Intestinal Microbiota, Lipids, and the Pathogenesis of Intestinal Failure–Associated Liver Disease

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Intestinal failure (IF) is considered the end result of gastrointestinal disorders in which functional intestinal mass is inadequate to promote adequate growth, hydration, and electrolyte balance.[1] Today, a substantial number of infants and children with IF, caused by short bowel syndrome, necrotizing enterocolitis, gastroschisis, intestinal atresias, motility disorders, and genetic enterocyte transport defects, depend on long-term parenteral nutrition (PN) for survival and the promotion of normal growth and development.

PN–associated cholestasis (PNAC), which refers to the development of conjugated hyperbilirubinemia and impaired bile flow, implies that PN itself is the predominant factor responsible for liver injury.[2] A recent understanding of the various factors that cause liver injury in patients receiving PN, however, has led to the broader descriptive term of IF–associated liver disease (IFALD),[3] which replaces the previous term PN–associated liver disease (PNALD). IFALD is defined as cholestasis and progressive biliary cirrhosis in the setting of PN in a patient with underlying intestinal disease, resection, or dysfunction, if other specific causes of liver injury have been excluded.[4] It is in these patients that the most severe, progressive, and sometimes-fatal phenotypes of PNAC develop; hence, IFALD has become the leading indication for intestinal and multivisceral transplantation in children. In addition to progressive biliary cirrhosis and portal hypertension, hepatocellular carcinoma has been reported as a rare complication in children with liver cirrhosis secondary to long-term PN.[5]

Advanced IFALD is one of the most significant risk factors associated with mortality in infants on long-term PN.[6,7] There are several recent reviews on the pathogenic mechanisms predisposing infants to IFALD and various strategies to prevent or reverse established IFALD.[2,4,8-10] Prematurity and small for gestational age, length of bowel remnant in those who had bowel resection, lack of enteral feeding, duration of PN, recurrent sepsis, protein undernutrition, and an excess of intravenous carbohydrate load have been considered as important factors in the development IFALD.[3] Mechanisms receiving the most recent attention include the role of omega(ω)-6 polyunsaturated fatty acids (PUFAs) and plant sterols found in the intravenous lipid emulsions (ILEs),[8] bacterial overgrowth and microbiome dysbiosis of the small intestine,[11] the role of bacteremia and fungemia related to microbial translocation across the intestinal barrier and central line–associated bloodstream infections, and increased intestinal permeability leading to absorption of bacterial products from injured intestine inducing innate immune responses in the liver.[12,13] The purpose of the present review is to discuss the latest understanding of the role of various ILEs and intestinal microbial dysbiosis.[14,15]

DSS	Dextran sodium sulfate
FO	Fish oil
IF	Intestinal failure
IFALD	Intestinal failure–associated liver disease
ILE	Intravenous lipid emulsion
LPS	Lipopolysaccharides
PN	Parenteral nutrition
PNAC	Parenteral nutrition–associated cholestasis
PNALD	Parenteral nutrition–associated liver disease
PUFA	Polyunsaturated fatty acid
SMOF	Soybean oil, medium chain triglycerides, olive oil, and fish oil
SO	Soybean oil
TLR-4	Toll-like receptor-4

Prevalence and Epidemiology of IFALD

The prevalence of IFALD varies with age and the underlying cause of IF. Criteria used to define IFALD generally include the presence of serum direct or conjugated bilirubin ≥2 mg/dL in an infant with duration of PN ≥14 days and no other cause for the cholestasis.[16,17] Others have included increased serum liver enzymes[18,19] and the presence or absence of end-stage liver disease[20,21] as other categories of IFALD. A recent systematic review of 23 studies reported the overall incidence of IFALD as 29.9%, with the incidence of 25.5% among extremely low birth weight and very low birth weight preterm neonates receiving PN, and incidence of 30.6% in term infants and children without IF.[2] The incidence was greatest (49.8%) in pediatric patients with IF receiving PN.[2] The authors noted that there has been no obvious changes in the prevalence of IFALD during the last 4 decades (excluding very recent experience), although there is a lack of high-quality, prospective studies.[2] In support is a population-based, retrospective survey in infants with gestational age <30 weeks in Stockholm county, Sweden, which reported the incidence of PNALD to be 14.8% in those born between 2006 and 2008 and 12.7% for those delivered between 2010 and 2011 (P = .52).[22] Thus, the incidence of

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W.L. was funded by the Ministry of Higher Education, Malaysia (UM.C/625/HIR/MOHE/CHAN/13/1). R.S. receives funding from the National Institutes of Health (UL1TR001082 and U01DK062453). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.05.048

IFALD has been stable during the last few decades despite various previous efforts to prevent IFALD.

