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. Today, a substantial number of infants and children with IF, caused by short bowel syndrome, necrotizing enterocolitis, gastrochisis, 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. 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), 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. 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.

Advanced IFALD is one of the most significant risk factors associated with mortality in infants on long-term PN. There are several recent reviews on the pathogenic mechanisms predisposing infants to IFALD and various strategies to prevent or reverse established IFALD. 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. Mechanisms receiving the most recent attention include the role of omega(3)-6 polyunsaturated fatty acids (PUFAs) and plant sterols found in the intravenous lipid emulsions (ILEs), bacterial overgrowth and microbiome dysbiosis of the small intestine, 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.

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. Others have included increased serum liver enzymes and the presence or absence of end-stage liver disease 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. The incidence was greatest (49.8%) in pediatric patients with IF receiving PN. 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. 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). Thus, the incidence of
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 1). Host factors, including prematurity, small for gestational age, abdominal surgery, and episodes of sepsis, have been reviewed elsewhere. However, none of the listed risk factors has been studied carefully in a prospective, controlled trial. 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). 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. Several mechanisms have been proposed. 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. 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.

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. 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 cholestatic liver.

FO-ILEs contain far greater amounts of alpha-tocopherol than SO-ILEs.

**Table 1. Risk factors and pathogenic mechanisms for developing IFALD**

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

FXR, farsenoid X receptor.

Classification of evidence:
Class I: prospective, randomized, controlled clinical trial. Primary outcome and inclusion/exclusion 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.
To more clearly understand the role of lipid emulsions in IFALD, several models in animals have been developed in recent years. By using an IFALD mouse model, which combines PN infusion with intestinal injury (which was accompanied by increased intestinal permeability) induced by dextran sodium sulfate (DSS) (PN/DSS mice), we have demonstrated that the SO-based PN solution caused hepatic injury, cholestasis, and hepatic macrophage activation; however, neither intestinal injury nor PN alone led to these hepatic perturbations. In contrast, isocaloric PN solutions that were either FO-ILE based or were devoid of all lipids were not associated with these hepatic abnormalities. Importantly, the addition of stigmasterol, the putative cholestatic phytosterol, to the FO-ILE–based PN solution recapitulated the hepatocyte injury, cholestasis, and macrophage activation, which was similar to that observed in the SO-PN group. Furthermore, studies in vitro demonstrated that stigmasterol itself, in addition to absorbed intestinal lipopolysaccharides (LPS), had the capacity to activate macrophages into a proinflammatory state. In addition, treatment of the PN/DSS mice with oral antibiotics or the use of toll-like receptor-4 (TLR-4) mutant mice that did not respond to LPS prevented liver injury, cholestasis, and macrophage activation, confirming the role of bacterial products absorbed through injured intestine.

On a molecular basis, the expression of the canalicular exporter for stigmasterol, Abcg5/g8, was down-regulated in the mouse model, resulting in hepatic accumulation of stigmasterol, which was associated with inhibition of expression of the nuclear receptor Fxr, which in turn reduced the hepatocyte expression of Fxr-dependent genes, including the bile salt export pump, responsible for driving bile flow. Thus, our studies in this novel mouse model provided experimental evidence that plant sterols in ILEs combined with increased absorption of LPS from the hyperpermeable injured intestine may play major roles in the pathogenesis of IFALD.

There are also human data supporting the role of plant sterols in IFALD. Clinical studies in neonates and children with IFALD who received PN demonstrated that serum stigmasterol (and other phytosterols) was increased markedly compared with infants and children on PN who did not develop IFALD. Other studies in animals have not supported the contribution of phytosterols to PNALD. Vlaardingerbroek et al, using premature piglets fed exclusively with PN, compared the effect of different ILEs (SO-ILE, FO-ILE, and a mixture of SO, medium chain triglycerides, olive oil, and FO [SMOF]-based ILE [Fresenius-Kabi AG, Bad Homburg, Germany]) in inducing hepatic injury and cholestasis. Although the plasma and hepatic phytosterol concentrations were greatest in piglets fed with SO-based PN solution, there was only weak correlation between these phytosterol concentrations with the severity of

Figure. Proposed pathogenesis of IFALD. LPS and other intestinal bacterial products are absorbed through the inflamed intestinal mucosa into the portal circulation as result of small bowel bacterial overgrowth, intestinal dysbiosis, and increased intestinal permeability and also may circulate in high concentrations as result of bacteremia and sepsis. LPS, through TLR-4 binding, leads to activation of hepatic macrophages, promoting release of cytokines that stimulate hepatocyte pathways that lead to interruption of farsenoid X receptor (FXR) and liver X receptor (LXR) signaling. Reduced FXR signaling leads to suppression of bile salt export pump (BSEP) and multidrug resistance–associated protein 2 (MRP2) expression, resulting in reduced canalicular secretion of conjugated bile acids and bilirubin and cholestasis. Phytosterols (particularly stigmasterol) derived from SO-ILE also may activate hepatic macrophages. Macrophage-derived cytokines impair LXR signaling, causing reduced expression of ABCG5/G8, resulting in hepatocyte retention of sterols, such as phytosterols. Phytosterols interrupt FXR signaling and further reduce BSEP and MRP2 expression, resulting in cholestasis. LPS also may potentially directly affect hepatocytes, which express TLR-4, and suppress FXR and LXR signaling.
hepatic injury and cholestasis. Moreover, the SMOF-based ILE, although containing phytosterols, was equally protective against PNALD compared with FO-based ILE, which was devoid of phytosterols. The authors suggested that other lipid components present in SMOF-based and FO-based ILE, such as vitamin E or $\omega$-3 PUFA, may be protective against PNALD.

