

Intestinal Failure–Associated Liver Disease: A Position Paper of the ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation

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ABSTRACT

Intestinal failure–associated liver disease is the most prevalent complication affecting children with intestinal failure receiving long-term parenteral nutrition. This paper reviews the definition, diagnostic criteria, pathogenesis, and risk factors. The authors discuss the role of enteral nutrition, parenteral nutrition, and its components, especially lipid emulsions. The authors also discuss the surgical treatment, including intestinal transplantation, its indications, technique, and results, and emphasise the importance of specialised intestinal failure centres.

Key Words: intestinal failure, intestinal failure–associated liver disease, lipids, parenteral nutrition, parenteral nutrition–associated liver disease, portal hypertension, small bowel transplantation

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INTRODUCTION AND DEFINITION

Intestinal failure–associated liver disease (IFALD) is the most prevalent complication affecting children with intestinal failure (IF) receiving long-term parenteral nutrition (PN). Liver disease may be partly because of toxic effects of the PN solution, or because of physiological and anatomical abnormalities associated with the underlying aetiology of IF. With advances in the management of PN including developments in formulation of nutrient products, the term IFALD replaces the old terminology of

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“PN-associated liver disease/cholestasis (PNALD, PNAC),” and “PN-liver disease.”

IFALD is defined as “hepatobiliary dysfunction as a consequence of medical and surgical management strategies for intestinal failure, which can variably progress to end-stage liver disease, or can be stabilized or reversed with promotion of intestinal adaptation” (1). This condition is not well demarcated, and it is unclear whether IFALD should be diagnosed on the basis of clinical, biological, or histological criteria, making prevalence difficult to define. The diagnosis is usually made on clinical grounds in children with IF, long-term PN dependency, and cholestasis (2). IFALD may present at early reversible stages, or become evident as an end-stage and lethal liver disease. Many of the factors associated with its development are preventable, and treatments of the disease and its complications are instigated before considering referral for transplantation (Tx).

The aim of this position paper from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition is to describe IFALD and its risk factors, guide the prevention and treatment of early IFALD, and give reference points for referral to a specialised IF centre, where more severe or progressive IFALD can be properly addressed within a multidisciplinary medicosurgical team. The literature was searched for basic studies, case series, or significant case reports, if these contained important new data. General reviews were used only if they brought additional information from large centres. In many instances, references are, however, not new, or are only case reports. Personal experience of the authors (all paediatricians with expertise in either nutrition or liver diseases) was included. Each author wrote 1 or 2 sections related to particular topics, and the whole paper was then reviewed by all of the authors, until a consensus was reached. As the level of evidence is weak, the decision was to provide practice points and recommendations (for all of the age groups), without grading the level of evidence.

DIAGNOSIS

As in many liver diseases, clinical signs, biological liver tests, and radiological investigations can be misleadingly normal because of the gradual and symptomless development of liver injury. Abdominal examination is often difficult in children who have had repeated surgical interventions. Splenomegaly can also be seen in infection, or fat overload (2), and is therefore not specific for portal hypertension, whereas stomal varices do point to this diagnosis. In biochemical terms, early IFALD is defined mainly in relation to bilirubin (2). Isolated hyperbilirubinaemia (>20 $\mu\text{mol/L}$) should be considered as a “red flag.” Total bilirubin persistently >100 $\mu\text{mol/L}$ for at least 2 to 4 weeks is a sign of marked liver injury, predicting progression to severe IFALD (3). Children with IF but without IFALD frequently

have an isolated increase in transaminases (alanine transaminase and aspartate aminotransferase), or a moderate increase in gamma-glutamyl transferase (usually <150 IU/L) (4). In advanced IFALD, portal hypertension is demonstrated by the presence of varices (oesophageal or stomal), whereas liver failure is heralded by an abnormal clotting profile. In this situation, the bilirubin is usually high (3), together with a low platelet count as result of hypersplenism. Clotting is not easy to interpret in the presence of hypersplenism because of peripheral consumption of coagulation factors. Ultrasound examination can be used to assess spleen size as well as liver texture that when grossly abnormal may be indicative of fibrosis or cirrhosis.

PREVALENCE, PATHOGENESIS, AND RISK FACTORS

There are few studies reporting large series of patients, making it difficult to define the exact prevalence of IFALD. In a series of 302 children on home PN (1980–1999), 23% developed IFALD, 7 patients (2%) died of liver failure, and 7 (2%) underwent liver–small bowel Tx (5). In another study of 90 adults on home PN (1985–1996), 50% developed permanent IFALD during 6 years of follow-up (6). In a recent retrospective study on 279 hospitalised children receiving long-term PN, 22% developed IFALD, and 4% progressed to end-stage liver disease. IFALD was associated with younger age, longer treatment, longer hospitalisation, surgical diagnosis, and prematurity (7). In patients with established IFALD, mortality as high as 40% has been reported, representing the main indication for intestinal Tx in children (4,8). Different aetiologies of IF, such as short bowel syndrome (SBS), congenital enteropathies, and motility disorders, can all be associated with IFALD, but data are scant on the prevalence of IFALD in these separate groups.

