ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 05 | May - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

FROM BOWELS TO BILIRUBIN UNRAVELING THE MECHANISM OF INTESTINAL FAILURE ASSOCIATED LIVER DISEASE: A NARRATIVE REVIEW

Internal Medicine

Dr. Yugam Rajeshkumar Oza* Intern Doctor, M.P Shah Medical College, Jamnagar, Gujarat, India *Corresponding Author

Dr Helly Mayankkumar Joshi Intern Doctor, GMERS Himmatnagar, Gujarat, India

Sameeha Fatima Khan 4th Year Medicalstudent, Gandhi Medical College, Telangana

Amna Shahid Bilal 4th Year Medical Student, Akhtar Saeed Medical And Dental College, Lahore

Ali Zeeshan Murtaza 4th Year Medical Student, Akhtar Saeed Medical And Dental College, Lahore

Dr Vidhi Mashru Junior Resident, General Medicine, GMERS, Valsad

ABSTRACT

Intestinal failure associated with liver disease (IFALD) is an intricate illness having the prevalence of 40-60% in paediatric population and 15-40% in adults [1]. The diseases corresponding with liver include cholestasis, gall bladder disease, steatohepatitis, and biliary cirrhosis [1]. Since IFALD has a complicated etiology there are many factors causing it but parenteral administration (PN) remains the key reason. Each patient of a different age group presents with varying symptoms and signs, so the treatment strategy is tailored accordingly. This review encompasses the risk factors causing IFALD along with the intricate pathogenesis, the changes that can be bought in our diet to prevent it from occurring and last most importantly the management techniques along with the line of treatment.

KEYWORDS

Intestinal Failure Associated With Liver Disease, Parenteral Nutrition, Liver Failure, Malabsorption.

INTRODUCTION

Intestinal failure associated with liver disease (IFALD) is a life-threatening complication having a multiplex aetiology. The prevalence of IFALD is seen up to 40-60% in paediatric population, 85% in neonates and 15-40% in adults [1] Intestinal failure (IF), also known as the short bowel syndrome, is a condition in which the small intestine is unable to absorb the nutrients required for growth and survival resulting in being subjected to parenteral administration (PN). Type I and II of IF are acute conditions lasting for weeks to months such as after abdominal surgery and type III is a chronic condition that can last for years with increased risk of mortality. PN is thus being used religiously in both the acute and chronic conditions of IF.

Parenteral administration, although is a lifesaving therapy, has a composite mechanism associated with intestinal failure. Proper administration of parenteral nutrition can save the patient from the metabolic complexities however improper administration can result in innumerable complications including thromboembolism, infectious (central line associated blood stream infections) and metabolic (abnormal liver function tests, cholelithiasis)[1].

Resulting from the comprehensive analysis of the etiopathogenesis of IFALD, it has therefore replaced the postulation of parenteral nutrition associated liver disease (PNALD) and parenteral nutrition associated cholestasis (PNAC) [1]

ETIOLOGY

The following table presents an outline of the risk factors of IFALD [1], [2]

Table 1. Etiology of IAFLD

Parenteral Nutrition related factors	Gut related factors	Systemic factors
Soyabean oil based Intravenous lipid emulsion (ILE) >1g/kg/day	Lack of enteral feeding	Central line associated bloodstream infection (CLABSI)
Phytosterols	Alteration of gut microbiome	Sepsis
Glucose overload >7mg/kg/min	Anatomical factors	Prematurity
Deficiency of choline	Short bowel syndrome	Low birth weight
Carnitine deficiency	Small intestinal bacterial overgrowth	Hepatotoxic agents like alcohol, drugs, viral hepatitis and autoimmune diseases
N– acetylcysteine/ antioxidant deficiency		Genetic predisposition

PATHOGENESIS

The pathogenesis of IFALD is broad and intricate. As discussed, all contributing factors can be grouped into three facets:
Gut related factors
Parenteral nutrition-related factors
Systemic factors

Before diving into the various pathways causing IFALD, it is essential to understand the gut-liver cross talk. The gut and liver are intricately synced via Farnesoid X receptor (FXR) and Fibroblast growth factor 19 (FGF 19) signaling. FXR is the master regulator of bile acid synthesis and secretion through FGF-19. FXR is a nuclear receptor, mainly found in the intestine and liver.