In subsequent experiments, the addition of alphatocopherol to SO-ILE prevented the increase in serum and hepatic markers of PNALD compared with PN solution containing SO-ILE alone. Furthermore, the addition of phytosterols to 100% FO-ILE did not reproduce evidence of PNALD. It should be pointed out that there are important differences in this piglet model of PNALD and the mouse model of IFALD described previously. In the piglet model, there was no intestinal injury or inflammation and by inference no major increase in intestinal permeability, components that are believed to be essential in the development of IFALD in infants. In addition, all piglets received broad-spectrum antibiotics throughout the course of the PN administration (which would alter intestinal microbiota and reduce absorbed intestinal LPS), the levels of circulating phytosterols achieved were only modestly elevated in the piglets supplemented with phytosterols, and macrophage activation was not investigated. Thus, the applicability of this piglet model to IFALD, in which intestinal inflammation and altered permeability are intrinsic factors, is not clear. It is intriguing that addition of large amounts of alphatocopherol to the PN solutions in the piglet provided protection against PNALD, inasmuch as cholestasis and toxic bile acid accumulation in the hepatocyte generate oxidative stress through mitochondrial pathways, and alphatocopherol and other antioxidants have been shown to reduced bile acid-induced hepatic injury.

**Intestinal Microbiome and Intestinal Permeability**

It is well established in animal models that prolonged PN leads to a shift in the intestinal microbiota, favoring Bacteroidetes, such as *Clostridium difficile*, as compared with Firmicutes, which was associated with activation of intestinal Paneth cells. Moreover, the presence of bacterial overgrowth of the small intestine was demonstrated in a large series of infants and children with IFALD, and it was observed that this bacterial overgrowth was related to the severity of small intestine inflammation, presumably impairing intestinal barrier function and promoting absorption of small molecules across the small bowel mucosa. This relationship between bacterial overgrowth and inflammatory pathways was demonstrated elegantly in a PN-dependent mouse model in which a shift in the intestinal microbiota was associated with intestinal epithelial cell apoptosis, increased expression of mucosal proinflammatory cytokines, and a loss of intestinal barrier function.

Altered intestinal microbial communities were demonstrated in the described mouse model combining intestinal injury with total PN. A specific intestinal microbiome, identified by a metagenomic evaluation of colonic bacteria, was limited to those mice with PNAC. Specifically, overgrowth of *Erysipelotrichaceae* and S24-7 taxa of Bacteroidetes was observed in DSS/PN mice that developed cholestasis and liver injury, which was associated with increased intestinal permeability and absorption of LPS. In addition, these authors showed that treatment with a combination of 4 oral antibiotics, resulting in significant suppression of intestinal microbiota, prevented liver injury, cholestasis, and activation of hepatic macrophages.

On the basis of these observations, a restoration of intestinal integrity and barrier function would in theory prevent the occurrence of IFALD in patients receiving prolonged PN. Thus, the potential use of antibiotics, prebiotics, or probiotics to modify the microbiome is an attractive strategy to prevent IFALD. An interesting study in preterm newborn pigs receiving PN showed that feeding with amniotic fluid before initiation of milk feeding led to a reduction in intestinal permeability and a change in intestinal microbiota, presumably related to growth or immunologic factors transferred in the amniotic fluid. However, whether such novel therapeutic approaches or other manipulations of the intestinal flora would be effective in preventing or treating human IFALD remains to be determined. Currently, there are no clinical data supporting the use of probiotics to prevent or treat IFALD in children or adults, and concerns remain about bacteremia from such agents in patients with central venous catheters. Surgical approaches to reduce bowel dilation, lengthen the intestine, and improve motility appear to be the best current approaches for preventing bacteria overgrowth of the small intestine.

**Bacteremia and Innate Immune Response**

Another important factor in the pathogenesis of IFALD resulting from increased intestinal permeability is the promotion of bacterial translocation, bacteremia, or simply absorption of bacterial cell wall products capable of activating the innate immune system. Indeed, the number and earlier timing of episodes of bacterial or fungal sepsis has been associated consistently with the development of IFALD. In the mouse IFALD model, interruption of TLR-4 signaling was associated with prevention of liver injury and hepatic macrophage activation, suggesting that LPS or other TLR-4 agonists absorbed from the intestine were involved in IFALD pathogenesis. Meticulous care of central venous catheters, including ethanol locks, has been recommended to prevent central line–associated bloodstream infections to potentially reduce the risk for innate immune cell activation and IFALD.

