New insights into intestinal failure–associated liver disease in adults: A comprehensive review of the literature

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Abstract
Intestinal failure–associated liver disease (IFALD) remains one of the most common and serious complications of parenteral nutrition (PN), causing a wide spectrum of hepatic manifestations from steatosis and mild cholestasis to portal hypertension and end-stage liver failure. The prevalence of IFALD depends on the diagnostic criteria and ranges from 4.3% to 65%. Moreover, many factors are shown to contribute to its development, including nutrient deficiencies, toxicity of PN, infections, and alterations of bile acid metabolism and gut microbiota. Prevention and management of IFALD aim at ameliorating or eliminating the risk factors associated with IFALD. The use of PN formulations with a lower ratio omega-6-to-omega-3 polyunsaturated fatty acids, cycle PN, optimization of enteral stimulation and prevention and early treatment of infections constitute the main therapeutic targets. However, failure of improvement and severe IFALD with end-stage liver failure should be considered as the indications of intestinal transplantation. The aim of this review is to provide an update of the epidemiology, pathophysiology, and diagnosis of IFALD in the adult population as well as to present a clinical approach of the therapeutic strategies of IFALD and present novel therapeutic targets.

Keywords: Intestinal failure–associated liver disease, liver injury, parenteral nutrition, parenteral nutrition associated liver disease

INTRODUCTION

The European Society for Clinical Nutrition and Metabolism (ESPEN) defines intestinal failure as “the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth.”[1] It is classified into three types: acute, prolonged acute, and chronic [Table 1].[2] Parenteral nutrition (PN) is frequently used in clinical practice to prevent malnutrition and provide most of the necessary nutrients in patients with inadequate intestinal absorption or in patients where enteral nutrition is contraindicated.[3] PN contains protein, carbohydrates, fat, vitamins, water, and trace elements, whereas the solution and duration of PN depends on the underlying diseases and nutrition status of the patient.[4] Despite the various benefits, the administration of PN has been associated with many complications, including hyperglycemia,[5] refeeding

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syndrome in malnourished patients, thromboembolic complications, infections, metabolic bone disease, cholelithiasis, and PN-associated liver disease (PNALD).

Recently, the terminology "intestinal failure–associated liver diseases (IFALD)" has replaced the term PNALD. In particular, ESPEN recommends that the term IFALD should refer to liver injury as a result of one or more factors relating to intestinal failure including, but not limited to, PN and occurring in the absence of other primary parenchymal liver pathology, other hepatotoxic factors, or biliary obstruction. Particularly, IFALD has been commonly found in patients with PN, presenting with a wide spectrum of manifestations, including cholestasis, steatosis/steatohepatitis, and fibrosis. Progression to cirrhosis and development of end-stage liver failure occurs only in a minority of adults in comparison to infants. The disease etiology seems to be multifactorial. The aim of this review is to present the epidemiology of the disease in the adult population and analyze the possible pathogenetic pathways. In addition, a great emphasis has been placed in the management of IFALD, including the prevention and treatment and the presentation of new therapeutic strategies.

LITERATURE SEARCH

A thorough review of the literature up to April 2020 was performed using PubMed to identify articles regarding IFALD in adults.

The search was performed using the search string: ("intestinal failure–associated liver disease" OR "parenteral nutrition associated liver disease") AND ("etiology" OR "causes" OR "diagnosis" OR "prevalence" OR "epidemiology" OR "treatment" OR "prevention" "management" OR "novel therapy"). Only articles in English were reviewed.

DIAGNOSIS

The diagnosis of IFALD mainly requires the exclusion of other causes of liver injury and the temporal association between the administration of PN and elevation of liver function tests. IFALD usually causes mild elevation of liver enzymes, i.e., γ-GT >5 times the upper limit of normal (ULN), ALT >2–3 ULN, and the increase of total bilirubin 2–3 times than the pre-PN levels. The elevation of liver enzymes occurs between the first and third week after the initiation of PN. In addition, alkaline phosphatase is predominantly elevated in the majority of patients with IFALD. Usually, individuals who receive PN, are critically ill or postoperative patients, being at a high risk of ischemic hepatitis, acalculous cholecystitis, reactivation of virus hepatitis, and drug-induced liver injury. Therefore, the aforementioned causes of liver injury should be ruled out. In all cases, abdominal ultrasound should be performed for the exclusion of biliary complications, such as acute cholecystitis or cholelithiasis or thrombosis of hepatic vessels. Exclusion of viral hepatitis is mandatory.

The pattern of liver enzyme elevation plays a critical role in the diagnostic approach. Consequently, ischemic hepatitis, acute viral hepatitis or exacerbation chronic viral hepatitis should be considered, if the aminotransaminases level is greater than 1,000 IU/L. Notably, benign postoperative cholestasis may be confused with IFALD. In benign postoperative cholestasis, conjugated bilirubin progressively increases within the first 2 to 10 days of surgery and cholestasis due to hypoxemia, hypotension, administration of halogenated anesthetic agents, and when resorption of hematomas occur.

The standard diagnostic criteria for IFALD have not been established. Consequently, the prevalence of IFALD depends on the diagnostic criteria used and ranges from 4.3% to 65% [Table 2].