In healthy individuals, bile acids stimulate intestinal FXR (Farnesoid X receptor) . This leads to release of FGF19 (fibroblast growth factor) into portal circulation. FGF19 binds fibroblast growth factor receptor 4 (FGFR-4) on hepatocytes and downregulates bile acid synthesis in the liver by suppressing CYP7A1 gene which codes for cholesterol-7α hydroxylase, the rate limiting enzyme of bile acid synthesis [3]. On the other hand, hepatic FXR prevents the synthesis of steroids for bile by inhibiting CYP8B1[1].

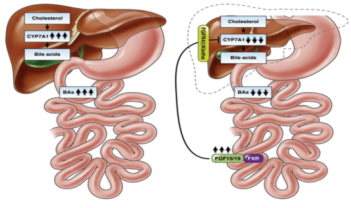

Figure1: Pathogenesis of IAFLD[4]

Gut Related Factors
Gastrointestinal conditions like short bowel syndrome (SBS), small intestinal bacterial overgrowth (SIBO), ileal resection, and lack of enteral feeding act via common and overlapping pathways to result in IFALD.

Lack Of Enteral Feeding
Enteral feeding stimulates release of bile acids in the duodenum. Bile acids bind to TGR5 (Takeda G protein coupled receptor) thereby driving the release of glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). GLP-2 plays a pivotal role in sustaining gut growth and integrity[5] The prolonged absence of nutrients and bile acids in gut leads to decreased secretion of GLP-2. This leads to intestinal mucosal atrophy and increased intestinal permeability. This enhances bacterial lipopolysaccharide translocation and Kupffer cell activation through TLR4 signaling, producing pro inflammatory molecules like interleukin-6 and tumor necrosis factor alpha that in turn decreases FXR activity leading to cholestasis via down regulation of bile acid transporters and fibrosis by stellate cell activation[2].

Retrospective reviews conducted by Javid et al have shown that aggressive weaning from parenteral nutrition to enteral feeding can reverse PN associated liver dysfunction[6].

Gut Microbiome
The gut microbiome consists of 100 trillion commensal organisms belonging to 1000s of species. In healthy individuals the gut microbiome is relatively stable. Firmicutes and Bacteroidetes phyla are the dominant microbes and, followed by species from Verrucomicrobia, Proteobacteria, and Actinobacteria [2].

Patients with SBS, SIBO and inflammation demonstrate disturbances in the gut microbiome[1].Animal studies have found an increase in Bacteroidetes phylum in animals receiving PN[7]. These bacteria have a pro inflammatory effect on intestinal mucosa leading to increased intestinal permeability and enhanced translocation of bacterial LPS. LPS then activates the Kupffer cells through TLR-4 which stimulates nuclear factor κβ causing suppression of genes encoding FXR [8]

Anatomical Factors
Luman and Shaffer in their retrospective report on 107 adult patients receiving parenteral nutrition, had noted that a length of small bowel of less than 100 cm was the only significant variable for deranged liver function tests[9].

In patients with Ileal resection, bile acids cannot bind to absent ileal FXR, thus the serum concentration of FGF19 is reduced, resulting in up regulation of bile acid synthesis. A study revealed that patients with fibrosis demonstrated FGF19 levels 2-3 times lower compared to healthy controls and those without fibrosis[10].

Low FGF-19 mediated increase in bile acid synthesis when, combined with bacterial Lipopolysaccharide induced activation of Kupffer cells leading to down regulation of bile acid excretion from the liver, results in cholestasis.

Parenteral Nutrition Related Factors
Parenteral nutrition (PN) is a lifesaving resort for patients that cannot tolerate enteral feedings for any reason. While it is indispensable for them, it has been incriminated in causing IFALD. Particular components of Intravenous lipid emulsions (ILE), glucose overload and deficiency of certain nutrients play key roles in pathogenesis of IFALD.

