Abnormal liver function tests in the parenteral nutrition fed patient

S M Gabe,[1,2] A Culkin[1]

[1]Lennard-Jones Intestinal Failure Unit, St Mark's Hospital, Harrow, UK
[2]Division of Surgery, Oncology, Reproductive Biology and Anaesthetics, Imperial College, London, UK

Correspondence to
Dr S M Gabe, Lennard-Jones Intestinal Failure Unit, St Mark's Hospital, Watford Road, Harrow HA1 3UJ, UK;
s.gabe@imperial.ac.uk

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Liver dysfunction is common in individuals receiving parenteral nutrition (PN) and particularly in neonates and infants. Abnormalities of liver function tests in patients receiving short term PN are usually transient but in individuals receiving long term PN, substantial liver damage and ultimately end stage liver disease may occur. The aetiology is complex, involving a large number of patient related and nutrition related factors. The terminology intestinal failure associated liver disease (IFALD) is therefore more appropriate than PN associated liver disease. Effort should be made to prevent liver dysfunction by managing sepsis, avoiding parenteral overfeeding, employing cyclical parenteral feeding and encouraging enteral nutrition where possible. Intake of soybean based parenteral lipid emulsions should be reduced in individuals with established IFALD, possibly to be replaced by lipid emulsions containing medium chain triacylglycerol, monounsaturated fatty acids or fish oil although larger clinical studies are needed. Similarly, evidence supporting the widespread use of parenteral choline and taurine supplementation in the prevention or treatment of IFALD remains limited. There are more data to support the use of oral antibiotics to treat bacterial overgrowth and oral ursodeoxycholic acid in neonates. Ultimately, severe IFALD may necessitate referral for small intestine and/or liver transplantation.

Introduction

Since it was developed in the second half of the 20th century, parenteral nutrition (PN) has become established as a life saving treatment for patients with intestinal failure. However, patients receiving PN are at risk of developing hepatic complications. PN associated liver disease was first described in the early 1970s.[1] The incidence of hepatic dysfunction, possible aetiologies and strategies to avoid and manage these complications will be discussed. The term intestinal failure associated liver disease (IFALD) is used in place of PN associated liver disease in this review as the liver dysfunction that occurs in patients on PN may be caused by factors other than PN.

Incidence of liver dysfunction in patients receiving PN

Short term home parenteral nutrition

Abnormalities of liver function tests (LFTs) are common in adults with acute intestinal failure receiving short term PN. Early reports[2] describe the development of abnormal LFTs occurring after only 2 weeks of a lipid free PN with a high glucose content (elevated aspartate aminotransferase, alkaline phosphatase and bilirubin concentrations in 68%, 54% and 21% of patients, respectively). More recent reports in which more balanced parenteral regimens are used[3] describe less frequently abnormal LFTs although this is still clearly a common phenomenon (after 4 weeks of PN, aspartate aminotransferase, alkaline phosphatase and bilirubin concentrations were elevated in 27%, 32% and 31% of patients, respectively). In general, these elevations are mild, often normalise even if PN is continued and usually resolve fully once it is discontinued,[4] possibly also due to the initiation of enteral feeding. A more recent audit of patients revealed that 34% patients had abnormal LFTs before PN was started.[5] In those patients, LFTs worsened in 60% and resolved in 30% while receiving PN. Only 9% of patients developed abnormal LFTs during PN. For patients who developed abnormal LFTs or worsening LFTs on PN, the underlying cause was thought to be sepsis in 46% and the underlying liver disease in 24%.

Abnormalities of LFTs observed in patients receiving acute PN are therefore significantly influenced by factors relating to underlying disease, especially ongoing sepsis and pre-existing liver disease.

Long term PN

The incidence of abnormal LFTs, abnormal liver histology and more advanced

liver disease in adults receiving long term home parenteral nutrition varies between studies (table 1).

