Published in final edited form as:

Nutr Clin Pract. 2020 February ; 35(1): 63–71. doi:10.1002/ncp.10461.

Mechanisms of Parenteral Nutrition–Associated Liver and Gut Injury

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Abstract

Parenteral nutrition (PN) has revolutionized the care of patients with intestinal failure by providing nutrition intravenously. Worldwide, PN remains a standard tool of nutrition delivery in neonatal, pediatric, and adult patients. Though the benefits are evident, patients receiving PN can suffer serious cholestasis due to lack of enteral feeding and sometimes have fatal complications from liver injury and gut atrophy, including PN-associated liver disease or intestinal failure–associated liver disease. Recent studies into gut-systemic cross talk via the bile acid–regulated farnesoid X receptor (FXR)–fibroblast growth factor 19 (FGF19) axis, gut microbial control of the TGR5–glucagon-like peptide (GLP) axis, sepsis, and role of prematurity of hepatobiliary receptors are greatly broadening our understanding of PN-associated injury. It has also been shown that the composition of ω -6/ ω -3 polyunsaturated fatty acids given parenterally as lipid emulsions can variably drive damage to hepatocytes and cell integrity. This manuscript reviews the mechanisms for the multifactorial pathogenesis of liver disease and gut injury with PN and discusses novel ameliorative strategies.

Keywords

liver diseases; microbiome; nutrition support; parenteral nutrition; sepsis; short bowel syndrome

Introduction

Parenteral nutrition (PN) has revolutionized the care of patients with intestinal failure by providing nutrition intravenously, thus bypassing the gut in the setting of limited ability to

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Statement of Authorship

H. Madnawat, A. L. Welu, E. J. Gilbert, D. B. Taylor, K. Blomenkamp, S. Jain, C. Manithody, and A. K. Jain equally contributed to the conception and design of the review and drafted manuscript; H. Madnawat, A. L. Welu, E. J. Gilbert, and D. B. Taylor contributed to the acquisition and analysis of data; K. Blomenkamp, S. Jain, C. Manithody, and A. K. Jain contributed to the interpretation of the data; and H. Madnawat, A. L. Welu, E. J. Gilbert, D. B. Taylor, K. Blomenkamp, S. Jain, C. Manithody, and A. K. Jain drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflicts of interest: A. K. Jain reports honorarium from Alexion Pharmaceuticals outside/unrelated to the submitted work; the other authors have indicated they have no potential conflicts of interest to disclose.

provide enteral nutrition (EN). This method is particularly useful for neonates with gut injury or prematurity as well as for patients with short-bowel syndrome, chronic diarrhea, gastrointestinal (GI) obstruction, GI motility disorders, or anastomotic leakage.¹ Worldwide, PN remains a standard tool of nutrition delivery in neonatal, pediatric, and adult patients, with its use growing exponentially in recent decades.

Though the benefits are evident, patients receiving PN can suffer serious and sometimes fatal complications from liver injury and gut atrophy.² However, despite several proposed mechanisms, the etiology of PN-associated injury remains unknown.

With decreased luminal content during PN, one leading theory maintains that a lack of hepatoprotective gut-derived signals contribute to liver disease manifested as PN-associated cholestasis (PNAC). PNAC is now more commonly referred to as PN-associated liver disease (PNALD) or intestinal failure–associated liver disease.³ Such is supported by the idea that because PN is typically utilized in the absence of enteral feeding, the lack of activation of enterocyte receptors by luminal agonists may decrease downstream signaling to the liver through the portal circulation, interrupting the normal gut-liver cross talk.⁴ Liver disease associated with PN includes steatosis, altered glucose and fat metabolism, and hepatic fibrosis or cirrhosis possibly via the downregulation of bile acid transporters.⁵

Other impairments during PN include a lack of gut mucosal integrity, gut inflammation, increased cytokine release, and bacterial translocation across the gut lining. More specific data indicate that the gut microbiome may play a critical role in homeostasis during EN and that PN drives a major microbial clonal shift, providing a critical role in homeostasis and immune function during EN.⁶ Differences in lipid emulsions can influence variable pathways, including those that are involved in phytosterol breakdown and drive downstream enzymatic and cytokine-regulated injury. In light of this evidence, the purpose of this review is to provide an overview of the multifactorial pathogenesis of PNALD and discuss novel ameliorative strategies.