PATHOPHYSIOLOGY

The etiology of IFALD seems to be multifactorial and nutrient deficiencies, nutrient toxicity, intestinal microbiome dysbiosis, altered bile acid metabolism, and catheter-related factors may contribute to its development [Table 3]. In recent years, studies have mainly focused on the gut–lipid–liver axis, demonstrating the molecular alteration of bile acid metabolism, such as the role of fibroblast growth factor-19 (FGF-19), the impact of fecal microbiota, and the role of lipid emulsion.

Nutrient deficiencies

Nutrient deficiencies occur frequently in patients with PN and may contribute to liver injury. Particularly, patients receiving PN are shown to have low levels of carnitine as low as 50% of the normal plasma carnitine level. Carnitine is an essential co-factor of β-oxidation into mitochondria and seems to be involved in the
All patients with end-stage liver disease. Exclusion criteria were a 2.5-fold the upper limit of normal on two of three liver function measures of γ-GT, ALP, and TBIL-that persisted for at least 6 months. Presentation of chronic cholestasis and exclusion of other causes. Chronic cholestasis was defined as a value at least 1.5-fold the upper limit of normal on two of three liver function measures of γ-GT, ALP, and TBIL-that persisted for at least 6 months.

Sasdelli et al. Exclusion criteria: presence of malignant disease, evident causes of liver injury or disease (viral infection, toxic drugs, autoimmune disease, chronic alcohol abuse). 9 diagnostic criteria for IFALD used. IFALD-cholestasis Caviggi criterion: a value >1.5 the upper limit of normal (ULN) on two of γ-GT, ALP, and serum conjugated bilirubin for >6 months. ConBil criterion: conjugated bilirubin >0.3 mg/dL for >6 months TotBil criterion: total bilirubin >1 mg/dL and conjugated bilirubin >0.3 mg/dL for >6 months IFALD-steatosis AAR index: AST/ALT ratio <1 when AST and ALT >ULN Ultrasound criterion: liver ultrasound echogenic appearance of steatosis IFALD-fibrosis APRI index: AST to platelets (PTL) ratio index = [(AST/ULN AST) x 100]/[PTL (10^4/L)] >0.88 FIB-4 index: Fibrosise-4 index=Age (years) x AST/PLT (10^4/L) x ALT^1/2; advanced fibrosis: >2.67: IFALD-unclassified Luman et al. criterion: any deranged LFT >1.5 the ULN after >6 months of HPN starting Beath et al. criterion: ALP and γ-GT >1.5 the ULN and US signs of liver steatosis Chan et al. End-stage liver disease. Exclusion criteria were a diagnosis of acquired immunodeficiency syndrome or the use of home TPN for less than 1 year.

Luman et al. Any biochemical parameter of liver function test that is 1.5 times above the reference range when the test was performed at least 6 months after initiation of PN.

Salvino et al. All patients on home PN for at least 6 months. Patients were excluded if they had active malignancy, underlying liver disease, or exposure to a hepatotoxin. Severe liver dysfunction was defined as having all of the following criteria: total bilirubin 3 mg/dL; albumin <3.2 g/dL; and prothrombin time 3 sec prolonged.

Cazals-Hatem et al. Adults with intestinal failure treated with PN and who underwent liver biopsy. Indications for liver biopsy were the appearance of unexplained chronic liver blood test abnormalities, and/or an assessment before potential intestinal transplantation.

regulation of liver regeneration. The administration of L-carnitine has been associated with suppression of skeletal muscle loss in cirrhotic patients and prevention of non-alcoholic steatohepatitis progression in animal models. In human studies, carnitine supplementation has been associated with the improvement of hepatic steatosis in patients with nonalcoholic fatty liver disease and diabetes. However, intervention studies have not demonstrated the benefit of L-carnitine administration in home PN with abnormal liver tests and low plasma carnitine concentrations, suggesting that carnitine deficiency is not a major cause of IFALD.
Moreover, a recent study has suggested that plasma-free choline levels are closely associated with the grade of liver steatosis and fibrosis in patients receiving long-term PN,\(^\text{[55,56]}\). In addition, taurine administration seems to offer a significant degree of protection against PN-associated cholestasis in neonatal patients.\(^\text{[33]}\) On the other hand, in a phase IV prospective clinical study, the administration of PN with taurine in postsurgical adult patients in the short term (5–7 days) had no effect on the liver function parameters.\(^\text{[57,58]}\)

Decreased plasma taurine levels have been reported in patients receiving long-term PN.\(^\text{[33]}\) Taurine is a sulfur-containing amino acid and plays a role in the metabolism of bile acids, formatting tauro-conjugated bile acids.\(^\text{[34]}\) Taurine supplementation in guinea pigs has been associated with increased bile flow and prevention of cholestasis induced by sulfated glycolithocholate.\(^\text{[35]}\) In addition, taurine administration seems to offer a significant degree of protection against PN-associated cholestasis in neonatal patients.\(^\text{[36]}\) On the other hand, in a phase IV prospective clinical study, the administration of PN with taurine in postsurgical adult patients in the short term (5–7 days) had no effect on the liver function parameters.\(^\text{[37]}\)

