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REVIEW ARTICLE

The hepatobiliary complications of malnutrition and nutritional support in adults

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Abstract

Hepatobiliary complications of hypoalimentation and parenteral nutrition (PN) are widely recognised. Hypoalimentation includes conditions such as anorexia nervosa (AN), obesity malnutrition and liver disease following bariatric surgery. Treatment of the underlying condition causing hypoalimentation can result in an improvement in liver dysfunction. Liver function test abnormalities are also commonly found in patients on PN, with the three main complications being steatosis, cholestasis and biliary system sludge/stones. Patients with intestinal failure receiving PN often have multiple possible aetiologies for liver dysfunction (rather than solely caused by the PN); hence, it is now more commonly referred to as intestinal failure-associated liver disease (IFALD). Liver enzyme abnormalities are very common with long-term PN use and do not always help with monitoring progression of IFALD. A systematic approach is required for investigating liver function abnormalities related to PN. The key management in IFALD is through prevention of sepsis, promoting intestinal health and restoring intestinal continuity where possible. A variety of imaging modalities can be used to investigate, and monitor, the liver disease. Most importantly, patients on PN for more than 28 days should be managed in a large centre with experience in managing intestinal failure to minimise the risk of such complications. Early identification of liver dysfunction is essential and, should it progress despite the above measures, early discussion with an intestinal transplant centre should be encouraged.

Keywords Cholestasis · Gallstones · Hepatobiliary · Hypoalimentation · Intestinal failure-associated liver disease · Intestinal transplantation · Parenteral nutrition · Steatosis

Introduction

In 1971, Peden and colleagues first described parenteral nutrition (PN) as a cause of hepatic dysfunction [1]. Since then, hepatobiliary complications related to malnutrition and artificial nutrition have been widely reported, particularly for patients receiving PN [2]. Patients with short bowel syndrome (SBS) who require long-term parenteral nutrition are at risk of development of liver disease and cholelithiasis [3]. Liver disease has also been noted to complicate severe hypoalimentation, such as in anorexia nervosa. Hypoalimentation is a term used to describe insufficient or inadequate nutrition.

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Aims

The aim of this article is to review the hepatobiliary complications of malnutrition and nutritional support in adults, focusing on hypoalimentation and liver disease associated with parenteral nutrition. Prevention and treatment strategies available will be discussed and will include a practical guide for the investigation and management of intestinal failure-associated liver disease (IFALD).

Hypoalimentation

The following conditions are due to hypoalimentation and are recognised to have hepatobiliary complications.

Anorexia nervosa

Anorexia nervosa (AN) is a difficult to treat body image disease. Mild liver injury is regularly detected as a complication

of AN but acute hepatitis with transaminases over 1000 IU/ml and deep coma has also been reported [4].

The mechanism of hepatic dysfunction appears to be multifactorial. Moderate transaminitis is most common and felt to reflect protein-energy malnutrition (PEM) states causing a fatty liver [5]. Histological analysis has suggested a causative factor may be hepatocyte glycogen accumulation and steatosis due to an imbalance between hepatic triacylglycerol synthesis and secretion [6]. In severe cases, decreased cardiac output causes a decrease in portal pressure, leading to hepatocyte hypoxia [7].

A recent study investigating hypertransaminasemia in patients with AN found the only independent risk factor for hepatic cytolysis was a BMI < 12 indicating a strong link between severe malnutrition and liver dysfunction [8]. Furthermore, numerous case reports have demonstrated rapid improvement in liver function tests in such patients with increased calorie consumption and weight gain [9].

Obesity malnutrition

Obesity has been projected to surpass tobacco use as the most economically important modifiable risk factor in public health and disease [10]. Obesity malnutrition is an adequate, or excess, daily calorie intake but inadequate intake of the necessary macro- and micro-nutrients, causing deficiencies [11]. Non-alcoholic fatty liver disease (NAFLD) is relatively common in the general population with a prevalence of approximately 9% [12]. This figure is much greater in obese individuals, with figures from 30 to 95% in such a population [13]. NAFLD contains a broad spectrum of liver disease, ranging from simple steatosis to cirrhosis. The crucial stage in the progression of NAFLD to advanced liver disease is non-alcoholic steatohepatitis (NASH). Fat accumulation occurs when the input, uptake or synthesis exceeds the liver's ability to degrade or export these lipids [12]. Deficiencies in vitamin D, thiamine, chromium and biotin have all been found in obese individuals [10].

