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Prevention and Treatment of Intestinal Failure-Associated Liver Disease in Children

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Abstract

Intestinal failure-associated liver disease (IFALD), a serious complication occurring in infants, children and adults exposed to long-term parenteral nutrition (PN), causes a wide-spectrum of disease, ranging from cholestasis and steatosis to fibrosis and eventually cirrhosis. Known host risk factors for IFALD include low birth weight, prematurity, short bowel syndrome and recurrent sepsis. The literature suggests that components of PN may also play a part of the multifactorial pathophysiology. Because some intravenous lipid emulsions (ILE) may contribute to inflammation and interfere with bile excretion, treatment with ILE minimization and/or ILEs composed primarily of omega-3 fatty acids can be helpful but requires careful monitoring for growth failure and essential fatty acid deficiency (EFAD). Data from randomized controlled trials are awaited to support widespread use of these approaches. Other IFALD treatments include cycling PN, ursodeoxycholic acid, sepsis prevention, photoprotection and polyvinylchloride-free tubing. Management and prevention of IFALD remains a clinical challenge.

Keywords

Intestinal failure-associated liver disease; parenteral nutrition associated cholestasis; parenteral nutrition; short bowel syndrome; intravenous lipid emulsions

Introduction

Parenteral nutrition (PN) is a life-saving therapy for children and adults who are unable to feed entirely via the gastrointestinal tract. This supportive therapy has transformed the care of premature infants, children with critical illness and patients with all types of intestinal failure (IF). Unfortunately, one of the serious and common complications from its long-term use is progressive liver disease. An association between cholestasis and PN has long been recognized. A case report from 1971 details the death of a premature infant with progressive cholestasis and cirrhosis associated with PN use¹. While there now are multiple innovative therapies for IF, this problem continues to confound clinicians.

Definitions

There are a few main definitions used for the liver disease associated with PN use. PN associated cholestasis (PNAC) is defined as cholestasis, or elevated serum conjugated bilirubin greater than 2.0 mg/dL on at least two consecutive weeks, in the setting of PN use without another identifiable specific cause. Besides PNAC, other related terms in the literature include intestinal failure-associated liver disease (IFALD), PN-associated liver disease, and PN-associated liver injury. Most authors therefore prefer the term IFALD, acknowledging the multi-factorial etiology including host factors, such as low birth weight, prematurity, short bowel syndrome (SBS), prolonged duration of PN, lack of enteral intake, and recurrent sepsis²⁻⁴. In addition, patients with IF may have hepatic disease even in the absence of prolonged PN use.

Diagnostic evaluation

Because clinical features of IFALD can mimic other causes of chronic liver disease, clinicians should consider a diagnostic work-up for other causes prior to attributing clinical and/or biochemical abnormalities to PN exposure alone. Precipitous cholestasis should prompt evaluation for sepsis, especially due to herpes simplex virus, urinary tract infection and central line-associated blood stream infection (CLABSI). Drug reactions should also be considered. Abdominal sonography is helpful to detect cholelithiasis, which is also common with prolonged PN use. In neonates, results from state newborn screen should be reviewed and metabolic conditions should be considered where clinically suspected, especially with hypoglycemia and/or acidosis. In infants and young children, testing for cystic fibrosis and alpha-1-antitrypsin deficiency are sometimes warranted. When cholestasis develops during the first several weeks of life, prompt diagnostic work-up for extra-hepatic biliary atresia is important. Liver biopsy is helpful both for evaluation of alternative diagnoses as well as assessing stage of liver steatosis and/or fibrosis. Histopathology is not specific for IFALD and can include normal or minimal changes, to cholestasis and/or steatosis, and finally to fibrosis and even cirrhosis⁵. Patterns of hepatic injury, such as steatosis or fibrosis, do not necessarily direct specific therapies. However, the diagnosis of cirrhosis is helpful for direction towards health maintenance screenings (yearly oxygen saturation level, serum alpha-fetoprotein and liver ultrasound) and consideration of transplantation evaluation in the appropriate clinical setting.