Choline is essential for normal hepatic VLDL secretion and the regulation of lipoprotein homeostasis.\(^\text{[38]}\) Low plasma-free choline has been detected in 80% of patients receiving long-term PN and has been associated with abnormalities of hepatic enzymes.\(^\text{[39]}\) Choline deficiency may result in progressive hepatic disease, which ranges from liver steatosis to cirrhosis,\(^\text{[40]}\) while choline-supplemented PN may contribute to the reversal of these abnormalities.\(^\text{[41,42]}\) Moreover, a recent study has suggested that plasma-free choline levels are closely associated with the grade of liver steatosis and fibrosis in patients with nonalcoholic steatohepatitis.\(^\text{[43]}\)

Detection of low serum levels of vitamins C and E have been reported in adult patients with short bowel syndrome receiving PN.\(^\text{[44]}\) Vitamin C and E deficiencies have been associated with the development of liver steatosis,\(^\text{[45,46]}\) while the administration of vitamin E seems to have a beneficial effect on nonalcoholic fatty liver disease.\(^\text{[47]}\) Furthermore, in piglet models, the addition of vitamin E in intravenous lipid emulsion prevented serum and liver increases in biliary and lipidemic markers of IFALD.\(^\text{[48]}\)

**Nutrient toxicity**

**Glucose overload**

Glucose stimulates insulin secretion and is a necessary energy source of the brain, renal medulla, and red blood cells.\(^\text{[49]}\) However, increased dextrose concentrations in PN induce hepatic steatosis due to elevated portal venous insulin–glucagon molar ratio,\(^\text{[50]}\) which could also be associated with the insulin-stimulated lipogenesis of liver.\(^\text{[51]}\) In contrast, in patients with steatosis, the use of cyclic TPN was not associated with prolonged abnormal insulin levels and it did not result in further deterioration of liver function tests.\(^\text{[52]}\) In addition, glucose infusion at rates \(> 5\) mg/kg/min seems to result in hepatic steatosis.\(^\text{[25]}\)

According to the American Society for Parenteral and Enteral Nutrition guidelines, the recommended glucose infusion rate is 4–5 mg/kg body weight/min in adults; however, the infusion rate should be adjusted to each patient in order to achieve normoglycemia.\(^\text{[53]}\)

**Lipids**

Parenteral lipids are necessary for patients with intestinal failure. However, many lipid emulsions used for PN are based on vegetable oils that contain a large amount of phytosterols. Intravenous administration of phytosterols has been associated with the development of liver steatosis in patients receiving long-term PN.\(^\text{[54,55]}\) Phytosterolemia may result in the accumulation of phytosterols in cell membranes and interferes with the function of transport proteins involved in the secretion of bile acids,\(^\text{[56]}\) causing cholestasis.\(^\text{[57]}\) Many studies have demonstrated higher phytosterol levels in patients on PN, although an association between phytosterol intake and development of IFALD has not been found in all studies,\(^\text{[57,58]}\) suggesting that phytosterolemia alone may not cause IFALD and other factors are involved.\(^\text{[59]}\)

**Trace elements overload**

PN contains trace elements, the increased levels of which may lead to liver injury. In detail, aluminum toxicity may rarely occur in adult patients receiving PN with predisposing factors, such as kidney failure,\(^\text{[59,60]}\) and may cause cellular degeneration as well as necrosis of hepatocytes.\(^\text{[61]}\) Increased levels of manganese have also been reported in patients on long-term PN receiving a multitrace element preparation.\(^\text{[62]}\) 90% of manganese is excreted via the biliary system\(^\text{[63]}\) and overload of manganese may induce cholestasis.\(^\text{[64,65]}\)

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**Table 3: Factors involved in the etiology of intestinal failure associated liver disease (IFALD)**

| Nutrient deficiencies                  | Carnitine deficiency | Taurine deficiency | Choline deficiency | Vitamin C deficiency | Vitamin E deficiency |
|----------------------------------------|----------------------|--------------------|--------------------|----------------------|----------------------|
| Nutrient toxicity                      | Glucose overload     | Large amount of phytosterols | Trace elements overload | Gut microbiota-related factors |
|                                        |                      |                    |                    | Small intestine bacterial overgrowth |
|                                        |                      |                    |                    | Increased intestinal barrier permeability |
|                                        |                      |                    |                    | Suppression of Paneth cell bactercidal response |
|                                        |                      |                    |                    | Decreased IgA secretion |
|                                        |                      |                    |                    | Increased translocation of endotoxins and bacteria |
|                                        |                      |                    |                    | Alteration of bile acid metabolism |
|                                        |                      |                    |                    | Loss of gut hormone stimulation |
|                                        |                      |                    |                    | Decrease of FGF 19 levels |
|                                        |                      |                    |                    | Catheter-related factors |
|                                        |                      |                    |                    | Sepsis |

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Gut microbiota-related factors
The gut microbiome plays an essential role in the human homeostasis and alterations of intestinal microbiome may disrupt the gut–liver axis and contribute to liver injury. In adult patients with short bowel syndrome, changes in the intestinal environment due to the overall adoption, which includes hyperphagia, mucosal remodeling of the remaining part of the intestine, and lower intestinal pH results in the alteration of microbiota composition that may result in altered bile acid metabolism and development of cholestasis. Furthermore, many studies have demonstrated small intestine bacterial overgrowth (SIBO) in patients with intestinal failure on home PN. SIBO may increase intestinal permeability, production of endotoxins, and release of proinflammatory cytokines in the liver, causing liver damage. Moreover, many studies have suggested an association between SIBO and nonalcoholic fatty liver disease.