Gut-Liver Cross Talk

Cholestasis and the Role of Enteral Feeding

Liver disease secondary to PN is known to be reversible upon restoration of enteral feeding. Although there is variability, PNAC can be associated with elevations in transaminases, alkaline phosphatase, γ -glutamyl transferase, and conjugated bilirubin, similar to other cholestatic diseases that must be ruled out.⁷ These elevations can resolve with short-term PN but may also result in cirrhosis and end-stage liver disease if early EN is not started.^{8,9} The use of PN is also known to lead to hyperlipidemia and accumulation of triglycerides in the liver.¹⁰ Earlier enteral feedings as noted from piglet and human studies have shown to be protective against PN-associated injury with reversal of cholestasis.^{11,12} The fact that EN remains critical in preventing liver disease begs the question of whether the gut and gut signaling are key to hepatic health.

Bile Acid–Regulated FXR Induction of FGF19

During normal enterohepatic circulation, bile acids can regulate activation of the gut nuclear receptor farnesoid X receptor (FXR).¹³ FXR is now believed to regulate hepatic bile acid production by suppressing bile acid synthesis from cholesterol by modulating cholesterol 7- α -hydroxylase (CYP7A1).¹³ FXR also activates intestinal bile acid binding protein, which maintains circulation of bile acids.¹³

By using a piglet PN animal model with intact gut, it has been reported that the potent FXR agonist chenodeoxycholic acid (CDCA) delivered enterally can prevent cholestasis and liver disease associated with PN therapy.¹⁴ Fibroblast growth factor 19 (FGF19), an enterokine released upon FXR activation (Figure 1A), decreased the protein signal that seems to regulate PNALD.¹⁵ The results suggest that decreased circulating FGF19 during PN may contribute to PNALD.¹⁴ In fact, FGF19 has also been shown to regulate CYP7A1 (Figure 1B) and is thought to be the signaling link between the gut and the liver.¹⁶

Kir et al showed that FGF19 stimulated hepatic protein and glycogen synthesis without lipogenesis.¹⁵ Mice lacking FGF15 (murine analog to human FGF19) were shown to be unable to maintain blood glucose concentration and liver glycogen postprandially.¹⁵ In addition, FGF19 helps improve glucose regulation by suppressing hepatic gluconeogenesis postprandially.¹⁷ Through study of knockout (KO) FGF receptor 4, which is a receptor for FGF19, not only an increased bile acid pool but also more body fat, glucose intolerance, insulin resistance, hyperlipidemia, and hypercholesterolemia were observed.^{18,19}

Hepatic vs Intestinal FXR Control of CYP7A1

FXR has hepatic and intestinal presence. To delineate the roles of hepatic FXR and intestinal FXR in mediating FGF19-driven regulation of CYP7A1,²⁰ Kim et al used tissue-specific FXR KO murine models. They concluded that CYP7A1 repression was more potently regulated by disruption of intestinal FXR and not hepatic FXR,²⁰ providing evidence of the gut having more of a modulatory effect on hepatic bile synthesis via CYP7A1. Stroeve et al examined increased CYP7A1 expression in the intestinal FXR KO exclusively at night when compared with wild type, with no significant difference in hepatic FXR KO,²¹ suggesting an additional time-dependent effect on hepatic bile acid synthesis.²¹

Kim et al also pointed to hepatic FXR being more important than intestinal FXR in suppressing synthesis of steroids for bile through regulation of sterol 12- α -hydroxylase (CYP8B1).²⁰ However, Stroeve et al showed more hydrophobic bile acids in intestinal KO FXR mice, pointing to variable activity of CYP8B1 and, thus, seeking exploration of additional insights into such mechanistic pathways.^{21,22}

Prematurity

In Beale et al, inverse correlation between birth weight and PNAC was noted, with half of infants under 1 kg having PNAC.²³ This group showed an overall 23% incidence of cholestasis with PN. The percentage of patients with cholestasis increased in premature infants to 80% with >2 months of PN use and to 90% with >3 months of PN use.²³ This prompts the question of whether prematurity predisposes to further PN-related injury.

