infants.[268]

Based on published reports, the role phenobarbital in relieving PNAC is uncertain. In addition, there is concern about worsening intrahepatic cholestasis with the agent in children with obstructive cholangiopathy.[269]

Rifampin

Rifampin may be more effective than phenobarbital in relieving pruritus in patients with primary biliary cirrhosis.[270] A dosage of 10 mg/kg/day was effective in relieving pruritus[271] and improving GGT levels in children with cholestasis who failed UDCA, phenobarbital, or antihistamine therapy.[272] Improvements in cholestasis and pruritus also were reported with the drug in adults with primary biliary cirrhosis.[270, 273] Although the exact mechanism of action of rifampin in relieving pruritus is unknown, proposed mechanisms include enhancing metabolism of bile acids or pruritogenic substances,[273] diminishing the pool of toxic bile acids,[270] and inhibiting bile acid uptake by hepatocytes.[274] Due to the drug's potentially serious side effects, such as toxic hepatitis,[273] hemolytic anemia, and renal failure,[270] other safer agents such as cholestyramine or UDCA should be considered first for treating the pruritus of cholestasis.[243, 275]

Cholestyramine

Cholestyramine is an insoluble ion exchange resin that forms a nonabsorbable complex with bile acids in the intestines. It relieves pruritus associated with intrahepatic cholestasis[276] and alleviates diarrhea after ileal resection.[277] Cholestyramine also binds the endotoxins in the intestines and may prevent their translocation.[278] However, this effect may be clinically insignificant because it is partial and short lived.[279]

The agent's role in treating bile acid-induced diarrhea in patients with ileal resection is explained by its binding capacity of excess bile acids in the colon to prevent salt and water secretion.[280, 281] Its ability to relieve pruritus of cholestasis is probably due to its effect on lowering levels of bile acids and other pruritogenic mediators.[275, 282]

The usual dosage of cholestyramine in children is 240 mg/kg/day divided in three doses.[283] Constipation, diarrhea, nausea, and abdominal discomfort are reported adverse effects.[276] Due to its drug-binding capacity, cholestyramine may bind UDCA when the two are given concurrently to patients with cholestasis.[284] To avoid clinically significant drug-drug interactions, other oral agents should be given 1 hour before and 4–6 hours after cholestyramine administration.[285]

Intestine Transplantation

Despite improvements in transplantation outcomes over the past 10 years, long-term results of liver and small bowel transplantation as alternatives to parenteral nutrition in patients with refractory short bowel syndrome are unknown.[286] The choice of isolated small bowel versus combined small bowel-liver transplantation depends on the extent of liver disease. The 1-year worldwide survival rate after 1995 was 69% for intestinal transplants and 66% for small bowel-liver transplants.[119] Worldwide 5-year survival was 50% for small bowel transplants and 40% for combined small bowel-liver transplants.[287]

Intestine transplantation resulted in stopping parenteral nutrition in 77% of survivors[119] who later were able to achieve normal growth and weight gain with oral feeding.[120, 287] When considering the procedure in parenteral nutrition-dependent patients, complications (rejection, infection, lymphoproliferative disease)[119, 287] and quality of life should be taken into consideration.[288] Until a higher survival rate is achieved, and given the high survival rate in patients receiving home parenteral nutrition,[289] intestine transplantation seems warranted only when all therapies fail and when the patient has life-threatening complications.[115, 119, 120] In addition, patients may benefit from other types of organ transplantations, such as isolated orthotopic liver transplantation, that might be an alternative in infants with end-stage liver disease. To be considered for that procedure, patients should have significant tolerance to enteral feeding and have sufficient small bowel with a good probability of eventual gut adaptation.[290] As experience grows, it may become possible to perform bowel transplantation early before hepatic failure develops, especially if more selective and powerful immunosuppressive therapies become available.

Summary

Several interventions can be undertaken to

Table 1. Measures to Prevent Parenteral Nutrition-Associated Hepatobiliary Dysfunction

Measure	Rationale
Avoid overfeeding	Avoid compulsive liver overload with nutrients
Avoid excessive dosages of any micronutrient	Avoid excessive liver overload with macronutrients (amino acids, dextrose, lipids), prevent deficiencies
Start enteral feeding early	Preserve intestinal integrity, maintain intestinal hormone and enzyme secretion, prevent bacterial translocation
Cycle parenteral nutrition	Avoid continuous liver overload with nutrients
Avoid sepsis, aggressively treat sepsis	Avoid bacterial and endotoxin hepatotoxic effects on hepatocytes and bile flow
Administer ursodiol	Enhance bile flow, reduce hepatotoxic bile acids
Administer cholecystokinin	Improve gallbladder contractility, stimulate bile
Administer enteral antibiotics	Inhibit bacterial overgrowth
Administer cholestyramine	Treat pruritus associated with cholestasis, reduce diarrhea with short bowel syndrome

prevent parenteral nutrition-associated hepatobiliary dysfunction (Table 1). The disorder is reversible when parenteral nutrition is discontinued and enteral feeding is begun early before irreversible liver damage has occurred. Recommended methods to prevent liver dysfunction include limiting the duration of parenteral nutrition, starting enteral feeding early, avoiding overfeeding, vigilant prevention and prompt treatment of sepsis, and cyclic parenteral nutrition. Prophylactic administration of UDCA is likely beneficial, but its role in treatment of PNAC requires further studies. Therapy with CCK-OP to prevent and treat PNAC yields inconsistent results, and its effects in advanced liver disease are questionable. Bowel decontamination with enteral antibiotics may be beneficial when clinical conditions predispose to bacterial overgrowth. It is essential to monitor liver enzyme concentrations regularly during parenteral nutrition to allow early detection of liver abnormalities. Liver biopsies may be necessary when the diagnosis is uncertain. Patients with short bowel syndrome and severe liver dysfunction should be assessed for combined bowel and liver transplantation.

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