

Review paper

# Review of parenteral nutrition-associated liver disease

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## Abstract

Parenteral nutrition has been widely used in patients whose gastrointestinal tract is anatomically or physiologically unavailable for sufficient food intake. It has been considered lifesaving but is not without adverse effects. It has been proven to cause liver injury through different mechanisms. We present a review of parenteral nutrition-associated liver disease.

**Key words:** total parenteral nutrition, liver disease, cholestasis, short bowel syndrome.

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## Introduction

First introduced in the late 1960s, parenteral nutrition (PN) has been widely used in adults and pediatric patients ever since. It has proved to be an effective method for providing nutritional support for patients who are not able to receive oral or enteral nutrition. Although in many cases PN is considered lifesaving, it may be responsible for a variety of adverse effects, cause comorbidity or be life-threatening.

In 1971, Paden *et al.* [1] first recognized hepatobiliary complications in infants on total parenteral nutrition (TPN). Well-described parenteral nutrition-associated liver disease (PNALD) has been known to be a complication of TPN used long term (over 14 days). PNALD is characterized by inflammation causing cholestasis, steatosis resulting in fibrosis and eventually in cirrhosis [2, 3]. Other terms for PNALD, intestinal failure-associated liver disease (IFALD) and parenteral nutrition-associated cholestasis (PNAC), have been used interchangeably [4]. The European Society for Clinical Nutrition and Metabolism (ESPEN) states: “The term intestinal failure associated liver disease (IFALD) refers to liver injury as a result of one or more factors relating to intestinal failure (IF) including, but not limited to, parenteral nutrition (PN) and occurring in the absence of another primary parenchymal liver pathology (e.g. viral or autoimmune hepatitis), other hepatotoxic factors (e.g. alcohol/medication) or biliary obstruction” [5].

## Epidemiology

The incidence of PNALD is much greater in infants than in adults (40-60% vs. 15-40%), being especially common among premature newborns with low birth weight [6]. In a report of neonates by Sondheimer *et al.* [7], cholestasis developed in 65% of patients while 13% had hepatic failure. The incidence of cholestasis in infants with birth weight less than 1000 g reached up to 50%, but was only 10% in those weighing over 1500 g. In this group of patients, decreased bile acid pools and immaturity of enzymatic systems participating in synthesis, conjugation, secretion and recirculation of bile play an important pathophysiological role [6]. In addition, numerous invasive procedures, infections and liver-injuring drugs may also contribute. Older studies have shown prevalence ranging from 7.4% to 85% [8-11].

The incidence of PNALD increases with time of TPN [12]. Cavicchi *et al.* [13] observed that disturbances in liver function tests meeting the criteria of PNALD occurred in 55% of patients who received TPN for a minimum of 2 months. After 6 years of parenteral nutrition, 72% of patients suffered from PNALD.

## Pathophysiology

Numerous risk factors have been recognized, including premature birth, short bowel syndrome, lack of enteral feeding, bacterial overgrowth (diagnosed

by employing two tests: anaerobic and aerobic colony counts of small bowel luminal contents and breath test), increased bile lithogenicity and subsequent bile duct obstruction, central venous catheter infection, nutrient deficiency and excessive caloric intake greater than 30 kcal/kg/day [14-18]. Parenteral nutrition components (soy-derived phytosterols and metals: chromium, manganese and aluminum) and the schedule of administration (constant being more detrimental than cyclic) have also been addressed [5, 19]. Mechanisms of PNALD, although studied by many centers, still remain unclear but are supposedly multifactorial. However, some mechanisms have been proposed.

## Infection

In 1983, Capron *et al.* studied a group of patients who received TPN due to intestine failure in the course of Crohn's disease. Patients with TPN who were administered metronidazole (500 mg twice daily) experienced either reduction or no pathologic changes in liver enzyme levels. The author concluded that intestinal bacterial overgrowth and subsequent bacterial translocation and production of endotoxins were associated with hepatotoxicity [20].

Another study, published in 2011 by Diamond *et al.* [21], suggested a 3.2-fold increase in the risk of developing PNALD after an episode of sepsis. Bacterial lipopolysaccharides (endotoxins) have been known to activate inflammatory cytokines (tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin (IL)-1 $\beta$ ) that have downregulating effects on transcription of bile salt transporters, leading to cholestasis and eventually ductal proliferation [22, 23]. Consecutive secretion of proinflammatory and chemotactic molecules (IL-6, IL-8 and monocyte chemoattractant protein-1) by proliferating cholangiocytes promotes the fibrotic process [24]. Moreover, endotoxins directly activate toll-like receptor 4 and, as a result, induce activation of hepatic stellate cells responsible for chronic inflammation and fibrosis [25].