It has been noted that infants receiving PN who did not get cholestasis were those who were able to feed enterally within 8 days of birth.^{24,25} Carter et al goes on to describe a multifactorial model with triggers of PNAC being lack of enteral feeding/hormone effects, PN toxicity, hepatic and gut prematurity, and central line sepsis/cytokine-induced inflammation.²⁶ The triggers have the ability to act alone or in combination, with hepatic immaturity predisposing neonates to further damage.²⁶

Animal and human studies have shown neonates to have a decreased bile acid reservoir, along with a higher production of dysfunctional bile acids.^{26,27} Transport processes such as FXR-mediated bile import and export, gallbladder contraction, bile acid secretion, and reuptake of bile acids into portal circulation are also not fully developed.^{28–30} Reduced bile transport is shown via decreased expression of sodium taurocholate cotransporting polypeptide (NTCP), which is a predominant transporter of bile salts on hepatic sinusoids, and BSEP (bile salt export pump) which helps mediate NTCP by exporting cytotoxic bile salts in states such as PNAC.²⁶ This elucidates an immaturity component to lack of bile acid transporter expression and, thus, susceptibility to PNAC.²⁶

TGR5-GLP Axis

TGR5 is a G-coupled protein receptor in the gut that drives secretion of metabolic hormones glucagon-like peptide-1 and 2 (GLP-1/2) upon its activation by bile acids (Figure 1C). GLP-2 is known to regulate gut growth and integrity, whereas GLP-1 increases insulin sensitivity and release and regulates hepatic steatosis (Figure 1D).^{31–33} Exogenous GLP-2 has been shown to have a protective effect with reduction in PN volume as well as the number of days receiving PN when given to patients receiving PN therapy, which causes GLP-2 reduction.^{34–38}

Mucosal Atrophy, Central Line Infection–Driven Liver Injury, and Bacterial Translocation

Gut Mucosal Atrophy

Mucosal atrophy can occur in the setting of PN and is characterized by decreased villous height, crypt depth, surface area, and epithelial cell numbers, which may occur as early as 24 hours following initiation of PN.³⁹ This rapid onset of mucosal atrophy may be due to the high metabolic rate and rapid turnover of intestinal epithelial cells, without their optimal replacement.⁴⁰ PN-related atrophy is believed to start at the proximal small intestine and progress distally and is also noted by decreased gut weight and nitrogen content.⁴¹

Bile acids have been shown to stimulate gut mucosal proliferation.¹⁰ Indeed, by using a neonatal pig model, it has been shown that bile receptor agonists prevented gut atrophic changes.¹⁴

Intestinal motility and presence of luminal chyme are also necessary to sustain intestinal mucosa. The absence of luminal nutrients and mucosal contact with luminal chyme has been shown to play a role in hypoplasia of the intestinal villi.⁴² Also, PN may drive a greater synergistic impairment with additional starvation effects to the gut mucosa.⁴³

Gut atrophy resulting from PN may significantly increase the permeability of the gut and the likelihood of sepsis.^{5,44} PN is believed to be associated with a diminished immunoglobulin A (IgA) response. In fact, using a murine model, PN administration was shown to be associated with increased proinflammatory lamina propria cytokines.⁴⁵ Additionally, rats receiving PN have been shown to have fewer Peyer's patches and more frequent interferon- γ -mediated apoptosis in the gut, resulting in decreased immune defenses.⁴⁶

Central Line Infection–Driven Liver Injury

PN requires the use of peripherally inserted catheters, which can increase the probability for infection. PN therapy has been demonstrated to be a significant independent risk factor for central line–associated bloodstream infections.^{47,48} Studies have reported adult trauma patients receiving enteral feeding have fewer incidents of line sepsis, intra-abdominal abscesses, pancreatitis, and other infections compared with patients receiving PN.^{47,48} The lack of enteral feeding further contributes to intraluminal bacterial overgrowth (notably, gram-negative Proteobacteria) due to decreased intestinal motility and change in nutrition availability.^{26,45} PN indeed appears to result in a disruption of the enterohepatic circulation and luminal microbial colonies, which have been shown to possibly increase hepatobiliary toxicity.

During normal enterohepatic circulation, primary bile acids, synthesized by the liver, undergo deconjugation to secondary bile acids by the gut microbiota.^{49,50} Because the primary bile acids are preferential ligands for FXR and secondary bile acids are preferential ligands for TGR5, this provides an interesting mechanism by which gut microbes can modulate bile acid signaling properties (Figure 1E).^{51–53} Changes in microbial communities could thus drive variable gut FXR and gut TGR5 activation and thus alter the course of PN injury.