The risk factors for IFALD relate to both patient characteristics and management of the IF. Patient-dependent risk factors include age, degree of liver maturation (prematurity), cause of IF, site and frequency of infection (gastrointestinal tract, central venous catheter [CVC]), small bowel bacterial overgrowth (SBBO), and enteral feed tolerance. Treatment-related risk factors include the composition of PN, its mode of administration (continuous/cyclical), the duration of PN dependency, the surgical interventions and their anatomical consequences (intestinal obstruction, disruption of the enterohepatic circulation, resection of the terminal ileum or the ileocaecal valve), and the use of antibiotics (liver/renal toxicity).

The pathogenesis of IFALD is therefore multifactorial, and involves the immaturity of bile secretion from the infant liver, its sensitivity to lipid peroxidation or damage from sepsis, the disruption of the enterohepatic circulation, and intestinal and biliary stasis. Major risk factors (prematurity, lack of enteral nutrition [EN], infection, PN), and their pathogenic effect, will be described in the following sections.

PREMATURITY

In infants receiving PN, cholestasis leading rapidly to cirrhosis was first reported 40 years ago (9); similar observations followed rapidly (10–13), with the incidence of IFALD being related to both birth weight and duration of PN (11,14). In the premature newborn, the reduced bile salt pool and immaturity of liver sulphation (important for solubilisation of toxic bile salts such as lithocholic acid) seem likely to contribute to cholestasis and high risk of IFALD. The infant liver is also probably more susceptible to damage from lipid peroxidation and sepsis (13,15).

Premature infants who develop necrotising enterocolitis (NEC) are at particular risk for IFALD because, in addition to liver immaturity, they are exposed to multiple risk factors, which include a higher rate of sepsis (from both the intestine and indwelling CVC), intestinal obstruction and stasis, short bowel, disrupted

enterohepatic bile acid circulation, withholding of enteral feed, high glucose and lipid intake to meet energy needs, and requirement for continuous rather than cyclical PN infusion.

Recommendations. Early recognition and prompt medical management of NEC may prevent SBS and therefore IFALD. Scrupulous aseptic technique and CVC care protocols reduce risk of infection. Enteral feeding should be commenced and advanced as early as possible.

ENTERAL NUTRITION

EN is defined as the supply of nutrients into the stomach or small bowel, irrespective of the route (oral, tube, stoma) or type of feed, and represents an important means for prevention or reversal of IFALD. The presence of food in the gut drives intestinal adaptation by promoting mucosal hyperplasia and hypertrophy, thereby increasing the surface area available for digestion and absorption, and decreasing requirements for PN (16,17). Moreover, EN is a major stimulus for secretion of gut hormones, resulting in improvement of intestinal motility and gallbladder contractility, decreasing the stasis known to be implicated in the pathogenesis of IFALD (18–22).

When to Initiate Feeding?

Early trophic feeding promotes gut function in parenterally fed preterm infants (23) and improves the postoperative outcome in newborns with respect to food tolerance, time required to first bowel movements, and achievement of full oral intake (24). Experts recommend initiation of EN as soon as possible after bowel surgery starting with small volumes of breast milk or diluted formula (25). This is best done after discussion within a multidisciplinary setting with the medical, surgical team, and the nutritional care team (dietician).

Recommendation. EN should be initiated as soon as possible after surgery in infants receiving full PN, and advanced to the maximal volume tolerated.

What Type of EN?

Recommendations are based on few data. A retrospective study found that breast milk and amino acid–based formula, but not hydrolysed formula, were associated with shorter duration of PN (26). The beneficial effect of breast milk may relate to its high levels of immunoglobulin A, nucleotides, leukocytes, glutamine, long-chain polyunsaturated fatty acids (PUFAs), together with other components that positively influence immune system maturation (27–29). Dilated small bowel may be accompanied by bacterial overgrowth and increased permeability (30), in turn leading to enteral feed intolerance (31). This can be owing to cow's milk–protein allergy (32,33). Although some recommend the use of extensively hydrolysed formula (34,35), case reports, and small case series indicate that amino acid–based formula are more efficient in decreasing PN requirements (26,36–39). The only (small) randomised study comparing hydrolysed with nonhydrolysed enteral feed did not find a difference in weight gain, tolerance, and energy expenditure (40). Polymeric feeds may be better at supporting intestinal adaptation and bile flow (41).

Recommendation. Breast milk is the best choice of enteral feed for infants with IF. In non–breast-fed infants present evidence is insufficient for recommendations.

Practice Point. In early infancy, particularly in patients with short dilated small intestinal segments, it is reasonable to start with elemental formula, switching to extensively hydrolysed and then to polymeric feeds, particularly if the patient is older than 1 year. Solid

foods can be slowly introduced at the developmentally appropriate stages.

Continuous or Bolus EN?

Continuous infusion is often recommended in children with SBS (17–19,26,42,43) because reduced absorptive surface area and transport proteins may be more efficiently used, intraluminal nutrients support intestinal growth and adaptation, and the osmotic load is better tolerated (44). Intermittent feeding, however, is more physiological, provides cyclical hormonal surge, and promotes regular gallbladder emptying (45). In addition, when delivered orally, this supports the development of oromotor skills (17–19,26,42,43,46).

Recommendation. After gastrointestinal surgery, it is preferable to use continuous EN during the night. Small, oral bolus feeds should be started as soon as possible as an adjunct.

Are There Individual Nutrients With Beneficial Effects?