IFALD is very common in neonates and infants. Unlike adults, intrahepatic cholestasis rather than steatosis is the commonest finding, perhaps reflecting the immaturity of the biliary excretion system in neonates. Neonatal cholestasis relates closely to birth weight, prematurity and duration of PN.[6 7] Ninety per cent of neonates who are receiving PN for >3 months develop cholestasis.[6] Neonatal cholestasis is also related to bacterial and fungal sepsis and is often rapidly progressive with hepatic failure occurring in 17% of patients.[8]

Liver histopathology in patients receiving PN

Abnormal LFTs in adults receiving short term PN are characterised by hepatic steatosis, with accumulation of macro- and microvesicular fat within the hepatocytes, which may be accompanied by an extent of steatohepatitis.[4] These abnormalities are strongly influenced by the underlying disease, state especially ongoing sepsis. Abnormal liver histology correlates more closely with the presence of intra-abdominal sepsis, renal failure and pre-existing liver disease than with the use of PN.[9]

For patients who develop abnormal LFTs receiving long term PN, the commonest histopathological features include intracellular and intracanalicular cholestasis, macrovesicular steatosis, microvesicular steatosis and periportal fibrosis. Other features include hepatocellular injury, multinucleated giant cells, phospholipidosis, portal inflammation, acute cholangitis, extramedullary haematopoiesis, bile duct proliferation, varying degrees of fibrosis and cirrhosis[10 11]

Table 1 Abnormal liver function in patients on long term parenteral nutrition

Reference	Liver function abnormality	Rate of abnormality in HPN patients (%)	Note
Luman[12]	Abnormal LFTs	48	↑Alkaline phosphatase commonest abnormality
Salvino[63]	Abnormal LFTs	95	
Cavicchi[10]	Chronic biochemical cholestasis*	65 after 6 months	High lipid content in PN
Lloyd[13]	Chronic biochemical cholestasis*	24	Point prevalence
Ito[64]	Advanced liver disease†	19	
Chan[65]	Advanced liver disease†	14	
Cavicchi[10]	Complicated liver disease†	26 at 2 years 50 at 6 years	High lipid content in PN
Salvino[63]	Severe liver disease‡	4	

*Persistent elevation to >1.5 times the upper limit of the normal range for >6 months of two of three biochemical variables (alkaline phosphatase, γ-glutamyl transferase and conjugated bilirubin).
†Fibrosis or cirrhosis.
‡Combination of total bilirubin >3 mg/dl, albumin <3.2 g/dl and prothrombin time >3 s prolonged.
HPN, home parenteral nutrition; LFTs, liver function tests; PN, parenteral nutrition.

Aetiology of IFALD

The aetiology of hepatic dysfunction in both adults and children receiving PN is complex and multifactorial. The possible aetiological factors can be divided into four groups (figure 1).

Patient dependent causes

Abnormalities of LFTs may relate to underlying liver disease in patients receiving PN rather than the effects of the PN itself. Other causes include the following.

Sepsis The presence of sepsis is an important precipitant of cholestasis in neonates and of abnormal LFTs in adults receiving short term PN. In addition, bacterial overgrowth can lead to cholestasis via generation of cholestatic secondary bile acids from the bacterial dehydroxylation of chenodeoxycholic acid,[4] endotoxaemia and bacterial translocation.

Intestinal anatomy IFALD has been shown to be related to small intestinal length in a number of studies. One study has reported that a small intestinal length of <1 m is associated with abnormal LFTs in adults receiving long term PN[12] while another study has reported an increased risk of chronic cholestasis in adults with a small intestinal length of <0.5 m.[10] The presence or absence of colon in continuity with the small intestine has also recently been associated with the development of IFALD.[13] Some authors have postulated that short bowel predisposes to liver dysfunction as a result of impairment of enterohepatic bile salt circulation and abnormal bile acid metabolism.[10] Others have argued that bowel length may simply be a surrogate marker of parenteral energy requirement.[12 13]

Infant prematurity IFALD is common in neonates with the smallest premature infants being the most