Epidemiology

In children, elevated conjugated serum bilirubin and gamma-glutamyl transferase (GGT) levels can occur within 1–4 weeks of initiating PN therapy⁶. Prematurity and low birth-weight represent significant risk-factors for IFALD^{2,4}. Cholestasis develops in forty to sixty percent of premature infants exposed to prolonged PN⁶. In children with all types of IF, twenty-two percent develop IFALD⁷. However, patients with intractable diarrhea of infancy have prevalence of IFALD as high as 48%⁸. Many children can receive prolonged PN safely, but mortality rates may be as high as 26–28%^{9,10}. In adults, prolonged PN use is associated with elevated transaminases but severe liver dysfunction is uncommon¹¹. Forty percent of adults on long-term PN develop persistent elevated transaminases¹².

Duration of parenteral nutrition and host factors

In multiple studies, the total duration of PN use has been the factor most strongly associated with the risk of cholestasis^{2,7,13}. Duro et al. reported that the odds of developing PNALD increased 2.4 fold for each additional week of PN exposure in patients with necrotizing enterocolitis¹⁴. The diagnosis of gastroschisis and jejunal atresia increases risk of cholestasis compared with other causes of SBS, possibly due associated intestinal stasis. The length of bowel resected is also a risk factor. In infants with necrotizing enterocolitis, pre- and post-operative exposure to PN and the creation of a proximal jejunostomy or small-bowel resection are strong predictors for development of liver disease¹⁴. The percentage of days with a diverting ostomy is also associated with peak direct bilirubin level in infants with SBS¹⁵. Establishment of full enteral feeds and discontinuing PN is perhaps the best treatment for IFALD. Retrospective studies have shown that the serum direct bilirubin normalizes by three to four months following PN discontinuation.^{16,17} Serum aminotransferase concentrations take longer to normalize than bilirubin level. Yang et al. reported that one year following PN cessation, ALT was elevated in 42.4% of patients, while bilirubin was normal in all patients. More study is needed to understand long-term outcomes with IFALD following PN discontinuation.

Lipids

Various components of ILE have been suspected for their possible role in IFALD, including plant sterols, omega-3/omega-6 fatty acid balance, vitamin E content and others. Plant sterols are steroid alcohols that are components of plant cell membranes, which humans cannot synthesize. Normally, humans only absorb 5% of plant sterols in the small intestine¹⁸. They are subsequently metabolized in the liver and excreted into bile. However, plant-based ILE deliver these components directly into the blood stream where they are transported via lipoproteins to the liver as well as other tissues. Blood plant sterols concentrations are four times higher in neonates with IFALD than controls¹⁹. In adults on home PN, blood plant sterols levels are closely associated with serum bilirubin levels²⁰. It is hypothesized that plant sterols lead to cholestasis through antagonism of farnesoid X receptor, which regulates bile excretion via the multi-drug resistance (MDR) transporter²²¹. This finding is consistent with a mouse model, where PN infusion is associated with reduced function of MDR transporters 1 and 2. Not all ILE contain equal concentrations of plant sterols. For example, the fish oil-based ILE, Omegaven (Fresenius Kabi AG, Bad Homburg, Germany), contains none. In a mouse model, plant sterols-supplemented Omegaven and soy-bean oil-based Intralipid (Fresenius Kabi, Bad Homburg, Germany) resulted in liver injury; PN without Intralipid and unaltered Omegaven did not²³.