Alterations of bile acid metabolism
The disruption of the enterohepatic circulation of bile salts may contribute to the development of IFALD. FGF-19 is predominantly produced in the terminal ileum, activated by the farnesoid X receptor (FXR), and participates in the metabolism of bile acids. FGF19 induces gallbladder smooth muscle relaxation and gallbladder refilling and decreases the hepatic bile acid synthesis by the repression of cholesterol-7a-hydroxylase, in response to increased levels of bile acids on terminal ileum. In a prospective study, serum FGF19 levels were measured in 52 patients with intestinal failure after 10 months on PN. FGF19 concentrations were lower compared to healthy matched controls. FGF19 levels were further decreased in patients without remaining ileum and were positively associated with the remaining ileum length. Furthermore, FGF19 correlated with portal inflammation and fibrosis, suggesting that FGF19 may contribute to the pathogenesis of IFALD.

In addition, enteral feeding promotes the secretion of several gastrointestinal hormones, such as gastrin, cholecystokinin, peptide YY, and secretin, which stimulate the bile flow and the contraction of gallbladder. Consequently, the lack of enteral intake may cause a reduction of bile flow.

Catheter-related factors
Sepsis seems to be a significant risk factor in the development of IFALD. A prospective study found that each septic episode increases the risk of IFALD development by 3.2-fold. Placement and handling of the central venous catheter are major sources of bacteremia and catheter-related complications have been associated with sepsis development.

MANAGEMENT
The management of IFALD is challenging, requiring early therapeutic interventions and elimination of predisposing risk factors [Figure 1], while a close collaboration between internists, hepatologists, dietitians, surgeons, and transplant centers is necessary.

Duration of nutrition
Cycle PN infusion (<24 hours, usually 8–12 hours) should be considered in patients with intestinal failure, especially

Figure 1: Algorithm of intestinal failure-associated liver disease management

- Rule out other causes of liver injury
  - Exclusion viral hepatitis (HBsAg, anti-HBc, anti-HCV, IgM-HAV), autoimmune hepatitis (ANA, AMSA, anti-LK, and IgG), metabolic liver disease (ferritin, transferrin saturation, serum ceruloplasmin, etc), ischemic hepatitis (transaminases greater than 1,000, history of hypotension, high LDH), drug induced liver disease (review of medications, temporal association)
  - Exclusion of biliary complications: abdomen imaging (US, CT, MRCP)
  - Exclusion thrombosis of hepatic vessels (Budd-Chiari, portal vein thrombosis): triplex US
  - Exclusion of sepsis or other infections: clinical examination, blood and urine culture, imaging

Management
- Cycle PN infusion (<24 hours, usually 8-12 hours)
- Soybean-based intravenous lipid emulsions (ILE) should not exceed 1gm/ kg body weight
- Glucose infusion rate: < 5 mg/kg body weight/min
- Reduction of omega-6 to omega-3 PUFA ratio
- Optimization of enteral stimulation: Fistuloclysis, intestinal lengthening via serial transverse enteroplasty or Bianchi procedure, and restoration of bowel continuity
- Prevention of catheter-related blood stream infections: cutaneous antisepsis with chlorhexidine upon the insertion of catheter, use of antimicrobial catheter locks and antimicrobial catheter coatings, bundle approach, maximal sterile barrier precautions, and frequent disinfection of hubs and needleless connectors

No improvement and severe IFALD with end-stage liver disease and/or portal hypertension
Refer to transplantation center for intestinal transplantation
in patients requiring long-term PN, because it has been associated with a lower risk of liver injury, compared to continuous PN infusion.\textsuperscript{[87]} Also, patients with elevated liver function tests receiving continuous PN infusion may experience stabilization or improvement with a switch to cyclic PN infusion.\textsuperscript{[89]}

**Composition of nutrition**

Appropriate regulation of components and PN dosage plays a critical role in the prevention and management of IFALD. According to ESPEN recommendations, the daily administration of soybean-based intravenous lipid emulsions (ILE) should not exceed 1 gm/kg body weight, because excessive administration may lead to hepatic steatosis and inflammation and has been associated with IFALD development.\textsuperscript{[89,90]} In recent years, there are many available formulations of ILE, such as soybean oil-based ILE, fish oil-based ILE and several mixtures of soybean oil, coconut oil medium-chain triglycerides (MCT), and fish oil ILE.\textsuperscript{[91]} Many studies have suggested that olive oil-based ILE presents better liver tolerability compared to soybean oil-based ILE, causing less frequent cholestasis and elevated hepatic enzymes.\textsuperscript{[92,93]} Both fish oil- and olive oil-based ILE contain a large amount of omega-3 polyunsaturated fatty acids (PUFA), reducing omega-6 to omega-3 PUFA ratio.\textsuperscript{[94]} Animal models have demonstrated that omega-6 PUFA may increase hepatic steatosis and inflammation compared to omega-3 PUFA.\textsuperscript{[95]} Furthermore, a recent meta-analysis of randomized control trials suggests that omega-3 PUFA supplementation in patients with NAFLD may decrease hepatic steatosis and liver enzyme parameters.\textsuperscript{[96]} In addition, several case reports and case series have documented that the use of omega-3 PUFA supplemented ILE or fish oil-based emulsion may reverse liver damage, improving liver function tests in patients with IFALD.\textsuperscript{[97-99]} However, further studies are required. Based on this data, ESPEN recommends the reduction of omega-6 to omega-3 PUFA ratio wherever possible.\textsuperscript{[100]}