In terms of infection occurring during PN, two major mechanisms must be taken into account. First and foremost is catheter-related bloodstream infection. Another proven source of pathogens is gut bacteria translocation, being caused by bacterial overgrowth and increased intestinal permeability. In 1988, Alverdy *et al.* reported significantly increased bacterial translocation to mesenteric lymph nodes in rats on PN [26].

An intact epithelial barrier ensures effective defense against intraluminal toxins, bacteria and other antigens. A few mechanisms potentially resulting in PN-associated impairment of the epithelial barrier

have been described. Animal models show atrophy of small bowel villi and decreased epithelial cell proliferation in opposition to increased apoptosis [27-29]. Moreover, pro-inflammatory cytokines, the production of which is increased during administration of PN, may result in increased permeability of the intestinal mucosa [29]. This pathology takes place after intraepithelial lymphocytes produce excessive amounts of interferon  $\gamma$  and TNF- $\alpha$ , while production of IL-10 is decreased. In 2008, Sun *et al.* described this mechanism using a mouse model [30]. TNF- $\alpha$  has also been known to cause dissociation of structural ZO-1 protein from tight junctions. Expression of other crucial tight junction proteins, such as claudins and occludins, is also downregulated in the PN-associated pro-inflammatory state. Since these proteins regulate the transport of molecules across the intestinal wall, defense mechanisms are compromised by organisms constituting the enteral flora. It is acknowledged that these species are often responsible for septic episodes in patients on TPN.

The above-described mechanisms occur in models where PN was the only route of nutrient administration with complete deprivation of enteral feeding; however, the presence of nutrients in the intestinal lumen regulates the selection of intraluminal bacteria. In enterally fed patients, *Firmicutes* have been reported to be a predominant group of microbiota [31]. In the state of starvation, overabundance of *Proteobacteria* and *Actinobacteria* has been observed. Lipo-polysaccharides found in the outer membrane of Gram-negative *Proteobacteria* are a potent agent of liver injury by activating Kupfer cells [32].

Additionally, the fasting state suppresses the secretion of cholecystokinin, gastrin and peptide YY, resulting in decreased stimulation of bile flow, gallbladder contraction and intestinal motility, leading to subsequent bile and intestinal stasis and bacterial overgrowth [33].

Wildhaber *et al.* [28] suggested a possibility of complete reversal of the pathological changes after initiating even limited enteral feeding. Phenotype including bacterial translocation, excessive production of pro-inflammatory cytokines and an increased epithelial T-subpopulation was eliminated with enteral provision of nutrients meeting only 25% of the caloric requirement. The volume of gut feeding considered trophic in infants is 10-12 ml/kg/day or 1 ml/h [34].

## Short bowel syndrome

In 2002, O'Brein *et al.* [35] described a similar mechanism in mice after resection of a large portion

of the small intestine. In patients with short bowel syndrome, after resection of the small intestine leaving less than 150 cm, there is impaired absorption of water, electrolytes and other nutrients to the point where intravenous administration is crucial to secure vital supply. In short bowel syndrome, deficiencies are compensated for by increased food intake and consecutive remodeling of the mucosa [36]. An excessive amount of improperly digested substrates cause a shift in fecal pH. While the normal range is from pH 6 to pH 7, patients with short bowel syndrome have fecal pH of 5.6 [37]. Another plausible cause of the change in the intestinal ecosystem is a higher concentration of oxygen due to the insufficient length of the remaining part of the intestine. Both mechanisms may result in a shift in microbiota composition. Again, *Proteobacteria*, especially *Enterobacteriaceae*, tend to overgrow in such an environment. Additionally, phyla known to be butyrate producers, providing nutrients to colonocytes, are likely to be suppressed (*Firmicutes*) or entirely eliminated (e.g. *Lachnospiraceae*, *Ruminococcaceae*) [38]. The shift in microbiome is strongly associated with gut inflammation and increased intestinal permeability leading to infections, potentially causing cholestasis in the mechanism described below.