Soluble fibre may serve as an additional source of energy, promote more efficient absorption of electrolytes, and decrease stool frequency, provided the colon is in situ (47,48). The effect of glutamine is controversial (38,49–51). A recent study described a beneficial effect of enteral fish oil in reducing bilirubin and transaminase concentrations in 6 infants with IFALD (52).

Practice Points. In children with preserved colon, soluble fibre may be beneficial for the treatment of diarrhoea. Enteral fish oil may have a role in improving IFALD.

Probiotics

In children with IF, normal colonisation with intestinal microflora is significantly disrupted as a result of early and frequent antibiotic use, withholding of enteral feeding, motility disorders and prolonged hospitalisations (53). Most frequently, probiotics are used to modify the intestinal microflora. Although there are an increasing number of randomised controlled trials with probiotics in the prevention of NEC and bacterial translocation in preterm neonates, there are none in the treatment or prevention of IFALD in infants or children (54). There is only 1 small crossover trial that assessed the changes in intestinal permeability owing to *Lactobacillus rhamnosus* (LGG) in children with SBS, and found no positive effect (55). One small case-control study evaluated nutritional parameters with synbiotics (*Bifidobacterium breve*, *Lactobacillus casei*, galacto-oligosaccharides) and reported a trend in increasing height and weight gain velocity and improvement in bacterial microflora (56). Several case reports reported the influence of different probiotics or synbiotics on outcome of SBS, with conflicting findings (57–59). Furthermore, several case reports described probiotics-associated septicaemia in children with CVC (60,61).

Recommendation. There is insufficient evidence to recommend use of probiotics in the prevention or treatment of IFALD.

PARENTERAL NUTRITION

Components

Imbalance (deficiency/excess) of parenteral nutrients has been associated with IFALD, and almost all of the components have been implicated as possible causative or aggravating agents.

Excess of Energy

Excess of energy, delivered as either dextrose (usually 8–18 g · kg⁻¹ · day⁻¹ of glucose according to age and disease) or fat, promotes

hepatic steatosis (62–64). At a high infusion rate, raised plasma glucose concentrations result in increased plasma insulin, triggering hepatic lipogenesis. Insulin also stimulates glycolysis, fatty acid synthesis, glycogen synthesis, and fatty acid esterification, while depressing fatty acid oxidation, glycogenolysis, and gluconeogenesis (65). Fat supplied intravenously is carried by liposomes, rather than chylomicrons, with “artificial” delivery of fat to the liver. Thus, fat infusion results in steatosis, even when given in physiological amounts, and even more so when given in excess. This fat is typically seen in Kupffer cells and hepatic lysosomes (66).

Recommendation. Energy intake should be adapted according to the disease state, always avoiding the delivery of excess energy by PN. A balanced PN formulation should usually provide approximately 75% of nonprotein calories as carbohydrate and 25% as fat. A higher intake of fat (maximum of 40% of energy) should only be given in exceptional circumstances of high energy needs or glucose intolerance (in patients with extensive burns), for short periods, and with close biochemical monitoring.

Practice Point. In the presence of hypertriglyceridemia, fatty liver, or IFALD, a reduction of parenteral energy, and an increase in EN, is advised, whenever possible. We would recommend that an upper triglyceride level of 2.5 g/L during lipid infusion in newborns and serum level of triglycerides of 3 to 4 g/L in older children are considered acceptable during infusion of lipid emulsions (LEs).

Research Needs. The relative contribution to fatty liver deposition, of either glucose or fat, during iso-caloric energy delivery, should be further evaluated.

Amino Acids

Although 1 study showed a similar incidence of cholestasis in premature infants receiving either 2.5 or 3.5 g · kg⁻¹ · day⁻¹ of amino acids, the highest dose was associated with earlier onset and increased magnitude (67). Higher dextrose intake also increased the prevalence of cholestasis (68–70). High cumulative infusion of amino acids may be associated with development of IFALD in children, although a definitive relation has not been demonstrated. It is not clear how composition and dose of amino acid solution affect the development of IFALD in older children and adults, but effects appear to be more marked in the newborn. Deficiency of specific amino acids, such as taurine and cysteine, may play a role, especially in premature infants (71,72). Excess of particular amino acids such as methionine has been associated with cholestasis in rabbits (72).

Recommendation. Use parenteral amino acid solutions specifically designed for children and avoid an excess of nitrogen supply.

Practice Points. Amino acid supply should be initiated at the recommended amount from the initiation of PN. Monitoring for adequate supply (growth, nitrogen balance, biochemical parameters), and excess (amino acid profile, blood urea nitrogen, acidosis), is advisable, especially in premature infants.

Research Need. Reliable and practical biomarkers for the evaluation of adequacy of nitrogen supply in children are needed.