**Optimization of enteral stimulation**

The improvement of enteral stimulation contributes to the reduction of PN calories and may ameliorate hepatic function in IFALD patients, as a result of the prevention of mucosal atrophy and of gut microbiota imbalance and improvement of gastrointestinal immunity.\textsuperscript{[100]} Fistuloclysis in patients with high-output upper enteric fistula has been associated with the improvement of liver function tests.\textsuperscript{[101]} In addition, intestinal lengthening via serial transverse enteroplasty or Bianchi procedure (longitudinal intestinal lengthening and tailoring) in adult patients with short small bowel seems to be an effective measure to increase intestinal capacity and weaning from PN\textsuperscript{[102]} and may improve or prevent IFALD.\textsuperscript{[103]} Furthermore, restoration of bowel continuity may reduce the risk of cholestasis. In a retrospective study of patients with a short bowel syndrome owing to mesenteric infarction, restoration of bowel continuity has been associated with the resolution of chronic cholestasis, probably because of the association with the discontinuation or reduction of PN.\textsuperscript{[104]} Segmental reversals of the small bowel is another surgical procedure for the improvement of intestinal absorption and reduction of PN in adult patients with short bowel syndrome.\textsuperscript{[105]} However, there are no data regarding the impact of this procedure on IFALD.

**Sepsis**

The prevention of catheter-related bloodstream infections (CRBSI) may include cutaneous antisepsis with chlorhexidine upon the insertion of catheter, use of antimicrobial catheter locks and antimicrobial catheter coatings, bundle approach, maximal sterile barrier precautions, and frequent disinfection of hubs and needleless connectors.\textsuperscript{[106]} In addition, early diagnosis and treatment of these infections are essential to avoid severe complications. When a CRBSI is suspected, a catheter culture must be obtained and empirical antibiotic treatment should be started after appropriate cultures.\textsuperscript{[107]}

**Transplantation**

Intestinal transplantation should be recommended as a life-saving procedure in patients with IFALD-induced life-threatening complications.\textsuperscript{[108]} In adults with IFALD, intestinal transplantation may be classified into two types: a) isolated intestine transplant and b) combined liver and intestine transplant depending on the progress of IFALD.\textsuperscript{[109]} Isolated intestinal transplantation is recommended in IFALD patients with a mild or moderate liver disease without signs of portal hypertension and absence of cirrhosis (platelets count >150,000/μl, minimal hepatosplenomegaly, total plasma bilirubin <6 mg/dl, stage 1–2 fibrosis on biopsy).\textsuperscript{[110]} In this subgroup of patients, main indications for intestinal transplantation include frequent episodes of severe dehydration, despite intravenous fluid supplement in addition to PN, frequent central line sepsis, thrombosis of two major central venous channels and high risk of death attributable to the underlying disease.\textsuperscript{[111]}

Combined liver and intestinal transplantation should be considered in patients with severe IFALD and portal hypertension development and/or end-stage liver disease.\textsuperscript{[110]} The liver and small intestine are implanted en
bloc in order to avoid hilar dissection and decrease the risk of vascular and biliary complications.\textsuperscript{[112]}

**NOVEL THERAPEUTIC STRATEGIES AND PERSPECTIVES**

Several medications have been suggested to improve or prevent the progression of IFALD. Glucagon-like peptide-2 (GLP-2) is released by the L cell of the distal ileum and colon, resulting in the reduction of proximal intestine motility whereas it increases the mucosal surface area.\textsuperscript{[113]} Several studies have reported the positive effect of GLP-2 analogues on the requirements of PN in patients with intestinal failure due to small bowel syndrome. However, their role on the management of IFALD remains largely unclear.\textsuperscript{[114]} Many studies in animal models have suggested that the administration of GLP-2 may improve cholestasis and liver injury in IFALD.\textsuperscript{[115,116]} A randomized phase 2 trial demonstrated that in patients with short bowel syndrome, glepaglutide administration, a novel long-acting GLP-2 analogue, may improve hepatic excretory function at the cost of enhanced liver macrophage activation and increased liver stiffness, which subsequently may result in unwanted liver damage. Thus, the benefit of GLP-2 in IFALD requires further investigation.\textsuperscript{[114,117]}

Ursodeoxycholic acid (UDCA) has been suggested as an effective treatment of IFALD. Studies on pediatric patients and infants with IFALD have demonstrated that the use of UDCA (10–30 mg/kg/d) may induce the full or partial remission of IFALD cholestasis and shorter duration of cholestasis.\textsuperscript{[118,119]} In adults, a small, nonrandomized study found that a one- or two-month course of UDCA (11 mg/kg/d) may induce the improvement of liver function tests.\textsuperscript{[118]} However, further studies are needed.