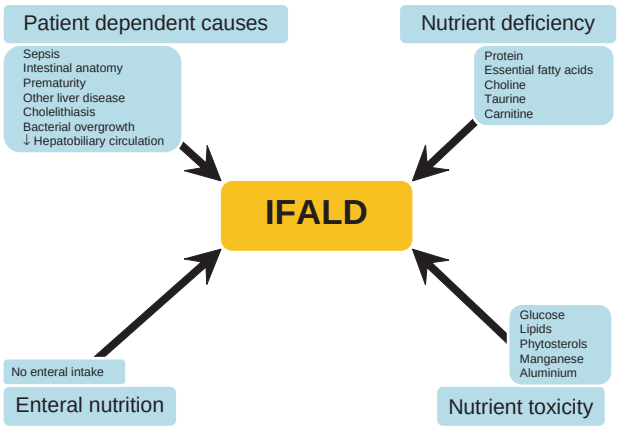

Figure 1 Factors implicated in the aetiology of intestinal failure associated liver disease (IFALD).

susceptible.[6 7] This may be due to immaturity of the hepatic transport mechanisms and metabolism of bile acids. Abnormalities have been demonstrated in neonates affecting bile acid synthesis and conjugation,[14] hepatic uptake and secretion,[15] and intestinal uptake and recirculation of bile acids.[16]

Lack of enteral nutrition Reduced enteral nutrition is associated with an increased reliance on PN. It is difficult to know if the increased risk of liver dysfunction in individuals with very little oral intake is a result of the lack of enteral nutrition or the effects of parenteral feeding. Fasting coupled with total PN reduces the secretion of a number of gastrointestinal hormones, including gastrin, motilin, pancreatic polypeptide, insulinotropic polypeptide and glucagon.[17] This reduction may reduce intestinal motility, promoting bacterial overgrowth, and may predispose to biliary stasis.

Nutrient deficiency Hepatic steatosis develops in kwashiorkor as there is insufficient protein for the manufacture of very low density lipoprotein (VLDL), which is needed for hepatic triacylglycerol (TAG) export.[18] However, patients receiving PN should receive adequate amino acids for VLDL synthesis. Steatosis also occurs in essential fatty acid deficiency[19] but this occurs rarely in patients on PN, unless fat free parenteral regimens are used in individuals with little or no enteral lipid intake.

It has been proposed recently that deficiencies of a number of methionine metabolites, such as carnitine, choline and taurine, may be responsible for both steatosis and cholestasis in patients receiving PN. Orally ingested methionine can be converted to these metabolites via hepatic trans-sulphuration pathways although these pathways are underdeveloped in premature infants.[20] Methionine administered parenterally to the systemic circulation rather than to the portal circulation is also transaminated to mercaptans, hence reducing the synthesis of carnitine, choline and taurine.[21]

Carnitine Carnitine is involved in the transport of long chain fatty acids across the mitochondrial membrane so that they can undergo oxidation. In deficiency states in which carnitine levels are very low (<10% normal levels), hepatic steatosis can develop.[22] Plasma carnitine is about 50% normal levels in patients receiving PN, which is considerably higher than in patients with a congenital or acquired deficiency.[23 24] Intervention studies have failed to show any benefit of parenteral carnitine supplementation in patients receiving long term PN in relation to hepatic abnormalities.[25]

Choline Choline is required for the synthesis of VLDL and hence hepatic TAG export. Plasma choline concentrations are low in >90% of patients receiving PN[26] and deficiency results in impaired hepatic TAG secretion and subsequent steatosis.[26] Choline deficiency in patients receiving PN has been shown to correlate with elevated transaminase levels and steatosis in adults and children.[26 27] Small studies have shown that these abnormalities can be reversed by either oral or parenteral choline supplementation.[28 29]

Taurine Taurine is important for bile salt conjugation, particularly in preterm infants. It promotes bile flow and attenuates the cholestatic effects of secondary bile salts such as lithocholate.[30] Taurine deficiency in neonates is associated with cholestatic liver disease[31] and this can be prevented by parenteral taurine supplementation.[32] Plasma and biliary taurine concentrations are also low in adults with a short bowel[33] and supplementation may improve plasma taurine but not biliary taurine concentrations.[33] Intervention studies have not demonstrated a significant benefit of parenteral taurine in adults.