**Preventive and Therapeutic Approaches**

Various strategies have been proposed to prevent IFALD, and in patients who have established IFALD, to reverse the cholestasis and hepatic fibrosis (Table II). We will focus on those related to ILE and the intestinal microbiota.
Reduced Soybean Intravenous Lipid Dose

The prevailing view linking the development of cholestasis and the use of SO- and other plant oil–based ILEs stemmed from several clinical observations showing a temporal relationship between the development of cholestasis and an increased dosage of SO-based ILE.43 This finding was supported by a more recent study that showed that the development of advanced IFALD was related to the number of days of exposure to ≥2.5 mg/kg/day of parental ILE.44 Subsequently, a prospective study comparing a cohort of surgical neonates receiving SO-ILE at a reduced dose (1 g/kg) with a historical standard dose cohort (2–3 g/kg) showed a reduction in the incidence of IFALD (22% vs 43%, P < .002).26 However, another retro­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­…
SO-ILE (1 g/kg/d of each) was attempted in surgical infants believed to be at risk for IFALD. Unfortunately, this relatively small study failed to show the development of IFALD in any of the infants; thus, it was not possible to determine whether there was any protective benefit of FO-ILE, if the low dose of both lipid emulsions was protective, or if the selection criteria for infants at high risk for IFALD were not optimal. Thus, although a properly powered randomized controlled trial has not been conducted, current evidence suggests that the use of FO-ILE is effective in reversing the established cholestasis associated with IFALD, but there is insufficient evidence for a preventative effect in neonates who require prolonged PN support. An alternative lipid emulsion containing a combination of oils, SMOF, was not associated with cholestasis in the premature piglet model, suggesting that it may also have protective effects in humans. However, 2 infants with surgical bowel conditions who developed IFALD while receiving SMOF (2-3 g/kg per day) required switching to a FO-ILE (1 g/kg per day) in order to reverse the cholestasis.

**Final Considerations of Lipid Modification**

Authorities agree that few high-quality clinical trials have been conducted to support use of alternative approaches to lipid emulsions. Most studies have been retrospective, used a historical comparison group, used different doses of lipid, and were conducted in patients with quite advanced IFALD. In addition, with the exception of improving biochemical measurements of cholestasis and delaying the need for intestinal transplant evaluation (2 important outcomes), there is evidence that the use of ILE containing ω-3 PUFA does not improve other important long-term clinical outcomes, such as the severity of hepatic fibrosis. Moreover, the long-term safety of reduced ILE doses in small infants remains to be proven, because infant brain growth and cognitive development depend on an adequate supply of PUFA and lipid.

Recently, lower brain weight and alterations of brain PUFA content were demonstrated in newborn piglets receiving total PN with reduced dose SO-ILE or FO-ILE compared with normal dose SO-ILE and control piglets, supporting this concern. Thus, there is an urgent need for high-quality, well-conducted clinical trials with clearly defined clinical outcomes and measurements, including cognitive and brain development, and longer-term follow-up. It is equally important to note that because FO-based ILE is not licensed for use in the US, its use increases the complexity and cost of care as it is more expensive than SO-ILE and can only be administered under Food and Drug Administration compassionate use protocols requiring special monitoring and reporting.

**Current Recommendations for Use of ILE**

The causal link between the use of standard dose SO-ILE and IFALD has not been established firmly in prospective, controlled clinical trials, leading most experts to conclude that the level of evidence in human trials for the proposed pathophysiologic mechanisms (role of SO-based, ω-6 rich PUFA, and high level of plant phytosterols) as weak. The evidence supporting the recommendation for a reduced dose of SO-ILE or replacing it with other source of ILE, such FO-based, is graded as weak or probably effective. Nevertheless, these practices have been widely adopted in the US based on clinical experience and absence of alternative effective approaches.

**Discussion**

IFALD is the greatest contributor to morbidity and mortality in infants and children with IF. Its pathogenesis is complex and multifactorial. Recently, interest has focused on the potential role of SO- and plant oil–based, ω-6 rich ILEs, altered intestinal permeability with absorption of bacterial products and activation of the innate immune system, and episodes of sepsis in the pathogenesis of IFALD. Reduction in the dose of SO-ILEs or replacement with non-SO-based ILEs (such as FO-ILE or mixed lipid ILE) appears to reverse the cholestasis (and abrogate the need for intestinal transplantation) but probably has little effect on hepatic fibrosis. Other biologic pathways under investigation, including activation of hepatic-based innate immunity mechanisms, may yield new therapeutic targets.

There is an urgent need to conduct high-quality, prospective trials with clearly defined outcome measures and long-term follow-up to ascertain the effects of these new strategies. Meticulous care of central venous catheters to prevent bacterial and fungal sepsis also may reduce innate system activation. Both surgical and medical measures taken to enhance intestinal adaptation and advancement of enteral feedings, thus allowing for reduction of PN dependence, will ultimately reduce the need for PN in infants with IF. The effect of alpha-tocopherol on the hepatotoxic effect of toxic bile acids and phytosterols, oxidative stress and the proinflammatory effect of SO-ILE, as well as restoration of intestinal mucosal integrity may provide novel therapeutic approaches in the prevention of IFALD in the future.

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