Intravenous LEs

Intravenous LEs based on soybean or safflower oil are implicated in IFALD. They contain a high concentration of the ω-6 PUFA linoleic acid and a lower concentration of the ω-3 PUFA α-linolenic acid (73) (Table 1). In adults, cholestasis was significantly associated with the intake of long-chain triglyceride (LCT)

TABLE 1. LEs, manufacturers, oil source and composition (as provided by manufacturers)*

	Intralipid Fresenius Kabi	Liposyn II Hospira	Lipofundin MCT/LCT B. Braun	SMOFlipid Fresenius Kabi	ClinOleic Baxter	Omegaven Fresenius Kabi
Source %						
Soybean	100	50	50	30	20	0
Safflower	0	50	0	0	0	0
Coconut	0	0	50	30	0	0
Olive	0	0	0	25	80	0
Fish	0	0	0	15	0	100
α-Tocopherol, mg/L	38	?	100	200	32	150–300
PS, mg/L	348	383	?	48	327	0
Composition, g						
Palmitic (16:0)	1	0.88	0.55	0.9	0.65	0.25–1
Stearic (18:0)	0.4	0.32	0.2	0.33	0.175	0.05–0.2
Oleic (18:1)	2.6	1.82	1.16	2.8	2.83	0.6–1.3
Linoleic (18:2)	5	6.54	2.66	2.85	0.86	0.1–0.7
α-Linolenic (18:3)	0.9	0.39	0.1	0.275	0.115	<0.2
EPA (20:5)	0	0	0	0.25	0	1.28–2.82
Arachidonic (20:4)	0	0	0	0.05	0.025	0.1–0.4
DHA (22:5)	0	0	0	0.05	0	1.44–3.09

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LCT = long-chain triglyceride; LE = lipid emulsions; MCT = medium-chain triglyceride; PS = phytosterols.

from 100% soybean oil of >1 g/kg body weight per day (6). Various mechanisms have been suggested and are outlined below.

Proinflammatory Effect of Linoleic Acid and Peroxidation of PUFA

Linoleic acid is converted into arachidonic acid, a precursor of proinflammatory agents (eg, tumour necrosis factor-α, interleukin-6, platelet activating factor, adhesion molecules), which may adversely affect the liver (74–77). Although chronic inflammation probably contributes to cholestasis and liver fibrosis, oxidative stress may also be toxic to the liver. Long-chain PUFA are prone to oxidation (15,78–80), the risk of oxidative stress being increased with soybean-derived LEs (81), because of the low concentration of α-tocopherol, a major lipophilic antioxidant (74,80,82) (Table 1). For this reason α-tocopherol is sometimes added as a supplement (83).

Plant Sterols

Plant sterols (phytosterols, PS) are found in soybean oil LEs, and are steroid alcohols found in plant cell membranes. Blood PS concentrations are closely associated with cholestasis in children and adults with IFALD (84–87). PS have been shown to reduce bile acid secretion and inhibit excretion of bile. The mechanism is believed to be the result of the antagonism to the nuclear Farnesoid X receptor. The Farnesoid X receptor regulates the expression through various genes and proteins, resulting in accumulation of bile and toxicity to hepatocytes (88,88a). A comparison of 8 LEs based on soybean and olive oil demonstrated a great variation in content of PS and cholesterol content. Table 1 shows the PS content of all of the available LEs including the newest fish oil-derived products; it is highest in soybean and lowest in fish oil-based LEs (89).

LE and Activation of the Liver Reticuloendothelial System

The metabolism of the oxidised fraction of the LE is relatively well known, whereas the destiny of the nonoxidised fraction is less clear. This involves take-up by the liver (Kupffer cells and hepatocytes), and spleen (reticuloendothelial cells [REC]), bone marrow, and lungs. Chronic administration of LE has the potential

to overload the REC and induce acute or chronic activation, leading to haematological disorders, liver dysfunction, and cholestasis (90,91). In a rat model, LE infusion resulted in downregulated hepatic lipase activity, fat vacuoles in Kupffer cells, and hepatocytes, with morphological signs of increased Kupffer cell activity. Although this suggests that LEs may activate macrophages (66), no relation between IFALD, liver REC function, and LE intake has been established in humans.

Medium-Chain Triglycerides and Olive Oil–Based LE

Theoretical advantages of medium-chain triglyceride (MCT) over LCT include preferential lipoprotein lipase hydrolysis, non-carnitine-dependent metabolism, and rapid oxidation (92). Intravenous MCT-based LEs, either as physical mixtures or as structured lipids, have been used clinically in adults and children (93). Neither animal models (94) nor clinical data have, however, demonstrated clear superiority of MCT- over LCT-based LEs with regard to prevention or reversal of IFALD (95,96). An olive oil-based LE (olive oil:soybean oil ratio 4:1, with lower (20% vs 60%) PUFA content, and high monounsaturated oleic acid and vitamin E content, has been evaluated in children on long-term PN (74,97,98). Benefits include decreased risks from excessive PUFA intake (eg, increased peroxidation) and decreased PS load (80,99); however, an improvement in liver function has not been demonstrated in clinical studies. As in 2005, there is presently no evidence based on clinical outcome data to support the superiority of any 1 particular LE in reducing the risk of IFALD (100).