Pro-inflammatory long-chain polyunsaturated fatty acids (LCPUFA) in ILE are also been suspected to contribute to the genesis of IFALD. Infusion of ILE results in rapid incorporation of LCPUFA into cell phospholipid membrane. Since Intralipid has a high concentration of omega-6 fatty acids, there is promulgation of pro-inflammatory mediators such as linoleic and arachidonic acid. Alternative ILE, such as Omegaven and SMOFlipid (Fresenius Kabi, Bad Homburg, Germany), contain high omega-3 fatty acid concentrations that have anti-inflammatory effects through the production of eicosanoids, prostaglandin E3,

leukotriene B5 and thromboxane A3. Omegaven is especially rich in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). By comparison, Liposyn II, Intralipid and ClinOleic contain neither DHA nor EPA. Therefore, different ILE formulations may have different pro-inflammatory and anti-inflammatory effects.

ILE also vary according to alpha-tocopherol content, which may have implications for development of liver disease. Alpha-tocopherol (a form of vitamin E) is a powerful anti-oxidant that helps reduce ILE peroxidation and free radical peroxidation. Intralipid contains 38 mg/L of alpha-tocopherol while Omegaven contains 150–296 mg/L. Whereas some data support a role for vitamin E supplementation in the treatment of non-alcoholic steatohepatitis, there is no literature to support exploiting the anti-inflammatory effects of alpha-tocopherol supplementation for the treatment or prevention of IFALD²⁴.

ILE minimization is one strategy suggested for the prevention and treatment of IFALD. ILE minimization is generally defined as limiting ILE dose to 1–2 grams/kg/day, although some centers choose to reduce the dose even further. Restricting enteral fat intake is not indicated as part of this strategy. In a case series of adults on long-term PN, reduction of ILE resulted in reversal of progressive cholestatic jaundice²⁵. A multi-center prospective study of 90 adults on home PN reported that exposure to intravenous soybean-based ILE higher than 1 gram/kg/day was a significant risk factor for developing IFALD³. A prospective cohort study of surgical neonates on long-term PN demonstrated a reduction in total bilirubin levels with soybean-based ILE of 1 gram/kg/day given twice weekly when compared with historical controls typically administered 3 grams/kg/day²⁶. A retrospective case series in children with IF demonstrated that temporary suspension of ILE resulted in improvement in cholestasis within one month. Unfortunately, weight gain faltered in all patients during the period of lipid cessation²⁷. In addition to poor weight gain, ILE minimization has potential risks for neurocognitive delay since lipids are vital to myelin formulation during brain development.

Recent literature also suggests that alternative ILE are an important treatment option for IFALD. For the treatment of cholestasis, a case series documented success by switching infants with cholestasis to fish-oil based ILE (Omegaven), with a median time to reversal of cholestasis in 18 infants with SBS of 9.4 weeks versus 44.1 weeks with soybean oil-based ILE in a historical cohort²⁸. These findings were consistent with other published small case series in preterm infants^{29,30}. Another case series reported that changing from Intralipid to 1:1 mixture of ClinOleic (Baxter S.A., Lessine, Belgium) and Omegaven resulted in rapid improvement in liver function parameters in 5 neonates with SBS²⁰. These striking outcomes have brought widespread attention to fish-oil ILE as a uniquely valuable treatment modality.

It is uncertain whether improving lab abnormalities also represent resolution of serious liver pathology. Two patients with IFALD switched from Intralipid to Omegaven showed persistent hepatic fibrosis despite normalization of liver tests³¹. The Birmingham group recently presented a case series of three patients where serial post-Omegaven liver biopsies showed resolving hepatic fibrosis in two specimens and no progression of fibrosis in four specimens³². Local availability greatly determines choices of ILE. In the US, only Intralipid

and Liposyn III (Hospira, Lake Forest, IL) are widely commercially available. A large, prospective study is needed to evaluate changes in serial liver biopsies to better understand any relationship between histopathology and treatment with alternative or low-dose ILE.