Antioxidants Individuals receiving PN may be deficient in antioxidants, in particular vitamin E and selenium.[34] Increased oxidative stress might predispose to lipid peroxidation of hepatic lipid stores resulting in inflammation and steatohepatitis.[35] However, studies in children suggest that the occurrence of IFALD is independent of oxidant load.[36] In addition, there is little evidence that antioxidant levels are depleted in patients receiving PN, and vitamin E is commonly added to intravenous lipid emulsions.[35]

Nutrient toxicity

Glucose Early PN formulations contained large amounts of energy supplied as glucose, and infusion rates often exceeded the maximum glucose oxidation rate. Glucose infusion at rates of >5 mg/kg/min result in steatosis[37] by stimulating insulin release (stimulating hepatic lipogenesis and acylglycerol production) and inhibiting mitochondrial fatty acid oxidation,[38] resulting in a build up of TAG within hepatocytes. The adverse effects of insulin hypersecretion may also explain why continuous PN infusions are associated with a greater extent of hepatic dysfunction than cyclic infusion. Allowing ≥8 h each day without parenteral glucose infusion has been shown to lower insulin levels and improve LFTs.[39]

Lipid The replacement of a proportion of glucose energy with parenteral lipid has been shown to reduce the incidence of steatosis.[40] However, excess lipid may also increase hepatic complications. Very high parenteral lipid intakes of >4 g/kg/day may result in lipid overload due to the inability of the reticuloendothelial system to clear large amounts of polyunsaturated fatty acids and phospholipids.[41] More modest parenteral lipid intake is also associated with IFALD. The parenteral intake of soybean based lipid emulsions of >1 g/kg/day is associated with a 2.3-fold increased risk of chronic cholestasis and a 5.5-fold increased risk of advanced liver disease (fibrosis or cirrhosis).[10] Postulated mechanisms include impaired phospholipid excretion,[10] inhibition of hepatic TAG release[12] or the accumulation of phytosterols.[42]

Second generation (medium chain triglyceride/long chain triglyceride mixtures and monounsaturated fatty acids) and third generation (fish oil, multiple combination lipids) lipid emulsions are associated with fewer hepatic complications[43–45] although more definitive studies are required before these become routine practice.

Other components A number of other components of parenteral infusions have been suggested to cause IFALD. High amino acid content is suggested to promote cholestasis in neonates.[46] Manganese and copper are both excreted via the biliary route and can accumulate in cholestasis, exacerbating hepatic dysfunction.[47 48]

Management of IFALD

The strategies used in the management of IFALD are illustrated in figure 2.

Treatment of non-nutritional causes

Given the importance of sepsis as a causative factor for IFALD, it is vital that every effort is made to reduce its incidence. Intra-abdominal sepsis should be treated using a procedure that is clinically appropriate, usually with a combination of antibiotics and/or minimally invasive drainage procedures. It is also important to avoid central venous catheter associated sepsis. Efforts to reduce bacterial overgrowth have been more successful in neonates than in adults, suggesting a greater pathophysiological role in the former. Several small studies have suggested that antibiotics such as metronidazole and gentamicin may reduce the incidence of cholestasis in both neonates and adults receiving PN.[49–51]

Cholelithiasis is common in both adults and children receiving PN due to a combination of factors, including reduced oral intake, ileal resection, weight loss and drug treatment.[34] The incidence of biliary sludge in adults receiving PN has been estimated to approach 100% after >6 weeks of treatment[52] and gallstones have been demonstrated to form in 45% of patients with short bowel syndrome.[53]

Medications, especially antibiotics, are a common cause of abnormal LFTs and should always be considered in a patient receiving PN with abnormal LFTs. All hepatotoxic medication should be minimised.