Fish Oil–Based LE

The composition of fish oil containing LE has several advantages, including a high concentration of α-tocopherol (4–8-fold more than soybean oil LE) and the absence of PS. Moreover, fish oil is a source of docosahexaenoic acid (important for neurodevelopment and visual function), and eicosapentaenoic acid. Eicosapentaenoic acid favourably modulates inflammation, directly by decreasing the production of proinflammatory cytokines and indirectly by increasing secretion of the anti-inflammatory cytokine interleukin-10 by hepatic macrophages (101). In animal

models, intravenous fish oil improves biliary flow and decreases cholestasis (102). Fish oil also reduces de novo lipogenesis, stimulates β -oxidation, and decreases hepatic steatosis (103,104). First reports of parenteral fish oil (Omegaven, 1 g · kg⁻¹ · day⁻¹; Fresenius Kabi, Bad Hamburg, Germany) as the sole parenteral lipid source in children with chronic IF and severe IFALD were provided by a team from the Boston Children's Hospital (105). Further case series described the use of fish oil as monotherapy for the treatment of IFALD (106–109). In most of the studies, a high dose of soybean-based LE was replaced by 1 g/kg of fish oil. Reversal of cholestasis may therefore derive from the withdrawal of soybean oil, an effect of fish oil itself (including its high α -tocopherol content), or both. Two studies (105,108), which compared children treated with pure fish oil with those treated with soybean oil LE, used historical control groups (with ω -6 LE), and so cannot account for the confounding effects of the underlying disease, and other important factors such as enteral feeding. Such observations do not allow conclusions to be drawn regarding the relative contribution of the type of LE, the dosage used, or other disease-related factors. In 2008, a report of fish oil (1 g/kg) combined with soybean oil LE (1 g/kg) in 12 infants with SBS and severe IFALD was published. Recovery from IFALD occurred in 4 patients, whereas in further 5 cases this was only achieved after stopping soybean oil LE (110). More recently, SMOFlipid, a mixture of 30% soy, 30% MCT, 25% olive, and 15% fish oil, has become available, and appears to be well tolerated by infants and children (111). In 2012, a small retrospective study compared the outcomes of 2 groups of parenterally fed children with cholestatic jaundice, receiving either a soybean oil LE (Intralipid, Fresenius Kabi, Bad Hamburg, Germany) or SMOFlipid. After 6 months, although patients were still receiving at least 50% of their energy needs parenterally, there were significant differences in plasma bilirubin concentration, with a median fall of 99 μ mol/L in the SMOFlipid group, and an increase of 79 μ mol/L in the Intralipid group (112). Long-term studies (including liver histology following reversal of cholestasis with fish oil) are still lacking. In a small group of adults, histological improvement was seen after 4 weeks of treatment with pure fish oil, with a decrease in inflammation and cholestasis (113). Some animal and human studies, however, suggest that fibrosis persists, or even progresses, despite normalisation of cholestasis markers, after giving fish oil (114–117). These, and other studies, underline the limitation of cholestasis as the single endpoint for assessment of IFALD (118). Although both a decrease in soybean oil-based ω -6 LE load and administration of fish oil seem promising interventions for the treatment of IFALD in children, decisive data regarding the role for different LE in the prevention of IFALD are lacking, although clinical trials are awaited (119,120).

Lipid Dose

Liver toxicity has been linked to the dose of LE, although types of LE (fatty acid composition and PS content) are also clearly important factors. A high rate of LE infusion, exceeding the ability of the liver to clear phospholipids and fatty acids, can lead to steatosis. Cholestasis and severe IFALD were strongly associated with a supply of soybean-based LE >1 g · kg⁻¹ · day⁻¹. In 152 infants, days of maximal lipid (>2.5 g · kg⁻¹ · day⁻¹) was identified as a strong predictor for severe IFALD (14). In another paediatric study, reduction or temporary suspension of soybean-based LE administration improved cholestasis; bilirubin level generally dropped rapidly during the first month, and normalised after 3 months (96). Adult studies have also reported improvements in liver function following a reduction in soybean-based LE intake (6,121). Nevertheless, as seen in these studies, the origin of LE is probably as important as the dose, and these results cannot be extrapolated to new LE containing MCT, fish, or olive oil. In as many as 25% of

patients in some studies, restriction of LE was associated with mild essential fatty acid deficiency, reversed with additional days of lipid infusion (122).

Recommendations. A well-balanced energy supply of fat and dextrose is essential to sustain protein accretion and growth, but excess energy intake should be avoided. PN should usually provide 15% to 30% of nonprotein calories as fat. Reducing, or temporarily discontinuing LE, should be considered in the presence of hyperbilirubinaemia. The use of LE with lower ω -6 content should be preferred. Decreased soybean oil-based ω -6 LE load and administration of fish oil both seem promising interventions; however, there is a lack of high-quality data to support the use of parenteral ω -3 (fish oil) LE in children outside clinical trials.

Practice Points. The advantage of reducing fat intake must be balanced against the risks of giving insufficient energy, especially in newborns with high energy demands for growth. A minimum 0.5 g · kg⁻¹ · day⁻¹ of soybean oil-based LE is necessary to prevent essential fatty acid deficiency. Increasing glucose delivery to maintain adequate energy supply may be associated with fatty liver.

Further Research. The optimal dose and source/composition of LE to provide appropriate energy supply without causing liver complications are yet to be determined.