A further reason for increased rates of liver disease in obese populations is the higher rate of development of diabetes mellitus. Obesity increases the risk of developing type 2 diabetes fourfold [14]. As there is an increased risk of NAFLD in diabetic individuals, it follows that obesity, and therefore obesity malnutrition, is strongly linked to liver disease [15].

Liver disease following bariatric surgery

Bariatric surgery is generally reserved for patients with severe obesity (BMI > 40 kg/m^2) or those with BMI > 35 kg/m^2 and major comorbidities such as hypertension, type 2 diabetes, heart failure and sleep apnoea [16]. Rapid weight loss with fasting and gastric bypass surgery may decrease hepatic fat content but can also induce hepatic inflammation and exacerbate NASH [17]. Therefore, gradual weight loss post-surgery is favoured in order to prevent development, or progression, of liver disease. Fifty to 70% of excess body weight (the difference between the patient's pre-operative weight and the ideal body weight) lost over 2–3 years is the expected outcome following bariatric surgery [18].

Malnutrition with co-existent liver disease

Co-existent liver disease can also complicate malnutrition and many patients with advanced liver disease will have malnutrition but these areas are well described in the literature and are not the focus of this paper.

Management of hypoalimentation

Introduction of adequate nutrition to patients with anorexia nervosa has been shown to reverse the liver abnormalities [9]. In obese individuals with NAFLD, weight loss of even 10% has been shown to correct the abnormal liver function as well as reduce the hepatic fat content [12]. When bariatric surgery is used in the management of obesity, subsequent significant weight loss may improve, or even reverse, the degree of hepatic steatosis and fibrosis in patients with NASH [19]. Hypoalimentation is a well-recognised cause of liver dysfunction and management of the underlying cause of hypoalimentation, rather than the subsequent liver disease, can result in an improvement of the liver impairment.

Intestinal failure-associated liver disease

Intestinal failure is defined as 'the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth' and can be divided into three sub-types [20]. Type 1 intestinal failure is short term (less than 4 weeks), with a self-limiting requirement for PN and frequently follows major abdominal surgery or an admission to an intensive care unit. Such patients are generally very unwell but improve if/when the patient recovers from the acute episode that caused their intestinal failure [21]. Type 2 intestinal failure is a short- to medium-term condition and is commonly caused by intestinal resection, obstruction, inflammation, fistulisation or the effects of sepsis on the intestine. Often, it is not just one of these factors, but a combination that leads to the intestinal failure. Control of sepsis must be the primary aim, before improvement of nutrition can be attained. Specialist management of such patients is essential in order to reduce the likelihood of type 3 intestinal failure developing [22].

Type 3 intestinal failure is a chronic condition, generally requiring long-term nutritional support. They are typically metabolically stable but unable to absorb sufficient fluid,

nutrients or food via the intestinal tract, thus requiring nutritional support. Both type 2 and type 3 intestinal failures should be managed in specialist centres, where multi-disciplinary teams are experienced in managing such patients, due to their complex needs [22].

Nutritional support is a vital part of the standard care of critically ill patients as well as those with an inaccessible or non-functioning GI tract [23]. PN is often the mechanism for delivering this support. All patients receiving PN are at risk of developing a range of hepatobiliary complications. The incidence of liver disease is concerning in adult patients on longer-term PN and was investigated in a French study of 90 patients with type 3 intestinal failure [24]. Chronic cholestasis was seen in 58 patients (65%) after a median of 6 months. The rate of complicated liver disease ranged from 26% at 2 years to 50% at 6 years, suggesting a proportional increase in rates of IFALD with duration of treatment [24].

Although generally multifactorial, PN is commonly blamed as the sole causative agent for the liver dysfunction and it is commonly referred to as parenteral nutrition-associated liver disease (PNALD). Intestinal failure-associated liver disease (IFALD) is a more accurate terminology as other factors can contribute to the liver dysfunction.

Studies from various investigating groups suggest that life-threatening liver disease caused by PN is rare, but when it occurs, it appears to be associated with recurrent sepsis due to venous catheter infections, small intestinal bacterial overgrowth or a complication of multiple drug therapy [25]. Prognosis on long-term PN is generally good with the outcome related to the underlying condition. Patients with inflammatory bowel disease have a 5-year survival of approximately 92% whilst those with underlying malignancy have a 1-year mortality rate of 70% [26].