### Bile acid metabolism and gut microbiota

Primary bile acids (chenodeoxycholic (CDCA) and cholic acid (CA)) synthesized from cholesterol in the liver after conjugation with taurine and glycine are secreted into the bile as bile salts. Bile salt exporting proteins (BSEP) are responsible for this process. Most bile salts are reabsorbed to the enterohepatic circulation, while the remaining portion is further metabolized to secondary bile acids (deoxycholic acid (DCA), ursodeoxycholic acid (UDCA), and lithocholic acid (LCA)) by gut microbiota. Both primary and secondary bile acids act as natural emulsifiers aiding digestion of fats and have a direct antibacterial effect. Moreover, bile acids have the ability to regulate metabolism by interacting with specific receptors, of which farnesoid X receptor (FXR) and G protein-coupled receptor (TGR5) play the most important role [39]. In hepatocytes, activated FXR induces expression of small heterodimer partner (SHP), which inhibits transcription of the gene for cholesterol 7 alpha hydroxylase (CYP7A1). In enterocytes, FXR stimulates production of fibroblast growth factor 19 (FGF19) and its transport to the liver via the portal vein. FGF19 binds to the FGFR4 receptor on the hepatocyte surface, repressing CYP7A1. CYP7A1 is a rate-limiting step of bile acid synthesis in hepatocytes [40, 41].

Additionally, FXR indirectly takes part in innate immunity mechanisms. It regulates expression of inducible nitric oxide synthase (iNOS) and angiogenin (Ang1) factors, playing a role in the response to infection and inhibiting bacterial overgrowth in the intestine [42]. It also controls expression of cathelicidin, an antimicrobial peptide active in bile ducts [43], and carbonic anhydrase 12 (CAR12), regulating intestinal pH and ion balance [44]. Pro-inflammatory cytokines, IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, and TNF- $\alpha$  are down regulated by activated TGR5.

The shift in the microbiota composition results in differences in bile acid transformation, blunted FXR response and FXR signaling [45], which was observed by Lapthorne *et al.* using the short-bowel syndrome-PNALD model of newborn piglets [46]. An association of bacterial overgrowth and inflammatory mechanisms was demonstrated in a PN-dependent mouse model in which a disturbance in normal intestinal microbiome resulted in gut epithelial cell apoptosis, increased expression of mucosal proinflammatory cytokines and a loss of intestinal barrier function and therefore impaired bile acid metabolism [47].

### Nutrient deficiencies

Deficiency of both products of hepatic transsulfuration pathways, choline and taurine, is postulated to contribute to pathophysiological mechanisms of PNALD. Choline can be produced from methionine, the concentration of which is often low in patients with ongoing PN [48]. The supplementation in PN mixture may be insufficient due to an inadequate route of administration (not entering the liver via the portal vein) [49]. Hepatic steatosis due to choline deficiency may be reversed by administration of choline in the PN mixture [50].

Lack of taurine, which can also be synthesized from methionine, may play a role in development of PNALD in premature infants. Prematurity of the liver results in a lack of essential enzymes – cystathionase being one of them. Cystathionase is an intermediate enzyme in metabolizing methionine to taurine, a rate-limiting step in the formation of cysteine from cystathionine [51].

### Nutrient toxicity

Parenteral nutrition solution may be toxic due to calorie overload and its components. Hepatic steatosis and hepatitis may occur in any case of overfeeding, regardless of the route of nutrient administration. An increase in portal insulin : glucagon ratio takes place when dextrose is infused in an amount providing

over 50 kcal/kg/day [52, 53]. Mitochondrial carnitine acetyltransferase, a rate-limiting step in oxidation of fatty acids, is inhibited by increased insulin concentration [54]. Li *et al.* demonstrated that accumulation of fatty acids in the liver in rats was significantly decreased if glucagon was added to a PN solution [55]. Fatty acids are also produced in a greater amount after acetyl-coenzyme A accumulates due to excessive intake of carbohydrates [56].

Parenteral nutrition solution is rich in lipids. Even though the exact mechanism of liver injury by lipids is still unclear, it is known that lipid emulsion infusion may be complicated by lipid overload syndrome. Cholestasis, thrombocytopenia, hypoxia and disseminated intravascular coagulation are the described symptoms of the syndrome. It occurs after fatty acids are provided in the amount greater than 3.0 g/kg/day [57]. Since growth is the crucial part of recovery in premature infants, these patients are more likely to receive such doses of lipids and are therefore more susceptible to PNALD. However, studies suggest that even > 1.0 g/kg/day may have a detrimental effect on the liver in preterms [58, 59].