There is limited literature on using alternative ILE for the prevention of IFALD. In a mouse model, Omegaven appears to prevent the development of liver disease^{23,33}. In a limited pilot study of neonates randomized to Omegaven or Intralipid, there were no differences in liver test changes from baseline³⁴. In a randomized prospective trial of stable children on home PN, SMOFlipid group versus controls had significantly lower total bilirubin level and higher blood alpha-tocopherol concentration after 29 days, but there were no significant differences in clinical outcomes³⁵. More study is needed before alternative ILE are considered for primary prevention of IFALD.

Concern has been raised for the potential development of essential fatty acid deficiency (EFAD) when using exclusive fish oil-based ILE or ILE minimization. Fish oil-based ILE contains very low amounts of alpha-linolenic and linoleic acids compared with standard dose soybean-based ILE (Table). EFAD is conventionally defined as a triene to tetraene ratio greater than 0.2. An elevated mead acid and clinical symptoms (scaly skin, growth failure, alopecia) are also supportive of the diagnosis. Of note, EFAD did not occur in 10 infants and children with limited enteral intake and monotherapy with parenteral fish oil-based ILE of 1 gram/kg/day³⁶. ILE minimization can also lead to EFAD. To avoid the risks of EFAD, some advocate for using a mixture of Omegaven 1 gram/kg/day and Intralipid 1 gram/kg/day³⁷. In children suspected to require long-term PN, our group limits soybean-based ILE to 1 gram/kg/day; if cholestasis occurs, we switch to fish oil-based ILE 1 gram/kg/day.

With minimal enteral intake and/or significant malabsorption, there is a risk of choline deficiency, since there are only trace amounts of choline supplied by standard ILE. The function of choline is lipid transport and transmembrane signaling. Choline deficiency manifests clinically as elevated transaminases and steatohepatitis, not unlike IFALD³⁸. In neonates, whole-blood phosphocholine concentration was decreased in relation to the amount of PN received, suggesting deficiency³⁹. A pilot study in adults on long-term home PN suggested that plasma-free choline levels are low and choline supplementation reduces steatosis versus placebo³⁸. Choline is not commercially available for intravenous supplementation.

Amino acids

In contrast to ILE, there is limited literature on the role of amino acids (AA) in IFALD outside of infancy. AA solutions are a standard component of PN meant to support lean mass and growth. In a prospective controlled study of 43 infants, there was no change in incidence of cholestasis with high AA intake; although higher concentrations of amino acids was associated with a faster and earlier cholestasis⁴⁰.

In the neonatal period, taurine and cysteine are conditionally essential amino acids because of low levels of hepatic cystathionase and cysteine sulfinic decarboxylase⁴¹. Taurine is also involved in forming taurine-conjugated bile acids, as opposed to glycine-conjugated bile

acids. In a hamster model, taurine supplementation increases bile flow rate as well as bile acid excretion rate⁴². However, there were no significant differences in liver biochemical tests with taurine supplementation⁴³. Amino acid solutions have been formulated to match pediatric needs. In an uncontrolled, unblinded multi-center study of 31 infants and children on PN using Trophamine (Kendall-McGaw Laboratories, Irvine, CA), only one patient developed cholestasis, which is a lower incidence than generally quoted in the literature⁴⁴. There was no comparison arm of this study, however, and several subsequent studies have not confirmed preventive effects of using Trophamine during infancy^{45–47}. Our group uses Trophamine exclusively for children under one year. There is no evidence that taurine supplementation is necessary or beneficial in older children.

Carbohydrate

Excessive glucose administration leads to hyperinsulinemia and increased fatty acid synthesis, which can lead to hepatic steatosis. American Society for Parenteral and Enteral Nutrition guidelines recommend limiting glucose infusion rate to 12–14 mg/kg/min in infants and young children, 8–10 mg/kg/min in adolescents and 4–5 mg/kg/min in adults⁴⁸. These recommendations are based upon glucose oxidation rates. With ILE minimization, however, high dextrose concentrations are commonly needed to substitute for energy provision. When advancing glucose infusion rates, patients should be monitored for hyperglycemia with finger stick glucose and urinalysis for glucose during peak PN infusion.