Various studies have suggested that the use of probiotics may play a protective role against alcoholic hepatitis\textsuperscript{[121]} and nonalcoholic fatty liver disease,\textsuperscript{[122]} improving intestinal barrier function and preventing bacterial translocation.\textsuperscript{[123]} A recent study investigated the use of probiotics to prevent SIBO in patients with intestinal failure and demonstrated a higher prevalence of IFALD in patients who did not use probiotics (54.4% vs 39.1%). Nevertheless, the multivariable analysis did not confirm a statistically significant difference (OR: 0.303–1.146, 95%CI: 0.303–1.146).\textsuperscript{[124]} It is also worth noting that there are few data on the use of empirical antibiotic therapy to treat suspected SIBO or bacterial translocation and to improve IFALD. Specifically, a retrospective analysis demonstrated that the use of metronidazole during TPN was associated with a lower elevation of liver enzymes,\textsuperscript{[125]} while another study documented that metronidazole use may reduce or stabilize cholestatic enzymes in adult patients receiving PN.\textsuperscript{[126]} Nevertheless, the prophylactic use of antibiotics to prevent IFALD is not recommended due to the risk of the side effects of antibiotics, the possible bacterial resistance development, and the limited data on long-term outcomes.\textsuperscript{[127]}

Activation of bile acid receptors, such as FXR, leads to reduced hepatic bile salt load and has been associated with antiinflammatory effects. Because of these beneficial effects, bile acid signaling is an interesting therapeutic target for hepatic disease treatment.\textsuperscript{[127]} In rat models of IFALD, the administration of FXR agonists (GW4064, INT-747) alleviated liver injury by regulating the bile acid metabolism.\textsuperscript{[128,129]}