Soybean derivatives (soybean oil-based lipid emulsions – SOBLE) have been conventionally used as the primary source in lipid emulsions [60]. Phytosterols (stigmasterol,  $\beta$ -sitosterol and campesterol among others) present in SOBLE have the same functions in plants as cholesterol has in animals. There are also structural similarities. Phytosterols act therapeutically by lowering plasma cholesterol and preventing atherosclerosis by competitive replacement of dietary and biliary cholesterol in mixed micelles, which results in decreased absorption of cholesterol [61]. In 2005, Javid *et al.*, using a mouse model, provided evidence that lipids administered via the enteral route along with the PN solution play a protective role against developing PNALD, whereas lipids infused only intravenously are associated with liver damage [62]. It is possible that phytosterols have a beneficial impact only when absorbed through the gastrointestinal tract. Recent evidence shows that phytosterols present in SOBLE are potentially hepatotoxic and contribute to the pathophysiology of PNALD by inhibitory effects on bile acid production and circulation. Long-term use of soybean intravenous lipid emulsions results in accumulation of phytosterols in cell membranes and plasma lipoprotein, especially in preterm infants, whose inability to eliminate phytosterols additionally explains their vulnerability to PNALD [63]. Addition of stigmasterol to the PN solution has been associated with Kupffer cell activation, resulting in augmentation of the inflammatory state. A mechanism involving toll-like receptor 4

has been proposed [64, 65]. Moreover, in a study on mice, presented by Carter *et al.*, stigmasterol acetate (StigAc), a water-soluble stigmasterol derivative, suppressed bile acid activated expression of FXR target genes, resulting in compromised hepatoprotectant mechanisms acting to prevent cholestasis (e.g. activation of bile salt export pump, FGF-19, short heterodimer partner (SHP) of orphan nuclear receptor). This mechanism was observed in FXR+/+, but not in FXR-/- mouse hepatocytes [66].

Fish oil-based lipid emulsions (FOBLE) might be an alternative to soybean derivatives. The first report of using fish derivatives was in a 17-year-old male who developed an essential fatty acid deficiency due to a soy allergy [67]. His soybean-based PN was replaced with fish oil. Not only was the deficiency reversed, but also lower activity of alanine transferase (ALT) and aspartate transferase (AST) and lower concentrations of direct and total bilirubin were observed. A year later, clinicians from the same hospital reported complete recovery from PNALD in 2 infants after 60 days of fish-oil based PN solution [68]. Similar results were obtained in an animal model using neonatal piglets. After only 14 days of administration of a fish oil-based formulation, a reduction of liver function tests was observed in comparison to groups receiving soybean oil or lipid mixtures (soy, olive, fish and medium- and long-chain triglycerides – MCTs and LCTs) [69].

The positive outcome of changing the source of lipid in a PN formulation emerges from a different concentration of polyunsaturated fatty acids (PUFA). Soybean derivatives predominantly contain  $\omega$ -6 fatty acid, whereas fish-oil based mixtures are rich in  $\omega$ -3 PUFA. It has been shown that the nuclear factor- $\kappa$ B pathway, leading to activation of TNF- $\alpha$  and disruption in hepatobiliary transport, is activated by  $\omega$ -6 fatty acid PN solutions [70]. Moreover, high concentrations of  $\omega$ -6 fatty acids increase peroxidation and decrease the level of antioxidants, mainly tocopherol [71]. In contrast,  $\omega$ -3 fatty acids have been supplemented as part of treatment of inflammatory diseases such as cardiovascular diseases, asthma, sepsis, autoimmune diseases, and malignancy [72].  $\Delta$ 5 desaturase preferably metabolizes  $\omega$ -3 PUFAs, resulting in the production of anti-inflammatory derivatives.  $\omega$ -3 PUFAs compete effectively with  $\omega$ -6 fatty acids as a substrate for  $\Delta$ 5 desaturase, causing a decrease in pro-inflammatory eicosanoids derived from  $\omega$ -6 PUFAs in favor of anti-inflammatory products of  $\omega$ -3 PUFAs [73]. A proposed mechanism of suppressing the inflammation by  $\omega$ -3 PUFAs is reduction of TNF- $\alpha$  gene transcription by inactivating the NF- $\kappa$ B signaling cascade secondary to decreased I $\kappa$ B phosphorylation at serine 32 [74].