Bacterial Translocation

The human gut microbiota plays a critical role in health. It has been proposed that PN alters the gut microbiota because of enteral starvation.^{26,54}

Firmicutes and Bacteroidetes are dominant phyla in the gut. It has been shown that there are significant alterations in the gut microbiota secondary to PN, including a significant reduction in the normal ratio of Firmicutes to Bacteroidetes. In fact, animal studies have shown a significant increase in the proinflammatory Bacteroidetes phylum in animals receiving PN, while maintaining dominance of the Firmicutes phylum in the control EN animals.^{55–57}

Bacteroidetes are efficient in using host glycans in a nutrient-deprived state and can interact with toll-like receptors (TLRs) to activate cytokines and nuclear factor- κ B and drive the proinflammatory cascade (Figure 1F). Additionally, in a mouse model, PN administration was associated with an upregulation of TLRs along the small intestine and colon that was due to microbial clonal shifts, which may further contribute to an increased risk of sepsis secondary to bacterial translocation.⁵⁸ Using a murine model, a decrease in mucosal atrophy was demonstrated in TLR4 KO mice receiving PN, along with a reduction in tumor necrosis factor- α (TNF- α).⁵⁹ Also, relative to chow and complex enteral diet, intravenous PN

reduces messenger RNA expression of Th2 cytokines interleukin(IL)-4 and IL-10, resulting in a decrease in protective IgA production within the lamina propria.⁶⁰

Deitch et al demonstrated in a murine model that malnourishment along with the introduction of endotoxin caused greater translocation of bacteria to systemic organs, resulting in greater mechanical damage of the mucosal barrier.⁶¹ Hence, the loss of barrier in patients receiving PN creates a gateway for gram-negative, endotoxin-containing bacteria to become more prevalent in the gut and allows for their greater spread systemically. This bacterial translocation resulted in endotoxin- and cytokine-mediated suppression of bile acid transporters and ultimately hepatic injury.^{62–64}

The lack of enteral feeding further contributes to intraluminal bacterial overgrowth due to decreased intestinal motility and change in nutrition availability.²⁶ PN indeed appears to result in a disruption of the enterohepatic circulation and luminal microbial colonies, and such have been shown to increase hepatobiliary toxicity. In fact, targeting gram-negative bacteria with antibiotics can mitigate PN injury, as noted by Freund et al, who demonstrated a reduction in inflammatory liver injury with oral metronidazole and/or tetracycline treatment.⁶⁵

Emerging data suggest that the gut microbiota plays an important role not only in inflammation and proliferation but also in the individual processing of nutrients and essential vitamins and minerals. This gives further evidence that an individual is very susceptible to changes in gut biota as noted with PN, and therapeutics targeting these pathways are challenging current paradigms to develop novel ameliorative interventions.

The Role of Lipids

Parenteral Lipids and Soybean-Oil Derivatives, Polyunsaturated Fatty Acids, and Phytosterols

To maintain a balance of macronutrients, it is necessary to provide patients receiving PN with essential fatty acids to maintain proper growth. Studies have shown that when lipids are administered parenterally, lipid metabolism can become dysfunctional, potentially leading to hepatic steatosis in the patient.⁶⁶ When consumed enterally, fats are absorbed by intestinal enterocytes as micelles and are transported via chylomicrons into lymph before returning to the liver, and they are potentially protective against hepatic injury when compared with patients receiving PN.⁶⁶

Traditionally, the primary source of lipids in PN is soybean-oil derivatives. The lipids in soybean-oil derivatives contain ω -6 polyunsaturated fatty acids (PUFAs), other PUFAs, triglycerides, and phytosterols.^{66,67} It has been shown that high levels of PUFAs and a high ω -6/ ω -3 ratio in PN may contribute to increased incidence of cholestasis, steatosis, sepsis, changes in neutrophil function, and upregulation of matrix metalloproteinases (MMPs).^{68–72} The ω -6 PUFA arachidonic acid (AA) produces prostaglandins (PGs), thromboxanes (TXs), 5-hydroxy-eicosatetraenoic acid, and other 4-series leukotrienes (LTs) that are proinflammatory.^{73,74} The ω -3 fatty acid eicosapentaenoic acid (EPA) produces 3-series

PGs, TXs, and 5-series LTs, which have less detrimental effect than AA-derived mediators have.^{75,76}

Preservation of the matrix is critical to the reduction of liver disease progression.⁷⁷ MMP activity is involved in breaking down extracellular matrix proteins during normal tissue turnover and is controlled by TNF- α . Increased MMP activity, as seen with fats having high ω -6/ ω -3 ratio, is known to cause liver damage, and it has been shown that silencing of TNF- α through TNF- α -converting enzyme inhibitor might reduce injury by inhibiting inflammatory pathways.⁷⁷⁻⁷⁹