**CONCLUSION**

IFALD remains a major complication in adult patients requiring long-term PN, causing a wide range of manifestations. The pathophysiology of IFALD seems to be multifactorial, including nutrient-related factors and alteration of the gut–liver axis. The management requires a multidisciplinary approach, including alteration of PN preparations and surgical management to reduce or revert the progression of liver injury. Future research is essential to clarify the pathogenetic mechanisms of IFALD and the development of new therapeutic agents and procedures.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Pironi L, Arends J, Baxter J, Bozzi F, Pelaez RB, Cuerra C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015;34:171-80.
2. Pironi L, Arends J, Bozzi F, Cuerra C, Gillanders I, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247-307.
3. Lappas BM, Patel D, Kumpf V, Adams DW, Seidner DL. Parenteral nutrition: Indications, access, and complications. Gastroenterol Clin North Am 2018;47:39-59.
4. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on Parenteral nutrition: Intensive care. Clin Nutr 2009;28:387-400.
5. Gosmanov AR, Umpeirez GE. Management of hyperglycemia during enteral and parenteral nutrition therapy. Curr Diab Rep 2013;13:155-62.
6. Moureaux N, Poole S, Murdock MA, Gray SM, Semha CP. Central venous catheters in home infusion care: Outcomes analysis in 50,470 patients. J Vasc Interv Radiol 2002;13:1009-16.
7. Dreessen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pauw L, et al. Epidemiology of catheter-related infections in adult patients.
receiving home parenteral nutrition: A systematic review. Clin Nutr 2013;32:16-26.
8. Pironi L, Labate AM, Perkowiec M, Pezzellacci J, Tjellesen L, Staun M, et al. Prevalence of bone disease in patients on home parenteral nutrition. Clin Nutr 2002;21:279-90.
9. Messing B, Bories C, Kunstlinger F, Bernier JJ. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology 1983;84:1012-9.
10. Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. Nutr Clin Pract 2006;21:1-7.
11. Laacre F, Gupte G, Colomb V, D’Antiga I, Hartman C, Hojsak I, et al. Intestinal failure-associated liver disease: A position paper of the ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation. J Pediatr Gastroenterol Nutr 2015;60:272-83.
12. Lal S, Pironi L, Wanten G, Arends J, Bozzetti F, Guedea C, et al. Clinical approach to the management of Intestinal Failure Associated Liver Disease (IFALD) in adults: A position paper from the Home Artificial Nutrition and Chronic Intestinal Failure Special Interest Group of ESPEN. Clin Nutr 2018;37:1794-7.
13. Kelly DA. Intestinal failure-associated liver disease: What do we know today? Gastroenterology 2006;130 (2 Suppl 1):S70.
14. Grant JP, Cox CE, Kleinman LM, Mahar MM, Pittman MA, Tangrea JA, et al. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. Surg Gynecol Obstet 1977;145:573-80.
15. Mitra A, Ahn J. Liver disease in patients on total parenteral nutrition. Clin Liver Dis 2017;21:687-95.
16. Faust TW, Reddy KR. Postoperative jaundice. Clin Liver Dis 2004;8:151-66.
17. Cavichioli M, Beau P, Crenn P, Degoet C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med 2000;132:525-32.
18. Lloyd DA, Zabron AA, Gabe SM. Chronic biochemical cholestasis in patients receiving home parenteral nutrition: Prevalence and predisposing factors. Aliment Pharmacol Ther 2008;27:552-60.
19. Chan S, McCowen CK, Bistrian BR, Thibault A, Bistrian BR, McCowen CK, et al. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. Surg Gynecol Obstet 1977;145:573-80.
20. Gastre RA, Balsi JA, da Pautra C, Botella J, Zamaron I, Elias E, et al. Phase IV prospective clinical study to evaluate the effect of taurine on liver function in postsurgical adult patients requiring parenteral nutrition. Nutr Clin Pract 2014;29:672-80.
21. Vancs DE. Role of phosphatidylcholine biosynthesis in the regulation of lipoprotein homeostasis. Curr Opin Lipidol 2008;19:229-34.
22. Buchman AL, Moukarzel A, Jenden DJ, Roch M, Rice K, Ament ME. Low plasma free choline is prevalent in patients receiving long term parenteral nutrition and is associated with hepatic aminotransferase abnormalities. Clin Nutr 1993;12:337-7.
23. Corbin KD, Zeisel SH. Choline metabolism provides new insights into nonalcoholic fatty liver disease and its progression. Curr Opin Gastroenterol 2012;28:159-65.
24. Buchman AL, Ament ME, Sohel M, Dubin M, Jenden DJ, Roch M, et al. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: Proof of a human choline requirement: A placebo-controlled trial. J Parenter Enteral Nutr 2001;25:260-8.
25. Buchman AL, Dubin M, Jenden DJ, Moukarzel A, Roch MH, Rice K, et al. Lecithin increases plasma free choline and decreases hepatic steatosis in long-term parenteral nutrition patients. Gastroenterology. 1992;102:1363-70.
26. Imajo K, Fujita K, Yoneda M, Shinhara Y, Suzuki K, Mawatari H, et al. Plasma free choline is a novel non-invasive biomarker for early-stage non-alcoholic steatohepatitis: A multi-center validation study. Hepatol Res 2012;42:757-66.
27. Braga CB, Vannucchi H, Freire CM, Marchini JS, Jordao AA Jr, da Cunha SF. Serum vitamins in adult patients with short bowel syndrome receiving intermittent parenteral nutrition. J Parenter Enteral Nutr 2011;35:493-8.
28. Trota E, Bortolotti S, Fugazzotto G, Geller C, Montagnese S, Amodio P. Familial vitamin E deficiency: Multiorgan complications support the adverse role of oxidative stress. Nutrition 2019;63-64:57-60.
29. Ilsen DH, Tveden-Nyborg P, Lylkesfeldt J. Does vitamin C deficiency promote fatty liver disease development? Nutrients 2014;6:5473-99.
30. Sato K, Gojo M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, et al. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials. Nutrition 2015;31:923-30.
31. Ng K, Stoll B, Chacko S, Saenz de Pipo AM, Lauridsen C, Gray M, et al. Vitamin E in new-generation lipid emulsions protects against parenteral nutrition–associated liver disease in parenteral nutrition–fed preterm pigs. JPEN J Parenter Enteral Nutr 2015;40:656-71.
49. Mundi MS, Nystrom EM, Hudley DL, McMahon MM. Management of parenteral nutrition in hospitalized adult patients. [Formula: See text]. JPEN J Parenter Enteral Nutr 2017;41:535-49.
50. Li S, Nussbaum MS, Teague D, Gapaen CL, Dayal R, Fischer JE. Increasing dextrose concentrations in total parenteral nutrition (TPN) causes alterations in hepatic morphology and plasma levels of insulin and glucose in rats. J Surg Res 1988;44:639-48.
51. Rui L. Energy metabolism in the liver. Compr Physiol 2014;4:177-97.
52. Hwang TL, Lee MC, Chen LL. Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function. Hepatogastroenterology 2000;47:1347-50.