Another beneficial factor of FOBLE is a significantly higher level of tocopherol in commercial  $\omega$ -3 PUFA solutions and its anti-oxidation effect [75]. Nevertheless, data on liver function improvement after use of novel lipid emulsions in adults are still insufficient [5]. There have been reports of risk of bleeding after infusion of  $\omega$ -3 PUFAs due to platelet dysfunction [76]. Moreover, certain concerns have been raised regarding other components of PN solutions. Manganese, aluminum and chromium have been addressed in this context. Anemia, neurotoxicity and cholestasis have been observed during manganese-containing PN administration. Manganese is excreted via the biliary route. Therefore, guidelines suggest monitoring manganese levels in patients receiving PN for over 30 days [77]. Aluminum present in PN solutions has been known to cause metabolic bone diseases and neurologic complications [78], whereas chromium was associated with peripheral neuropathy, weight loss and kidney damage [79]. Copper is also eliminated with bile and since it is only a trace element in PN solutions it does not have direct hepatotoxic effects; however, in patients who develop cholestasis, copper should be eliminated from the PN formulation due to potential hepatotoxicity [80].

## Diagnosis

PNALD is defined biochemically as 1.5 times the upper limit of normal elevation of two out of the three following liver enzymes: ALT, AST, or alkaline phosphatase (ALP). The elevation occurs within 1 to 3 weeks from the beginning of TPN [4, 24, 81]. Conjugated bilirubin was reported to be an accepted prognostic factor for liver injury during TPN, with a level of  $> 2$  or  $3$  mg/dl considered reflective for PNALD [82]. Other causes, e.g. viral hepatitis and drug-induced liver injury, have to be ruled out [4], which makes diagnosis of PNALD challenging.

## Histology

There are two major histologic presentations of PNALD. In infants and young children, cholestasis is a predominant finding (40-60% cases of infants on TPN) along with ballooning of hepatocytes, Kupffer cell hyperplasia and extramedullary hematopoiesis. In adults and older children, both microvesicular and macrovesicular steatosis commonly occur (40-55% of adults on TPN) [83, 84].

A significant overlap is observed between these two groups. Steatohepatitis, starting with periportal lymphocyte infiltration, then hepatocyte necrosis may evolve over time into pericellular and perivenular

fibrosis and bile duct hyperplasia, eventually leading to cirrhosis with all its complications [83, 84]. Children on long-term TPN may develop fibrosis after cholestatic jaundice has resolved [4].

Liver biopsy may be helpful in the diagnosis; nevertheless, due to the invasive character of the procedure it is rarely performed. Naini *et al.* [85] reported that: "Clinical markers of liver injury do not predict the degree of hepatocellular injury or fibrosis, and therefore, serial biopsies may be indicated for patients on TPN therapy". However, the latest ESPEN recommendations state: "Abnormal liver histology is not mandatory for a diagnosis of IFALD and the decision to perform a liver biopsy should be made on a case-by-case basis" [5].

## Clinical course

Although changes typical for PNALD occur in long-term TPN (up to 80% of cases), biochemical signs of cholestasis may occur even after the first week of feeding. An increase in hepatic enzyme activity usually starts with ALP and gamma-glutamylaminotransferase (within the first weeks). Transaminase level elevation may be observed later. Clinical manifestations are usually absent and nonspecific abdominal discomfort due to hepatomegaly may be the only symptom.

Beath *et al.* [4] subdivided PNALD into three stages according to its severity (Table 1). In moderate and advanced types of PNALD, liver fibrosis is associated with the development of portal hypertension. Ongoing exposure to blood pressure greater than 12 mmHg in the portal vein may result from the formation and bleeding of gastroesophageal varices. Liver capacity that is compromised to produce and metabolize leads to the well-known symptoms of end-stage liver disease.

Gall stones, though more likely in adults, may occur at any stage of PNALD and over the last 20 years have become more common in children. Patients who require chronic PN will undergo elective cholecystectomy [4].