ω-6 VS ω-3 POLYUNSATURATED FATTY ACIDS
Soybean oil-based ILE (SOLE) contains ω-6 polyunsaturated fatty acids, like linoleic acid which is a precursor of arachidonic acid that forms **proinflammatory** mediators like prostaglandins and leukotrienes through the cyclooxygenase and lipoxygenase pathways, leading to liver injury. On the other hand, fish oil-based ILE is rich in ω-3 polyunsaturated fatty acids, like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are not only **anti-inflammatory** but also crucial for the development of the brain, bones, and liver in neonates [1]. In one study it was found that in infants and children with IFALD, cholestasis caused by SOLE was reversed by substituting it with FOLE [11].

Another study showed that, the quantity of lipid rather than the specific type influenced cholestasis. Doses as low as 1g/kg/day of FOLE and SOLE similarly normalised serum direct bilirubin[12].

Phytosterols
SOLE being plant-derived has an abundance of phytosterols, specifically stigmasterol. In vitro studies demonstrated that stigmasterol can activate macrophages. Hepatic macrophage-derived interleukin-1 β caused down regulation of mice canalicular sterol transporter ABCG5/G8, which secretes phytosterols. This led to the accumulation of phytosterols in hepatocytes giving rise to hepatic steatosis.

Moreover, stigmasterol is an antagonist at hepatic Farnesoid X Receptor (FXR) and reduces the expression of genes for bile acid transporters like MDR3, MRP2, and BSEP ultimately leading to cholestasis[8].

Glucose Overload
Parenteral nutrition containing excessive glucose leads to increased insulin secretion. Insulin increases lipogenesis and acylglycerol synthesis while decreasing fatty acid oxidation. All this culminates in accumulation of triacyl glycerides in hepatocytes, thus inducing steatosis[13].

Research has shown that cyclic PN with an interval of more than 8h/day without parenteral glucose has improved insulin levels as well as liver function tests[14].

Deficiency Of Choline, Carnitine And N-acetylcysteine
Carnitine plays a key role in maintaining liver function as carnitine transport system serves to transfer long chain fatty acids from the cytosol to mitochondria for β-oxidation of fatty acids. Current PN is not supplemented with carnitine. Studies have shown that supplementation with carnitine helps reduce steatosis and improve liver function tests in patients with NAFLD[15].

N-acetylcysteine is a precursor of the antioxidant glutathione. Reduced N-acetylcysteine and thereby glutathione, predisposes the hepatocytes to increased oxidative stress and liver injury[1].

Choline isn't a component of PN. Choline deficiency is proven to cause IFALD. In a placebo-controlled trial comparing outcomes of patients receiving PN to those who received PN with choline supplementation, hepatic steatosis, elevated AST and ALT was found in the group that did not receive choline supplementation[16].

Systemic Factors
Prematurity And Low Birth Weight
A study on infants receiving PN reported inverse relationship between birthweight and IFALD. Of 62 preterm infants receiving parenteral nutrition, 50% of infants under 1 kg developed IFALD[17]. This can be attributed to hepatic and gut immaturity. One study showed that neonates have a decreased reservoir of bile acids and made a higher proportion of dysfunctional bile acids[18]. Moreover, neonates also have decreased expression of bile salt transporters like sodium taurocholate cotransporting polypeptide (NTCP) and bile salt export pump (BSEP), making them susceptible to IFALD[19] .

SEPSIS
Insertion of a catheter is a prerequisite to administering PN. This itself puts the patient at risk of acquiring Central line-associated bloodstream infections (CLABSI) and thereby bacteraemia and sepsis. Bacterial translocation through the atrophied gut lining can also give rise to sepsis.

Sepsis is a key risk factor of IFALD. A study conducted on 152 infants that received PN showed 3.2 times increased risk of IFALD in infants with septic episodes [20].

Research has demonstrated that infections and sepsis can downregulate FXR activity, which is a negative regulator of bile acid synthesis. This leads to increased bile acid production contributing to cholestasis in IFALD[21].