53. Raphael B, Duggan C. Prevention and treatment of intestinal failure-associated liver disease in children. Semin Liver Dis 2013;32:341-7.
54. Nandivada P, Carlson SJ, Chang MI, Cowan E, Gura KM, Puder M. Treatment of parenteral nutrition-associated liver disease: The role of lipid emulsions. Adv Nutr 2013;4:711-7.
55. Zaloga GP. Phytosterols, lipid administration, and liver disease during parenteral nutrition. JPEN J Parenter Enteral Nutr 2015;39 (1_suppl):395-608.
56. Clayton PT, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. Nutrition 1998;14:158-64.
57. Llop JM, Virgili N, Moreno-Villares JM, Garcia-Peris P, Serrano T, Forga M, et al. Phytosterolemia in parenteral nutrition patients: Implications for liver disease development. Nutrition 2008;24:1145-52.
58. Elleogard L, Sunesson A, Boscau J. High serum phytosterol levels in short bowel patients on parenteral nutrition support. Clin Nutr 2005;24:415-20.
59. Hernandez-Sanchez A, Tejada-Gonzalez P, Artetta-Jimenez M. Aluminium in parenteral nutrition: A systematic review. Eur J Clin Nutr 2013;67:230-8.
60. Gura KM. Aluminum contamination in products used in parenteral nutrition: Has anything changed? Nutrition 2010;26:585-94.
61. El-Sayed WM, Al-Kahtani MA, Abdel-Moneim AM. Prophylactic and therapeutic effects of tauroine against aluminum-induced acute hepatotoxicity in mice. J Hazard Mater 2011;192:880-6.
62. Abdalian R, Saqui O, Fernandes G, Allard JP. Effects of manganese from a commercial multi-trace element supplement in a population sample of Canadian patients on long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 2013;37:538-43.
63. Hardy G. Manganese in parenteral nutrition: Who, when, and why should we supplement? Gastroenterology 2009;137 (5 Suppl):S29-35.
64. Witzleben CL, Physiologic and morphologic natural history of a model of intrahepatic cholestasis (manganese-bilirubin overload). Am J Pathol 1972;66:577-88.
65. Arotte P, Pia GL. Hepatic subcellular distribution of manganese in manganese and manganese-bilirubin induced cholestasis. Biochim Pharmacol 1985;34:3857-65.
66. Cahova M, Brazova M, Wohl P. Parenteral nutrition-associated liver disease: The role of the gut microflora. Nutrients 2017;9:987.
67. Mayeur C, Gillard L, Le Beyec J, Bado A, Joly F, Thomas M. Extensive intestinal resection triggers behavioral adaptation, intestinal remodeling and microbiota transition in short bowel syndrome. Microorganisms 2016;4:16.
68. Joly F, Mayeur C, Bruneau A, Noordine M, Melyheuc T, Langella P, et al. Drastic changes in fecal and mucosa-associated microflora in adult patients with short bowel syndrome. Biochimie 2010;92:753-61.
69. Huang Y, Guo F, Li Y, Wang J, Li J. Fecal microbiota signatures of adult patients with different types of short bowel syndrome. J Gastroenterol Hepatol 2017;32:1949-57.
70. Pereira-Fantini PM, Laphthorne S, Joyce SA, Dellios NL, Wilson G, Fouhy F, et al. Altered FXR signalling is associated with bile acid dysmetabolism in short bowel syndrome-associated liver disease. J Hepatol 2014;61:1115-25.
71. Kaufman SS, Losche CA, Lupo JV, Young RJ, Murray ND, Pinch LW, et al. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with short bowel syndrome. J Pediatr 1997;131:356-61.
72. McGrath KH, Pitt J, Bines JE. Small intestinal bacterial overgrowth in children with intestinal failure on home parenteral nutrition. JGH Open 2019;3:394-9.
73. Ferolla SM, Armiliato GN, Couto CA, Ferrari TC. The role of intestinal bacteria overgrowth in obesity-related nonalcoholic fatty liver disease. Nutrients 2014;6:5583-99.
74. Wijanjeepreeka K, Lou S, Watthanasuntorn K, Kroner PT, Cheungpasitporn W, Lukens FJ, et al. Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease: A systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2020;32:601-8.
75. Fialho A, Fialho A, Thota P, McCullough AJ, Shen B. Small intestinal bacterial overgrowth is associated with non-alcoholic fatty liver disease. J Gastrointestin Liver Dis 2016;25:139-65.
76. Omata J, Pierre JF, Heneghan AF, Tsao FH, Sano Y, Jonker MA, et al. Parenteral nutrition suppresses the bactericidal response of the small intestine. Surgery 2013;153:17-24.
77. Heneghan AF, Pierre JF, Kudsk KA. IL-25 Improves IgA levels during parenteral nutrition through the JAK-STAT pathway. Ann Surg 2013;258:1065-71.
78. Alveryt JC, Aoyis E, Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. Surgery 1988;104:185-90.
79. Demehri FR, Barrett M, Ralls MW, Miyasaka EA, Feng Y, Teitelbaum DH. Intestinal epithelial cell apoptosis and loss of barrier function in the setting of altered microbiota with enteral nutrient deprivation. Front Cell Infect Microbiol 2013;3:105.
80. van Erpecum KJ, Schaap FG. Intestinal failure to produce FGF19: A culprit in intestinal failure-associated liver disease? J Hepatol 2015;62:1231-3.
81. Landseten T, Galman C, Angelin B, Rudling M. Circulating intestinal fibroblast growth factor 19 has a pronounced diurnal variation and modulates hepatic bile acid synthesis in man. J Intern Med 2006;260:530-6.
82. Ciccone C, Degirolamo C, Moschetta A. Emerging role of fibroblast growth factors 15/19 and 21 as metabolic integrators in the liver. Hepatology 2012;56:2404-11.
83. Mutanen A, Lohi J, Heikila P, Jalanko H, Pakarinen MP. Loss of ileum decreases serum fibroblast growth factor 19 in relation to liver inflammation and fibrosis in pediatric onset intestinal failure. J Hepatol 2015;62:1391-7.
84. Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. Hepatobiliary Pancreat Dis Int 2012;11:586-93.
85. Diamond IR, de Silva NT, Tomlinson GA, Pencharz PB, Moore AM, et al. The role of parenteral lipids in the development of advanced intestinal failure-associated liver disease in infants: A multiple-variable analysis. JPEN J Parenter Enteral Nutr 2011;35:596-602.
86. Guglielmi FW, Regano N, Mazzuoli S, Rizzi M, Fregnan S, Leogranda G, et al. Catheter-related complications in long-term home parenteral nutrition patients with chronic intestinal failure. J Vasc Access 2012;13:490-7.
87. Jensen AR, Goldin AB, Koopmeiners JS, Stevens J, Waldhausen JH, Kim SS. The association of cyclic parenteral nutrition and decreased incidence of cholestatic liver disease in patients with gastrochisis. J Pediatr Surg 2009;44:183-9.
88. Stout SM, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. Nutr Clin Pract 2010;25:277-81.
89. Klek S, Chambrier C, Singer P, Rubin M, Bowling T, Staun M, et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid)–a double-blind, randomised, multicentre study in adults. Clin Nutr 2013;32:224-31.
90. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247-307.