It has recently been shown that MMP inhibition-mediated upregulation of IL-6 and proliferator-activated receptor- α (PPAR- α) prevents hepatic injury.⁷⁸ PPAR- α is involved in the metabolism of fatty acids, and IL-6 is a hepatoprotective cytokine.⁷⁸ In Krohn et al, Kupffer cells were shown to mediate the initial cytokine related injury via IL-6 regulation after hepatocyte transplantation in rat models.⁸⁰ Pathways involving MMP activity and downstream cytokine-mediated effects are highly influential in understanding the role of lipid metabolism in PNALD.⁷¹

Phytosterols are plant-derived sterols in soybean-oil derivatives that are structurally similar to cholesterol. In enteral feeding, only a small amount of phytosterols are absorbed. Through PN, however, phytosterols can be fully delivered to the liver.⁸¹ In fact, it has been shown that patients receiving PN had significantly higher elevated plasma phytosterol concentrations. Interestingly, in children with severe liver disease who are receiving PN, the concentrations of phytosterols were similar to those in patients with hereditary phytosterolemia.⁸¹ It has also been proposed that because phytosterols modulate FXR signaling, they can disrupt bile acid homeostasis and contribute to the development of cholestasis.^{66,82} As previously discussed, patients receiving PN paradoxically have a larger reservoir of bile salts through increased CYP7A1 expression. Additionally, when phytosterols accumulate, there is greater hepatic toxicity due to altered 9-desaturase, 5-desaturase, and 6-desaturase activity.⁸³

Stearoyl-CoA desaturase 1 (SCD-1) is a 9 fatty acid desaturase that catalyzes the synthesis of monounsaturated fatty acids and is critical in regulating hepatic lipogenesis and fat oxidation,⁸⁴ with recent studies recommending SCD-1 as a therapeutic target for hepatic steatosis. Additionally, SCD-1 deficiency also plays a role in regulating TNF- α levels.^{71,84}

Notoriously, patients with severe phytosterolemia can have xanthomata, atherosclerosis, thrombocytopenia, and hemolytic anemia, as also seen with prolonged PN use.⁸¹

ω -6 vs ω -3 Lipid Emulsions

Commercially available ω -6 emulsions contain approximately 20% soybean oil, phospholipid, glycerin, and water.⁸¹ It has been suggested that there can be a progressive buildup of phytosterol with prolonged PN use, which may continue over weeks. Previous studies have also linked recurrent thrombocytopenia to the prolonged use of such lipid emulsions in children.⁸⁵ In fact, Clayton et al⁸¹ showed that improvement in liver function tests, thrombocytopenia, and reduction in conjugated bilirubin occurred within 2-4 weeks of decreasing such lipid content.⁸⁶

Mixed-lipid preparations have been introduced, which contain a mixture of soybean oil providing essential fatty acids, olive oil rich in monounsaturated fatty acids, medium-chain triglycerides, and fish oil for ω -3 fatty acids.⁸⁷ Pichler et al⁸⁸ noted a nutrition improvement with significant weight gain and reduced inflammation in patients receiving such mixed emulsions. These emulsions have advantages over emulsions based on ω -6 only through a reduction of soybean and, hence, less accumulation of phytosterols and mitigation of the proinflammatory effect of ω -6 fatty acids, as well as potentiate positive effects of other lipid sources, medium-chain triglyceride, olive oil, and fish oil.⁸⁸ Mixed emulsions have been known to improve the incidence of hyperbilirubinemia, cholestasis, and inflammation.⁸⁶

Treatment Strategies

Although PN is a life-saving therapy, it is unfortunately associated with liver disease, which can often be end stage. In 2006, liver or liver-bowel transplantation in PN-related failure in pediatric patients was linked to a 1-year and 5-year survival rate of 73% and 64%, respectively.⁸⁹ The survival in patients receiving long-term PN treatment has significantly increased over time (due, in part, to the use of multidisciplinary nutrition support teams), but more must be done to improve patient outcomes.⁹⁰

Recipe Alterations

Alterations to the composition of the PN formula have been widely debated. After determining that PN supplemented with partial (25%) oral feeding significantly improved health outcomes, several PN formulas were tested in an effort to prevent the common patterns of gut epithelium atrophy that are often associated with PN treatment. In one instance, the inclusion of glutamine to the PN formula corresponded to intestinal protection due to the proposed mechanism of intestinal taste-receptor stimulation.⁹¹ Unfortunately, little conclusive and reproducible evidence has been found concerning beneficial amino acid content, including regarding taurine supplementation.⁹²