Other PN Components

An absolute or relative deficiency of carnitine in PN is believed to contribute to the development of steatosis. Patients on long-term PN were shown to have carnitine deficiency, but the prophylactic effects of supplementation on steatosis have not been well documented (123–125). Choline is an important component of phosphocholine involved in lipid transport. Low serum concentrations have been found in children on PN, with a correlation between the serum free choline levels, the degree of steatosis, and elevation of aminotransferases (126). Choline supplementation can reverse hepatic abnormalities and steatosis (127,128). α -Tocopherol among the different vitamin E preparations has the greatest antioxidant activity. Soybean oil emulsions contain high amounts of γ -tocopherol (with only 25% of the antioxidant activity of α -tocopherol), whereas fish oil is rich in α -tocopherol (80,129,130) (Table 1). With present PN solutions, there is little evidence that components such as aluminium, chromium, or other trace elements are important factors in IFALD (131,132). In 2004, the US Food and Drug Administration required manufacturers to include the aluminium content of additives used in the compounding of PN solutions. The amount of aluminium in PN should be <5 μ g · kg⁻¹ · day⁻¹ (133). Other PN-related factors that have received attention include the need to protect feed solutions from light-induced peroxidation during administration. The results from the most recent study on a large cohort of premature infants, however, demonstrated no beneficial effect of partial light protection of PN on clinically relevant outcomes (134).

Recommendations. Individual components of PN should be of adequate quality, according to established international standards. Although most manufacturers comply with this requirement, nutrition support teams should evaluate the aluminium content of the products they use.

Practice Point. Protecting PN feed tubing from light is advisable because it may prevent degradation of components or loss of activity, although it may be that light-induced peroxidation is less detrimental than previously believed.

Mode of Infusion of PN

Cyclic infusion of PN (given for <24-hour period, usually 8–12 hours) may reduce the risk of liver complications, especially

in patients requiring long-term PN. Metabolic studies demonstrated that lipid oxidation was higher and dextrose use was lower, during cyclic versus continuous PN (135,136). Cyclic infusion has also been shown to result in a reduction of serum liver enzymes and conjugated bilirubin in adults and children when compared with continuous infusion, and is associated with a reduction in both hyperinsulinaemia and fat deposition in the liver (137,138). Overall, cyclic PN was shown to be well tolerated, without significant hypo- or hyperglycaemia. In newborns and infants, hypoglycaemia limits its application.

Recommendations. Cyclic PN delivery is recommended in the stable patient receiving prolonged PN in hospital, and during home PN, provided normal blood glucose can be maintained.

Practice Points. Acutely ill patients and newborns require PN as a continuous infusion for 24 hours. In those needing long-term PN, cyclic delivery with monitoring for hyper- (during infusion) and hypoglycaemia (after disconnection) should be started before discharge, especially in children younger than 2 to 3 years.

Research Needs. The effects of long-term cyclic supply of PN nutrients on the cardiovascular system, renal function, and bone accretion need further assessment.

SEPSIS

Recurrent CVC infection (catheter-related blood stream infection [CRBSI]) is an established factor contributing to the development of IFALD. In a single-centre study of 74 postsurgical newborns, significant risk factors for IFALD were catheter sepsis, low gestational age, and use of PN. Each episode of CRBSI produced a 30% rise in serum bilirubin, which did not return to baseline, and increased progressively if infection recurred (14). Two other studies emphasised the importance of early CVC infection as a contributing factor to end-stage liver disease (139,140). There are, however, reports of IFALD despite avoidance of sepsis, highlighting its multifactorial origin (141). Debate continues about SBBO in dysmotile, dilated bowel loops, leading to translocation contributing to both CRBSI (cf, “surgical treatment”) and cholestasis. A study supporting the “bacterial translocation” theory shows that a Toll-like receptor 4[en dash]dependent activation of Kupffer cells by lipopolysaccharides absorbed from the gut microbiota may contribute to the liver injury in IFALD (141a). Preventive strategies including establishment of nutritional care teams, early discharge on home PN, and the use of taurolidine and ethanol locks have reduced the incidence of recurrent CRBSI (141–143).

Recommendation. Each centre should have an individualised protocol for prevention, recognition, and prompt treatment of CRBSI.

Research Needs. Simple, reliable tests for SBBO need to be developed, and the role of overgrowth on sepsis and IFALD further evaluated.

EVALUATION OF THE SEVERITY OF IFALD

Defining the severity of liver disease is of paramount importance, as the presence or absence of advanced liver disease and portal hypertension determines treatment options. Liver function tests and their limits are discussed in the section on “diagnosis”. Historically, the severity of IFALD has been correlated with plasma bilirubin concentration (14,140). Although some classifications have been based on results of liver function tests (144), as in many other liver diseases, severe fibrosis or cirrhosis is compatible with a normal bilirubin. With the use of newer LE, manifestations of cholestasis can be masked, while there is also subtle progression of IFALD (2,145–147). Noninvasive markers such as the aspartate aminotransferase to platelet index (APRI) have not been helpful in predicting the degree of fibrosis in children with IFALD, but may be

useful in predicting cirrhosis (148). Ammonia usually does not increase until late in illness, due to the absence of bacterial metabolism in the colon. Transient elastography (Fibroscan) is not validated in this indication, but could be used for the follow-up of an individual patient (149). A large spleen (on ultrasound or clinical examination) may reflect infection or fat overload; however, the presence of splenomegaly or decreased platelets (without sepsis or macrophage activation syndrome), in a patient with an enlarged firm or hard liver, is suggestive of portal hypertension.