## Differential diagnosis

Providing TPN is common in the postoperative state and in critically ill patients. A number of factors can be responsible for abnormal liver chemistries. In the setting of congestive heart failure, patients with hypovolemic or cardiac shock develop ischemic hepatitis. Hepatic hypoxia causes centrilobular necrosis, resulting in elevated aminotransferase levels. This pathophysiology also takes place in the course of respiratory failure. The dynamics of the changes in aminotransferases may be helpful in differentiating TPN

**Table 1.** Parenteral nutrition-associated liver disease is classified according to its severity [4]

Type	Biochemical findings	Ultrasound findings	Histology
Mild – type 1	LFT > 1.5× upper limit	Echogenic appearance of the liver	Steatosis (up to 25% of the acinus)
Moderate – type 2	LFT > 1.5× upper limit Bilirubin 3-6 g/l	Enlarged spleen	Fibrosis of more than 50% of portal tracts
Advanced – type 3	LFT > 3× upper limit PLT < 100 × 10 <sup>3</sup>	Symptoms of portal hypertension	

LFT – liver function test, PLT – platelet count

from ischemic hepatitis. In the setting of the latter, the increase of aminotransferases and ALP is rarely greater than twice the upper limit of normal level and normalizes soon after hemodynamic or respiratory stability returns [86].

Patients in postoperative or intensive care units commonly manifest jaundice that may be caused by sepsis. Liver injury occurs as a result of two mechanisms. Firstly, there may be hypoperfusion due to septic shock. In addition to aminotransferase and bilirubin abnormalities, compromised synthetic function of the liver results in hypoproteinemia and hypoglycemia. Since the liver has a major protective role in sepsis (detoxification of endotoxins and lipopolysaccharides, removing bacteria through the reticuloendothelial system), the other pathway of liver injury involves cytokines being produced by interacting cells present in the liver (Kupffer cells, neutrophils, hepatocytes and reticulocytes) [86, 87].

Benign postoperative jaundice starts soon after surgery and lasts no longer than 10 days, with slightly elevated or normal levels of aminotransferases. Cholecystitis, choledocholithiasis, drug-induced liver injury (anesthetics, analgesics, antibiotics) and viral infection (both acute and chronic) must also be taken into account [81].

Another chronic disease resulting in progressive liver injury is primary sclerosing cholangitis. Since multi-focal bile duct strictures are characteristic of this entity, employing magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography may be a diagnostic option of importance [88].

Transjugular liver biopsy should be strongly considered in diagnostic uncertainty accompanied by recalcitrant clinical course of liver injury in (especially chronically) critically ill patients in whom persistent abnormal conjugated bilirubin is not a result of biliary dilatation (proven by radiological imaging) and/or hyperbilirubinemia persists or worsens despite effective treatment underlying sepsis and/or any clinical or radiological features of chronic liver disease [5].

## Treatment

Prevention and management of PNALD are still to be improved, yet this change depends on the comprehension of risk factors. The pharmacological approach to treatment includes the use of ursodeoxycholic acid and antibiotic therapy for bacterial overgrowth (standard use of antibiotics in IFALD is not recommended). Taurine supplementation has been proven to decrease bilirubin levels in infants and preterm, but there are no supporting data in adults. Liver transaminase levels improve after choline supplementation, but sufficient quantities in PN solution may cause its instability; therefore adequate administration is difficult. Early reintroduction of gut feeding (including distal enteral tube feeding) aimed at minimizing parenteral caloric intake and overfeeding is recommended. Limiting SOBLE to < 1 g/kg/day, eliminating contaminations and reducing the  $\omega$ -6/ $\omega$ -3 PUFA ratio wherever possible are proven preventive options. Introducing newer mixtures of lipids based on fish and olive oils has been addressed but requires more study before exercising this option as a standard procedure. Investigation of all possible foci of infection or inflammation and their management is recommended. Also changing from a constant to a cyclic pattern of PN has been proven to reduce bilirubin levels in a prospective study in adults [89].

If possible, weaning of TPN stops further hepatic damage, yet in patients who have developed end-stage liver disease and for whom cessation of TPN is impossible, combined intestinal and liver transplantation should be considered [5, 90].

## Conclusions

Parenteral nutrition-associated liver disease is a potential complication of nutritional therapy in critically ill patients. Since it may be life-threatening, understanding its mechanisms, proper diagnosis and excluding other causes of liver injury yield possibilities of prevention and treatment. Even though the current state of knowledge helps in the introduction of numer-

ous modifications to different aspects of TPN, liver function deterioration is so severe in some patients that they may require liver transplantation. Therefore, further research is crucial to improve the safety of this nutritional therapy.

## Disclosure

The authors report no conflict of interest.

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