Adjustments to parenteral and enteral nutrition

It is important not to overfeed patients receiving PN, given the deleterious effects of infusion of excess parenteral glucose and lipid described earlier. Both USA and UK guidelines suggest a total daily energy intake of 105–146 kJ (25–35 kcal)/kg and a daily protein intake of 0.8–1.5 g/kg,[54 55] although more accurate assessment of the basal metabolic rate and energy requirements can be made by performing indirect calorimetry. Given that the majority of patients receiving long term PN will continue to eat, it is also necessary to estimate enteral energy and protein absorption and reduce parenteral provision accordingly. It is important to try to maximise either oral or enteral nutrition as this will counteract the adverse effects of fasting, reduce parenteral requirements and promote intestinal adaptation.

The optimal dose and type of parenteral lipid that should be provided to minimise hepatic dysfunction remains unclear. In patients who have no enteral intake, some parenteral lipid is needed to prevent essential fatty acid deficiency.[54] A linoleic acid intake of 2–4% total energy intake is adequate for this purpose[56] and, given the very high linoleic acid content of soybean based lipid emulsions, this level of intake is easily achievable. US guidelines suggest that parenteral lipid should supply 20–30% total energy and the daily intake should be <2.5 g/kg and ideally <1.5 g/kg.[54] Evidence suggests that the intake of soybean based lipid should be <1.0 g/kg/day.[10] Second and third generation lipid emulsions may be considered for patients with IFALD. However, generally it is sufficient to decrease the lipid prescribed rather than switching to a different lipid emulsion.

Finally, cyclical rather than continuous PN should be administered to minimise the adverse effects of prolonged insulin hypersecretion. Allowing an 8 h break from PN has been shown to improve LFTs and reduce insulin levels.[39] Cyclical PN also allows greater patient freedom, which may be associated with an improved quality of life in patients receiving long term PN.[55] At a practical level, this is achieved by slowly increasing the PN infusion rate and checking for hyperglycaemia. In diabetic patients it is more important to achieve tight glucose control and this may limit or preclude cyclical PN.

Pharmacological treatment

Ursodeoxycholic acid (UDCA) is an exogenous bile acid which promotes bile flow and is used in primary biliary cirrhosis and cholelithiasis. Several studies in neonates with short bowel and IFALD have shown a benefit of 10–30 mg/kg/day UDCA on LFTs.[57 58] Evidence of a benefit of UDCA in adults is limited to a single study showing that treatment with oral UDCA reduced γ-glutamyl transferase and alanine aminotransferase concentrations.[59] UDCA may also worsen diarrhoea in some individuals.

Plasma choline and taurine concentrations are reduced in patients receiving PN. Multivariate analysis of data collected as part of a larger multicentre trial suggests that parenteral taurine reduces the incidence of cholestasis in severely premature infants and those with necrotising enterocolitis.[32] There is considerably less evidence of a benefit of taurine supplementation in adults, with a reduction in aspartate aminotransferase levels being reported in a single small study of adults receiving long term PN.[33] Choline supplementation in adults has been shown to be associated with a reduction in hepatic steatosis and improvements in LFTs.[29] However, availability and stability issues prevent its use at the moment.