Bleeding from varices is a sign of end-stage IFALD. In patients with SBS and a reduced splanchnic blood flow, varices are less frequent than in other types of cirrhosis, as collaterals may develop along intraabdominal scars, preventing the development of oesophageal varices (144,150). Screening with upper gastrointestinal endoscopy or endoscopic ultrasound is nonetheless recommended. Stomal varices can represent a management dilemma (150). Prophylaxis with propranolol may be given, but it is not absorbed in most cases, and its efficiency in children with portal hypertension is not proven. A transjugular intrahepatic porto-systemic shunt should be considered if bleeding is life threatening (151). Liver biopsy may be misleading in assessing the type and severity of IFALD owing to patchy hepatic involvement, and does not help in defining the presence or absence of portal hypertension (12). Objective assessment of portal hypertension by catheterisation of the hepatic veins and measurement of wedge pressure gradient may be more useful (152,153).

The severity of liver failure is therefore evaluated by combining clinical features with degree of jaundice, presence of portal hypertension, and biochemical tests such as coagulation and serum albumin (although the latter may be low from inflammation or protein-losing enteropathy). If the waiting time for Tx is long, the hepatic venous wedge pressure, liver biopsy, and upper gastrointestinal endoscopy may be repeated, to follow the evolution of IFALD and confirm the indication for either isolated small bowel Tx or combined liver and small bowel Tx.

Recommendation. The presence of splenomegaly, or decreased platelets in a patient with an enlarged, firm or hard, liver should prompt consideration of portal hypertension.

Practice Point. Standard investigations for assessing the severity of liver disease should not be relied upon in IFALD. Hepatic wedge venous pressure measurement, along with liver biopsy and upper gastrointestinal endoscopy ± endoscopic ultrasound, is more appropriate for the assessment of possible portal hypertension.

Research Need. The best investigations in the assessment of type and severity of IFALD need to be established.

SURGICAL TREATMENT OPTIONS

Nontransplant Surgery

There are no robust data to support a role of nontransplant surgery in improving or preventing IFALD in children. Nevertheless, surgery has the potential to modify some mechanisms relevant to the pathogenesis of IFALD, including enteral feed tolerance, bile acid enterohepatic circulation, development of SBBO, and bacterial translocation (154). It is important to consider that, in children with SBS, the phase of greatest growing potential of the gut is the first year of life, and this should be taken into account when considering nontransplant surgery (155). It is to be emphasised that surgery in children with advanced IFALD should be approached with caution, especially in the presence of portal hypertension, low platelet count, and prominent abdominal veins that confer high risk of bleeding and surgical failure. Children with IF have a high incidence of acalculous cholecystitis, biliary sludge,

and gallstones (156), from a combination of disordered enterohepatic bile salt circulation (eg, following ileal resection (157)) and reduced secretion of cholecystokinin. Thus, cholecystectomy should be considered during any laparotomy if there is evidence of inspissated bile syndrome or gallstones (158). Primary anastomoses following resection, and closure of a stoma as soon as possible when primary anastomosis has not been feasible, are important surgical considerations (159). Restoring bowel continuity with any unused portion of small bowel or colon may prevent or ameliorate IFALD by improving the enterohepatic circulation and increasing absorptive capacity and enteral feed tolerance.

A large proportion of children with SBS eventually develop bowel loop dilatation, for anatomical or functional reasons (160). Abnormal transit time, SBBO, and translocation of bacteria and toxins to the portal circulation may lead to liver inflammation and impaired bile excretion, with further progression of IFALD (161). Two lengthening techniques have become popular: the serial transverse enteroplasty and the longitudinal intestinal lengthening and tailoring. Whereas the more complex longitudinal intestinal lengthening and tailoring procedure involves the longitudinal dissection of a dilated loop of the small bowel between the peritoneal leaves of the mesentery, the serial transverse enteroplasty technique takes advantage of a surgical stapling approach applied sequentially from alternate sides of the bowel loop, creating a “zig-zag” channel of approximately 2 cm in diameter (3). Surgical procedures should be considered in any patient on long-term PN with bowel dilatation (162,163). If bowel reconstruction produces an increased tolerance of enteral feed, improves transit time, and reduces bacterial overgrowth, this may theoretically have a positive effect on prevention or resolution of IFALD (164,165).

Recommendation. The complexities of IF management mandate a joint medical–surgical approach, including consideration of nontransplant surgery when there is dilated small bowel and a complicated clinical trajectory.

Practice Point. Optimal timing of lengthening procedure is undefined, and likely to vary according to individual patient characteristics. Gut growing potential is maximum in the first year of life, and while on the one hand early surgery may restore continuity and normal-sized loops, on the other hand many children can be expected to achieve enteral autonomy through gut adaptation without lengthening surgery simply through time. Bowel reconstruction may be justified only when there is limited enteral feed tolerance, recurrent sepsis, rapidly progressive IFALD, or the need to restore small bowel continuity.

Research Needs. Studies are required to test the efficacy of lengthening techniques in preventing IFALD through the achievement of bowel adaptation. Robust and simple methods for diagnosing SBBO and assessing gut motility before and after surgical intervention are warranted.

Surgical Options for Intestinal Tx

Planning surgery should take into account the degree of IF, the nature of the underlying disease (eg, microvillous atrophy with its specific liver disease (166)), and the anti-human leukocyte antigen presensitisation.

Isolated Small Bowel Tx

Isolated small bowel Tx is appropriate only when IFALD is mild or moderate, with neither jaundice nor portal hypertension (167–169).