Pathogenesis of IFALD

Many factors, including host factors and nutrient factors, have been implicated in the development of IFALD. Nutrient factors include components of ILEs and nonlipid nutritional considerations (Table I).[4] Host factors, including prematurity, small for gestational age, abdominal surgery, and episodes of sepsis, have been reviewed elsewhere.[4,8,9] However, none of the listed risk factors has been studied carefully in a prospective, controlled trial.[4,8,9] In addition, no single risk factor has been implicated as causative of liver injury in all patients on prolonged PN; thus, a multifactorial etiology seems likely.

Recent efforts to elucidate the mechanisms responsible for IFALD have focused on the role of soybean oil (SO)- and other plant oil–based lipid emulsions, the intestinal microbiome and the integrity and permeability of the intestinal wall, as well as the role of activation of the hepatic innate immune system, particularly Kupffer cells (Figure).[12,13] A better understanding of the pathologic mechanisms of IFALD is required to identify potential therapeutic targets for prevention and treatment, which will require the use of appropriate animal models followed by translation into well designed clinical trials in affected children.

ILEs

Interest has been focused in recent years on the potential role of ILE in the pathogenesis of IFALD after reports of the reversal of IFALD when ILE was switched from SO-ILE to a fish oil (FO)-based emulsion.[10,23] Several mechanisms have been proposed.[23-25] The first is the potential role of SO- or plant-based lipid emulsions, which are used commonly in the US. SO-ILEs are composed primarily of ω-6 PUFAs, including linoleic acid, which is the precursor of arachidonic acid, the structural backbone of proinflammatory eicosanoids.[26] In contrast, the ω-3 PUFAs found in FO products but not in plant oils, such as α-linolenic acid, are converted into anti-inflammatory derivatives.[27]

FO-ILEs, approved for use in Europe but not in the US, have a high ratio of ω-3 to ω-6 PUFA. It has been hypothesized that the potential benefit of FO-ILEs is attributable to downstream anti-inflammatory properties of ω-3 PUFA compared with the potential proinflammatory ω-6 PUFA forms. Although this hypothesis is an attractive one, there are few data in children affected by IFALD to support it. Second, in animal studies, phytosterols, plant-based naturally occurring sterols found in SO-ILEs, have been shown to interrupt hepatocyte farsenoid X receptor signaling and the expression of downstream bile acid transporters, thus decreasing bile flow.[28] Third, the cholestatic effect of ILE has been postulated to be related to the dose of lipid (and its constituents) itself. The dose of FO-ILE commonly administered in PN is only 30%-40% that of SO-ILE. Finally, SO-ILEs contain relatively low amounts of the antioxidant alpha-tocopherol relative to the amount of PUFAs, potentially putting the infant at risk for oxidative stress and lipid peroxidation, which have been demonstrated in the cholestastic liver.[29,30] FO-ILEs contain far greater amounts of alpha-tocopherol than SO-ILEs.

Table I. Risk factors and pathogenic mechanisms for developing IFALD[2,4,8,25]

Risk factors	Proposed pathophysiologic mechanisms	Level of evidence
Host factors		
Prematurity and small for gestational age	Immature enterohepatic circulation leading to accumulation of toxic bile acids precipitating secondary oxidant injury	Class III
Sepsis	Circulating endotoxin activates Kupffer cells within the liver, stimulating the release of proinflammatory cytokines, generating inflammatory cascade	Class III
Intestinal surgery	Absent of enteral feeding leads to decreased secretion of enteric hormones causing intestinal and gallbladder stasis, predisposing to small bowel bacterial overgrowth and dysbiosis; compensatory bowel dilation in short bowel syndrome. Altered intestinal permeability predispose infants to increased bacterial translocation	Class III
Necrotizing enterocolitis	Multifactorial: prematurity; abdominal surgery and bowel resection often necessary; prolonged absent/limited enteral feeding; peritonitis; altered intestinal permeability	Class II and III
PN		
Lipid emulsions: plant- or SO-ILE	Plant- or SO-ILEs contain greater ω-6 PUFA, which are precursors of proinflammatory eicosanoids. ω-6 PUFA administration predisposes infants to hepatic steatosis. Phytosterols interfere with FXR signaling and decrease bile acid transport. Relatively low alpha-tocopherol levels relative to PUFA in SO-based lipid emulsions.	Class III
Longer duration of PN	Longer exposure to PN	Class III
Excessive energy load	Excessive delivery of parenteral energy may lead to hepatic steatosis	No evidence
Amino acid component	Mechanism unclear	No evidence

FXR, farsenoid X receptor.
Classification of evidence:

Class I: prospective, randomized, controlled clinical trial. Primary outcome and exclusion/inclusion criteria clearly defined.
Class II: prospective matched group cohort study in a representative population with masked outcome assessment.
Class III: all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population. Outcome assessment is independent of patient treatment.
Class IV: evidence from uncontrolled studies, case series, case reports, or expert opinions.