MANAGEMENT
Management of Intestinal Failure-Associated Liver Disease (IFALD) is quite challenging and therapeutic approach depends upon the severity of the disease. The early therapeutic intervention involves

medical management which primarily focuses on reversing IFALD and ameliorating the intestinal absorption to enhance PN weaning. The later phase is an ultimate treatment that involve surgical intervention, which, depending on the severity, requires liver and/or intestinal transplantation[22].

1-Medical interventions:

❖ Cyclic parenteral nutrition (PN) weaning is preferably considered in patients with IF instead of continuous PN (>24h, often 8-12hours). PN in early phase has shown promising results in patients with IF as it lowers the chances of severe IFALD and subsequent risk of cholestasis[23]. Clinical trials have shown that this regimen leads to less risks of parenteral nutrition associated cholestasis (PNAC), hepatic cirrhosis and hyperbilirubinemia and deranged liver enzymes.

❖ Composition and regulation of enteral feeding holds a vital position in the management and prevention of IFALD. Recommend daily dose of soybean oil-based intravenous lipid emulsion (SOLE) is 1g/kg of body weight as overdosage will might result in subsequent inflammation and hepatic steatosis[24].

❖ Fish oil-based intravenous lipid emulsion (FOLE) and olive oil-based intravenous lipid emulsion (OOLE) are better tolerated and have been reported to show better results as they contain omega-3 polyunsaturated fatty acids (PUFA). Clinical trials have shown that omega-3 PUFA supplements decrease hepatic inflammation and steatosis. Furthermore, omega-3 PUFA in FOLE and OOLE may also revert liver damage and improve liver function test (LFTs)[24] .

❖ Ursodeoxycholic acid (UDCA), another effective agent in the management of IFALD. It promotes bile flow and reduces bile acid cytotoxicity[1] In patients of cholestatic liver disease, UDCA has shown to improve hyperbilirubinemia and liver enzymes mainly ALT and AST. Clinical studies show that UDCA administration resulted in prevention and successful resolution of cholestasis.

❖ Glucagon-like peptide 2 (GLP-2) Certain GLP-2 analogues have beneficial results in patients with IF. Teduglutide, a GLP-2 analogue lowers the requirement and support of parenteral nutrition and further enhances the stool frequency by improving enteric motility in patients with short bowel syndrome (SBS). Another GLP-2, apraglutide, that has shown to improve hepatic excretory function by promoting liver macrophage activation[1] .

❖ Antibiotics: Metronidazole, an antibiotic that serves to eradicate anaerobic intestinal bacteria involved in the pathogenesis of IFALD. Its use over the time has shown to improve the hepatic enzyme parameters and a decrease in the level of AST, ALT and GGT[1].

❖ Erythromycin: Like UDCA, Erythromycin has shown to decrease the time duration of PN and subsequent incidence of IFALD. It acts as a pro kinetic and enhances the enteral feeding especially in infants with feeding intolerance.

❖ Preventions of Sepsis: It can be achieved by using antisepsis along with chlorhexidine on the catheter insertion site. In addition, the use of antimicrobial catheter coatings and locks, persistent disinfection of hubs and connectors and maximal sterile barrier precautions can result in complete prevention of sepsis[23].

2-Transplantation:

Depending upon the severity and progression of the disease, intestinal transplantation is the last resort and considered as a life saving measure in patients with IFALD. It is classified into isolated intestinal transplantation and combined liver and intestine transplant.

Patients with mild signs of liver damage and portal hypertension, isolated intestinal transplantation is the preferred choice. However, in patients with severe IFALD and end stage liver failure with cirrhosis and fibrosis and marked portal hypertension, combined liver and intestinal transplantation is recommended[24].

Transplants are highly immunogenic and therefore at higher risk of acute allograft rejection and development of infection. In order to counter this, different strategies have been implemented to improve the post operative results like incorporating rituximab and bortezomib, belatacept and bortezomib[1]. As the surgical techniques continue to improve, these results will further improve in future.