FXR Agonists

A novel but promising therapy in combating PNALD is the use of FXR agonists. The primary bile acid CDCA is a potent FXR agonist that has been shown to significantly improve FGF19, bilirubin, and metabolic profiles.⁴⁰ In addition, the FXR agonist GW4064 has demonstrated hepatoprotective effects, including significant improvement of hepatic transaminase concentrations in a murine model of cholestasis.⁶⁶ It has been proposed that the selective FXR agonist, obeticholic acid, may better treat cholestatic liver disease.⁹³

Ursodeoxycholic acid (UCDA) is another pharmacologic therapy that is thought to promote both hepatobiliary and cholangiocyte secretion, inhibit bile acid induced hepatocyte apoptosis, and diminish bile acid cytotoxicity; however, its minimal effect on gut FXR or TGR5 has called to question its efficacy in patients receiving PN.⁹⁴

Nevertheless, some recent studies have noted that the use of UCDA was found to delay and reduce the symptoms of cholestasis in both term and preterm infants receiving long-term PN.⁹⁵

Antibiotics

Antibiotics have also been suggested to be useful in PNALD. Prolonged use of PN increases small-bowel bacterial overgrowth.^{96,97} Such can drive liver injury through a release of cytokines.⁹⁷ Indeed, rotation of antibiotics such as metronidazole, ciprofloxacin, gentamicin, and kanamycin have been used to suppress small-bowel bacterial overgrowth.^{97,98}

PN has been shown to increase TNF- α levels.⁹⁹ The proinflammatory cytokine TNF- α has been demonstrated to play a role in sepsis-related cholestasis.⁴⁰ In a murine model, the TNF- α inhibitor infliximab was shown to significantly slow the progression of PNALD.¹⁰⁰ Although promising, further studies are needed to definitively determine the therapeutic role of TNF- α antagonists in PNALD.

Mixed-Lipid Emulsions

Data also suggest that the use of immune-nutrition, with dipeptide glutamate and alanyl-glutamine, may mitigate some of the complications in patients receiving PN. Decreasing inflammation and enhancing host immunity can be driven by increasing ω -3 PUFAs such as EPA and docosahexaenoic acid and decreasing ω -6 PUFAs.^{68,69,101}

Conclusion

Typically utilized in the absence of enteral feeding, PN is a standardized tool for maintaining all nutrition needs intravenously, which is increasingly used for extended periods of time in neonatal, pediatric, and adult patients. However, it can cause significant morbidity and even mortality. Exciting research into gut-systemic cross talk via the FXR-FGF19 axis and the TGR5-GLP axis is greatly broadening our understanding of PN-associated injury. There is now greater mechanistic insight into the role of prematurity in driving PN-associated pathology as a consequence of the immaturity of hepatobiliary signaling. Newer lipid emulsions, better control of central line infections, and aggressive EN strategies are greatly assisting patients who are receiving PN to achieve enteral autonomy sooner. The role of gut microbiota in driving PN-associated injury and its modulation via therapeutics remains a fertile area.

Financial disclosure:

A. K. Jain received funding from the National Institutes of Health (grant K08DK098623, grant R03EB015955-01, and R13DK109671-01) as principal investigator. Additional funding was provided to A. K. Jain via the Saint Louis University, internal grant mechanism. We also acknowledge support to our students from the DeNardo Foundation.

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Figure 1.

Parenteral nutrition–associated injury. (A) During regular enteral nutrition, luminal bile acids activate gut farnesoid X receptor (FXR), releasing fibroblast growth factor 19 (FGF19). (B) FGF19 regulates hepatic cholesterol 7 α -hydroxylase (CYP7A1), fat, and glucose metabolism. (C) Gut TGR5 activation by bile acids releases glucagon-like peptide-1 (GLP-1) and GLP-2. (D) GLP-1 modulates hepatic steatosis, insulin, and glucose; GLP-2 modulates gut growth. (E) Gut microbes deconjugate primary bile acids (FXR agonists) to secondary bile acids (TGR5 agonists). (F) Gut microbes also regulate cytokines, interleukins (ILs), and tumor necrosis factor- α (TNF- α), modulating liver and gut injury. FGFR4, FGF receptor 4.