Cycling

Infusing daily allotment of PN over less than 24 hours, or so-called “cycling,” may be protective against the development of IFALD. The mechanisms for hepatoprotection include mobilizing free fatty acids from body stores, decreasing fatty acid storage, as well as matching cycling pattern of growth hormone, cholecystokinin and insulin⁴⁹. Cycling requires renal, endocrine and cardiac tolerance of fluid shifts and increasing glucose infusion rates. The use of cycling is limited in prematurity by diminished glycogen stores and immature glucose handling. Cycling is achieved by gradually increasing rate over shorter infusion time. In small infants without enteral feeds, cycling off may be limited to 6 hours⁵⁰. In a retrospective review of neonates with gastroschisis, cholestasis at 50 days was observed in 9.8% of the cycled group versus 48.8% in the group⁵¹ receiving continuous PN. We routinely provide PN in a cycled fashion as soon as metabolic and fluid status allow.

Ursodeoxycholic acid

Since ursodeoxycholic acid (UDCA) has been used to treat other types of cholestatic liver disease, it has also been used to treat IFALD. UDCA exchanges hydrophobic for hydrophilic bile acids, thereby improving bile flow. In adults with IFALD, 10–15 mg/kg/day of UDCA has been associated with improved liver biochemical tests⁵². In a pilot study of 7 children with clinically symptomatic liver disease, there was resolution of jaundice, hepatomegaly and splenomegaly as well as normalization of laboratory studies within 1–2 weeks of starting UDCA. UDCA discontinuation resulted in relapse, but re-initiating UDCA resolved GGT elevation again⁵³. In premature infants, UDCA (20 mg/kg/day every 6 hours) resulted

in improvement in GGT versus erythromycin or placebo. In a double-blind, placebo controlled trial, UDCA resulted in decreased GGT activity⁵⁴. In a retrospective study of non-surgical very low birth weight infants with cholestasis on long-term PN, UDCA was associated with shortened course of cholestasis and decreased peak serum bilirubin level compared with historical controls⁵⁵. In another trial of very low birth weight infants, UDCA was associated with a lower incidence of GGT elevation than placebo, but interestingly there was no difference in bilirubin and aminotransferase levels⁵⁶. UDCA use is sometimes limited by diarrhea, which could be a concern in children with SBS. There is rising awareness that UDCA may not be entirely innocuous. In adults with primary sclerosing cholangitis, high dose UDCA (28–30 mg/kg/day) was associated with increased mortality⁵⁷. The mechanism for increasing mortality is poorly understood. Our group treats IFALD patients with at least some enteral intake and any abnormal liver test with UDCA 20 mg/kg/day divided in two daily doses. We continually assess if UDCA is exacerbating diarrhea.

Prevention of sepsis

Sepsis is a significant risk factor for IFALD. Septic episodes during the first one to six months of life are a strong predictor of developing cholestasis^{2,58}. Episodes of sepsis are associated with a 30% rise in serum bilirubin level². In a mouse model, microbiota passage through injured intestinal tissue is absorbed through the portal vein and leads to toll-like receptor activation in Kupffer cells thereby promoting hepatocyte injury, cholestasis, apoptosis and fibrosis⁵⁹. Additionally, propagation of endotoxins and pro-inflammatory cytokines interfere in biliary transport.

One of the most common sources of sepsis with PN use is due to central line-associated blood stream infections (CLABSI). These infections, especially at a younger age, are associated with severe liver fibrosis⁶⁰. Therefore, efforts should be directed towards preventing infections wherever possible. Caregivers should practice aseptic technique when handling central venous catheters. A recent meta-analysis suggested that ethanol locks were associated with significant reduction in septic episodes⁶¹. Only four small-sized studies were included, as there were no randomized-controlled studies available^{62–65}. Our center uses ethanol locks prophylactically in all IF patients with a history of a CLABSI⁶⁴.