Combined Liver and Small Bowel Tx

Combined liver and small bowel Tx is the usual approach for a patient with severe IFALD (167,169,170). The liver and small

bowel are retrieved and implanted en bloc, with neither biliary nor portal vein reconstruction. The native portal vein is anastomosed to the inferior vena cava, the donor jejunum to the recipient proximal jejunum, and an ileostomy is created from the distal ileum. The pancreas may be included in the graft, as well as the right colon, for congenital enteropathies or motility disorders (171). The ileostomy is reversed several months later, the timing being influenced by post-Tx events such as rejection and stoma prolapse, as well as Tx centre protocol (169,172).

Multivisceral Tx

This strategy is necessary for patients with both IFALD and extensive motility disorders involving the foregut (ie, chronic intestinal pseudo-obstruction syndrome, long-segment Hirschsprung disease), and those with severe portal hypertension, where high risk of perioperative bleeding limits the dissection and the vascular reconstruction that may be performed (aorta and vena cava only need to be reconstructed in this type of Tx). The graft includes the whole digestive tract, with all or part of the stomach, down to the ileum or right colon, together with the liver and the pancreas (167,169,170). Splenectomy is usually performed and may lead to specific complications such as infections and graft-versus-host disease (172).

Isolated Liver Tx

Isolated liver Tx is indicated in a patient with severe IFALD and SBS in whom intestinal adaptation to the point of enteral autonomy is believed to be prevented only by portal hypertension (173–175). The criteria are established IFALD; at least 50 cm of functional small bowel in the absence of an ileocaecal valve, or 30 cm with the valve; at least 50% of the estimated daily calorie requirement previously tolerated as enteral feeds together with weight gain. The problem of biliary drainage may be an important technical problem. IF-related post-Tx complications are frequent, and this difficult procedure should be performed only in an experienced IF and Tx centre.

Results of Intestinal Tx

Depending on age, indication, and general status of the patient, 1-year survival following intestinal Tx is approximately 80% (170,176,177). Late graft loss and late death may occur. In the Intestinal Transplant Registry, the 10-year patient survival is approximately 40%, with a lower graft survival rate. At least 10% to 20% of the survivors need partial PN or intravenous fluids. The mortality rate of patients who return to long-term PN after needing removal of the intestinal graft is usually not recorded. Surgical mortality has declined in the last 10 years owing to earlier referral, better general condition of patients, improvements in immunosuppression, and control of post-Tx infections (170,172,176,177), but the tolerance of the graft in the long term remains poor. Intestinal Tx remains a major challenge and presently should be considered only for patients with chronic IF and life-threatening complications of long-term PN.

Recommendation. Patients with chronic IF (severe SBS, congenital enteropathies, severe dysmotility), and complications of long-term PN, should be discussed at an early stage with a Tx centre to develop a management strategy aimed at minimising risks and facilitating prompt referral for assessment should complications ensue.

Practice Point. Discussion should be held with a Tx centre as soon as early signs of IFALD appear, even when Tx is not yet

indicated. Evaluation of the severity of liver disease should not delay the referral. Waiting until IFALD is established before making a referral reduces the potential for successful outcome following Tx.

Research Needs. Trials exploring possible strategies to improve intestinal transplant tolerance are strongly advocated.

BENEFITS OF TREATMENT IN AN IF CENTRE

IF in children is a rare disease mandating an integrated and individualised approach to management (PN, EN, proper timing for whatever surgery is indicated), for the effective prevention of major complications including IFALD (1,4). An IF rehabilitation centre should have a multidisciplinary team including specialised paediatricians, paediatric surgeons, pharmacists, dieticians, and nutrition nurses (178). If intestinal Tx is not performed in this centre, there should be good networking arrangements with a Tx centre to which the patient can be referred. If necessary, consultation with the IF centre, video- or telephone-conferencing, and transfer if required should be a simple process because shared care will benefit the patient and the referring centre.

Criteria for referral to an IF centre are as follows:

1. Diagnostic uncertainty regarding cause of IF
2. Facilitation of home PN
3. Development of serious complications of PN, including IFALD
4. Discussion of nontransplant surgery or intestinal Tx

It should be remembered that IFALD may develop quite late, and without signs and symptoms, especially in children subjected to multiple operations. Isolated hyperbilirubinaemia ($>20 \mu\text{mol/L}$ of conjugated bilirubin) is therefore a “red flag” that must alert to the possibility of disease progression.

Additional criteria for referral include the following:

1. Bilirubin persistently $>100 \text{ mmol/L}$ for at least 2 to 4 weeks
2. Low platelets causing suspicion of portal hypertension
3. Bleeding from varices or stoma
4. Deranged synthetic function (prolonged clotting)

SUMMARY OF RECOMMENDATIONS

IFALD is multifactorial in origin. Optimal management requires the skills of an experienced multidisciplinary nutritional care team thoroughly familiar with this condition, aware of the potential for progression, and using the following management strategies to reduce risk:

1. Early and careful consideration of risk in newly diagnosed patients
2. Early introduction and optimisation of enteral feeds
3. Familiarity with dose and type of LEs (depending on local experience)
4. Primary prevention and prompt and effective management of CVC infection
5. Recognition of possible SBBO, and medical or surgical treatment strategies

Progression of IFALD should prompt early discussion with an experienced intestinal rehabilitation and transplant team, for consideration of further management including transplant options. The severity of IFALD should be established, bearing in mind that the results of endoscopy and liver biopsy can be misleading. It is essential that detailed consideration of Tx should take place before the development of end-stage liver disease.

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