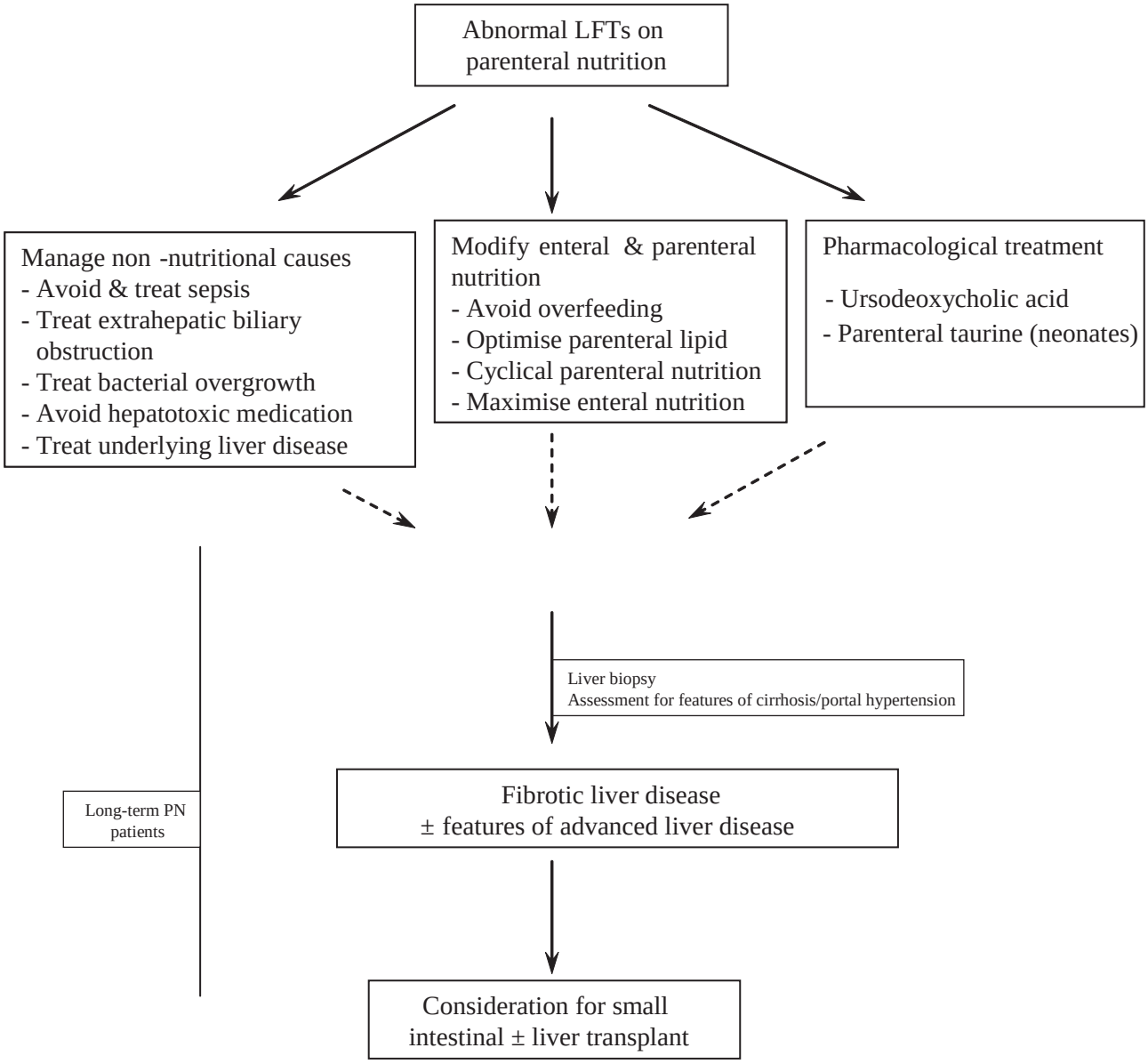

Figure 2 Management of intestinal failure associated liver disease. LFTs, liver function tests; PN, parenteral nutrition.

Small intestinal and liver transplantation

Impending or overt liver failure associated with IFALD is recognised as an indication for small intestinal transplantation,[54] and IFALD is one of the commonest reasons for performing intestinal transplantation.[60] UK transplant units have suggested consideration of transplantation only if there is portal hypertension, cirrhosis or bridging fibrosis.[61] In neonates and infants, for whom there is the possibility of an intestinal adaptation with weaning from PN, transplantation of liver alone, which has a considerably better outcome than combined small intestinal and liver transplantation, may be possible as a bridging measure until enteral nutrition is established. In the meantime, the selection of patients for intestinal transplantation (with or without a liver transplant) presents a considerable challenge and recent consensus guidance is now published.[62]

Competing interests None.

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