CONCLUSION:

From the above discussion we concluded that IFALD is a multifactorial disease. Although the treatment is based on the presenting complaints of the patient, we can still tailor some strategies i.e., supplementing SOLE (proinflammatory) with fish oil-based ILE (anti-inflammatory), increasing the interval between the parenteral glucose administration and adding carnitine, choline etc. in the PN. The management also include optimizing nutritional strategies using microbiome and pharmacologic therapies along with surgical care including transplantation and lengthening the gut since small bowel such as that in children is an anatomical factor leading to deranged liver function tests[1]. Over and above proper PN administration can still decrease the emerging rate of IFALD cases.

REFERENCES

[1] M. Zafirovska, A. Zafirovski, and N. Rotovnik Kozjek, "Current Insights Regarding Intestinal Failure-Associated Liver Disease (IFALD): A Narrative Review," *Nutrients*, vol. 15, no. 14, p. 3169, Jul. 2023, doi: 10.3390/nu15143169.

[2] L. Pironi and A. S. Sasdelli, "Intestinal Failure-Associated Liver Disease," *Clin Liver Dis*, vol. 23, no. 2, pp. 279–291, May 2019, doi: 10.1016/j.cld.2018.12.009.

[3] F. A. Rochling and H. A. Catron, "Intestinal failure-associated liver disease," *Curr Opin Gastroenterol*, vol. 35, no. 2, pp. 126–133, Mar. 2019, doi: 10.1097/MOG. 000000 0000 000503.

[4] Y. M. Shah and G. R. van den Brink, "c-Kit as a Novel Potential Therapeutic Target in Colorectal Cancer," *Gastroenterology*, vol. 149, no. 3, pp. 534–537, Sep. 2015, doi: 10.1053/j.gastro.2015.07.027.

[5] H. Madnawat *et al.*, "Mechanisms of Parenteral Nutrition–Associated Liver and Gut Injury," *Nutrition in Clinical Practice*, vol. 35, no. 1, pp. 63–71, Feb. 2020, doi: 10.1002/ ncp.10461.

[6] P. J. Javid *et al.*, "The role of enteral nutrition in the reversal of parenteral nutrition–associated liver dysfunction in infants," *J Pediatr Surg*, vol. 40, no. 6, pp. 1015–1018, Jun. 2005, doi: 10.1016/j.jpedsurg.2005.03.019.

[7] C. M. Hodin *et al.*, "Total Parenteral Nutrition Induces a Shift in the Firmicutes to Bacteroidetes Ratio in Association with Paneth Cell Activation in Rats ,2," *J Nutr*, vol. 142, no. 12, pp. 2141–2147, Dec. 2012, doi: 10.3945/jn.112.162388.

[8] K. C. El Kasmi *et al.*, "Macrophage-derived IL-1β/NF-κB signaling mediates parenteral nutrition-associated cholestasis," *Nat Commun*, vol. 9, no. 1, p. 1393, Apr. 2018, doi: 10.1038/s41467-018-03764-1.

[9] W. LUMAN and J. L. SHAFFER, "Prevalence, outcome and associated factors of deranged liver function tests in patients on home parenteral nutrition," *Clinical Nutrition*, vol. 21, no. 4, pp. 337–343, Aug. 2002, doi: 10.1054/clnu.2002.0554.

[10] A. Mutanen, J. Lohi, P. Heikkilä, H. Jalanko, and M. P. Pakarinen, "Loss of ileum decreases serum fibroblast growth factor 19 in relation to liver inflammation and fibrosis in pediatric onset intestinal failure," *J Hepatol*, vol. 62, no. 6, pp. 1391–1397, Jun. 2015, doi: 10.1016/j.jhep.2015.01.004.

[11] K. Gura, M. H. Premkumar, K. L. Calkins, and M. Puder, "Intravenous Fish Oil Monotherapy as a Source of Calories and Fatty Acids Promotes Age-Appropriate Growth in Pediatric Patients with Intestinal Failure-Associated Liver Disease," *J Pediatr*, vol. 219, pp. 98-105.e4, Apr. 2020, doi: 10.1016/j.jpeds.2019.12.065.