Photoprotection

Many centers have adopted practices to protect PN from ambient light in order to prevent the generation of lipid peroxidases and hydrogen peroxide. By protecting the entire system (PN bag, lipid syringe, and all tubing), hydrogen peroxide generation is reduced by 50%⁶⁶. This might prove especially helpful in very low birth weight infants who are at most risk of oxidative injury. Often it is impractical to protect the entire system, especially the tubing. Protecting the system except the tubing has limited effect on peroxide generation⁶⁶.

DEHP

A Di(2-ethylhexyl)phthalate (DEHP) is plasticizer found in polyvinylchloride (PVC), which is found in PN tubing. DEHP leaches into liquids, and leads to liver oxidative stress and decreased biliary excretion. Many institutions have stopped using PVC-containing tubing. Following the transition from PVC to PVC-free tubing at one neonatal intensive care unit, the incidence of IFALD decreased from 50% to 13%⁶⁷.

Aluminum, Copper and Manganese

Aluminum is a common contaminant of PN from glass containers, manufacturing process and organic phosphate salts. Clinical findings of aluminum toxicity include encephalopathy, neurological impairment, bone disease, microcytic anemia, and cholestasis. Beginning in 2004, the Food and Drug Administration mandated aluminum concentration labeling on all PN ingredients. Pharmacists should select products with minimum amount of aluminum contamination whenever possible. The measured amount of aluminum is often significantly less than labeled amount⁶⁸, suggesting that aluminum contamination is often overestimated.

Copper and manganese are trace elements usually added to PN that are both excreted via the biliary tract. Based upon limited expert opinion, there is concern for copper and manganese toxic accumulation in the liver in the setting of cholestasis. Serum levels of manganese and copper are not reliably associated with degree of cholestasis⁶⁹. Nevertheless, there is reason to believe excessive manganese intake can cause liver dysfunction. In an animal model, manganese infusion leads to decreased biliary excretion rate and changes in biliary canalicular ultrastructure⁷⁰. Because there is no known manganese deficiency state, our group does not add additional manganese above amount present in standard trace element solutions. In contrast, copper deficiency is common in SBS⁷¹. Copper should thus be added judiciously based upon anticipated needs as well as laboratory monitoring. In cholestatic infants, appropriate copper supplementation does not seem to lead to copper toxicity or worsening liver disease⁷².

Conclusion

The occurrence of intestinal failure-associated liver disease has plagued clinicians caring for intestinal failure patients for decades, and it likely has multiple possible etiologies. A modern approach combining various established therapies reduces IFALD incidence and mortality.⁷³ Alternative intravenous lipid emulsions such as fish oil products show great promise and further studies are anticipated. As with all medical approaches, the identification and minimization of risk factors for IFALD need to be individualized for each patient.

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Table

Comparison of intravenous lipid emulsions

	Intralipid	Liposyn II	Clinoleic	SMOFlipid	Omegaven
Oil source (grams/100 ml)					
Soybean	20	5	2	3	0
Safflower	0	5	0	0	0
MCT	0	0	0	3	0
Olive oil	0	0	8	2.5	0
Fish oil	0	0	0	1.5	10
α -tocopherol (mg/L)	38	NP	32	200	150–296
Phytosterols (mg/L)	348 $\pm$ 33	383	327 $\pm$ 8	47.6	0
Fat composition (grams/100 ml)					
Linoleic	5	6.5	0.9	2.9	0.1–0.7
α -linolenic	0.9	0.4	0.1	0.3	<0.2
EPA	0	0	0	0.3	1.28–2.82
DHA	0	0	0	0.05	1.44–3.09
Oleic	2.6	1.8	0.8	2.8	0.6–1.3
Palmitic	1	0.9	0.7	0.9	0.25–1
Stearic	0.35	0.34	0.2	0.3	0.05–0.2
Arachidonic	0	0	0.003	0.05	0.1–0.4

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