[12] J. Gonzalez-Hernandez, P. Prajapati, G. Ogola, V. Nguyen, N. Channabasappa, and H. G. Piper, "A comparison of lipid minimization strategies in children with intestinal failure," *J Pediatr Surg*, vol. 53, no. 1, pp. 96–100, Jan. 2018, doi: 10.1016/j.jpedsurg. 2017.10.030.

[13] S. M. Gabe and A. Culkin, "Abnormal liver function tests in the parenteral nutrition fed patient," *Frontline Gastroenterol*, vol. 1, no. 2, pp. 98–104, Jul. 2010, doi: 10.1136/fg.2009.000521.

[14] T. L. Hwang, M. C. Lue, and L. L. Chen, "Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function.," *Hepatogastroenterology*, vol. 47, no. 35, pp. 1347–50, 2000.

[15] D. Savic, L. Hodson, S. Neubauer, and M. Pavlides, "The Importance of the Fatty Acid Transporter L-Carnitine in Non-Alcoholic Fatty Liver Disease (NAFLD)," *Nutrients*, vol. 12, no. 8, p. 2178, Jul. 2020, doi: 10.3390/nu12082178.

[16] A. L. Buchman *et al.*, "Choline Deficiency Causes Reversible Hepatic Abnormalities in Patients Receiving Parenteral Nutrition: Proof of a Human Choline Requirement: A Placebo-Controlled Trial," *Journal of Parenteral and Enteral Nutrition*, vol. 25, no. 5, pp. 260–268, Sep. 2001, doi: 10.1177/0148607101025005260.

[17] E. F. Beale, R. M. Nelson, R. L. Bucciarelli, W. H. Donnelly, and D. V Eitzman, "Intrahepatic cholestasis associated with parenteral nutrition in premature infants.," *Pediatrics*, vol. 64, no. 3, pp. 342–7, Sep. 1979.

[18] R. Lester, J. St Pyrek, J. M. Little, and E. W. Adcock, "Diversity of bile acids in the fetus and newborn infant.," *J Pediatr Gastroenterol Nutr*, vol. 2, no. 2, pp. 355–64, May 1983.

[19] B. A. Carter and R. J. Shulman, "Mechanisms of Disease: update on the molecular etiology and fundamentals of parenteral nutrition associated cholestasis," *Nat Clin Pract Gastroenterol Hepatol*, vol. 4, no. 5, pp. 277–287, May 2007, doi: 10.1038/ncpgasthep0796.

[20] I. R. Diamond *et al.*, "The Role of Parenteral Lipids in the Development of Advanced Intestinal Failure–Associated Liver Disease in Infants," *Journal of Parenteral and Enteral Nutrition*, vol. 35, no. 5, pp. 596–602, Sep. 2011, doi: 10.1177/ 0148607 111413598.

[21] N. H. Al-Shahwani and D. L. Sigalet, "Pathophysiology, prevention, treatment, and outcomes of intestinal failure-associated liver disease," *Pediatr Surg Int*, vol. 33, no. 4, pp. 405–411, Apr. 2017, doi: 10.1007/s00383-016-4042-7.

[22] L. Norsa, E. Nicastro, A. Di Giorgio, F. Lacaille, and L. D'Antiga, "Prevention and Treatment of Intestinal Failure-Associated Liver Disease in Children," *Nutrients*, vol. 10, no. 6, p. 664, May 2018, doi: 10.3390/nu10060664.

[23] R. T. Khalaf and R. J. Sokol, "New Insights Into Intestinal Failure–Associated Liver Disease in Children," *Hepatology*, vol. 71, no. 4, pp. 1486–1498, Apr. 2020, doi: 10.1002/hep.31152.

[24] F. Fousekis, I. Mitselos, and D. Christodoulou, "New insights into intestinal failure–associated liver disease in adults: A comprehensive review of the literature," *Saudi Journal of Gastroenterology*, vol. 0, no. 0, p. 0, 2021, doi: 10.4103/sjg. sjg_ 551_ 20.