Mechanisms

There are three main categories of hepatobiliary disorders associated with parenteral nutrition: steatosis, cholestasis and biliary system sludge/stones [24]. These are not discrete and overlap can exist.

Steatosis

Steatosis is a relatively early complication of PN in adults, commonly found in patients after only 5 days of treatment and is a result of the accumulation of fat globules in hepatocytes without evidence of inflammation, cholestasis or necrosis [27].

Initially, the fat accumulation is periportal, but with more severe steatosis, the fat distribution is more panlobular or centrilobular [28]. It is the predominant hepatic histological abnormality seen in patients receiving PN with elevated liver enzymes and is a relatively benign, reversible and non-progressive condition [3]. It is rarely symptomatic in patients, and only then due to hepatomegaly [3].

Development of steatosis is thought to be due to excess calorie content of PN, especially in the form of carbohydrates [3]. The predominant liver function abnormality is elevated transaminases. Impairment of hepatic triglyceride secretion leads to steatosis [27, 29]. Fat deposition has been postulated to occur as a result of insulin release which promotes lipogenesis and inhibits carnitine which is a rate-limiting enzyme in fatty acid oxidation [30]. Therefore, the addition of lipid to PN leads to a reduction in the levels of dextrose and glucose infused, and steatosis appears to be reduced [31].

Excess lipid can also be detrimental to liver function. It has been reported that the amount of lipid delivered via PN is related to the risk of developing liver disease (with greatest risk at >1 g/kg/day) and inversely related to the residual length of small intestine [24]. Lipid content in PN is also important as it leads to macrophage activation resulting from excess omega-6 polyunsaturated fatty acids (ω-6 PUFA), thus causing hepatic phospholipid and phytosterol accumulation [24].

Numerous studies have suggested that replacing soy-based lipid components of PN with fish oil-based lipid could reverse IFALD, reduce the need for liver transplantation and decrease the death rate on treatment [32]. This is due to reducing the amount of ω-6 PUFA and increasing the levels of omega-3 polyunsaturated fatty acids (ω-3 PUFA). The postulated mechanism of action is through the anti-inflammatory properties of ω-3 PUFA which appear to inhibit tumour necrosis factor-α (TNFα) and other cytokines, thus reducing hepatic inflammation [33].

Cholestasis

A mixed lymphocytic and neutrophilic periportal infiltration is the initial histological picture caused by cholestasis, before progression to fibrosis and eventually the development of cirrhosis [3]. Cholestasis is very common in children receiving PN, thought to be due to the immaturity of the biliary secretory system, whilst in adults, it typically affects only those on long-term PN [34]. Peak enzyme levels commonly occur 1–4 weeks post-commencement of PN and these are usually mild and transient, falling even with continuation of therapy [28, 34]. The most commonly raised liver enzyme is alkaline phosphatase (ALP) along with a rise in bilirubin [29]. Although common, elevations in gamma-glutamyl transferase (GGT) tend to be less specific [29].

Unlike steatosis, cholestasis is more likely to progress to cirrhosis and liver failure [35]. Cholestatic liver dysfunction may lead to cirrhosis and portal hypertension, which is an indication for combined liver/intestinal transplantation [36]. The exact mechanisms for cholestasis remain unclear but there are several theories including bacterial overgrowth causing portal endotoxaemia, resulting in secondary bile acid

production and cholestasis [35]. Bacterial translocation may also have a role [37].

Sepsis can play an important role in the development of cholestasis. The classic systemic features of leucocytosis and pyrexia may not be present in patients with intestinal failure, especially those with type 2 intestinal failure as they may have a contained intra-abdominal collection. Occult sepsis will often be manifest through abnormal liver function tests (LFTs) (including hyperbilirubinaemia), cachexia, hypoalbuminaemia and hyponatraemia [21]. Screening all IF patients admitted for possible sepsis with blood cultures (from both peripheral sites and indwelling lines), wound swabs (including MRSA swabs), urine culture, chest X-ray and possibly cross-sectional imaging is required. Further investigation for unusual sites of infections such as osteomyelitis may need to be considered if no cause is identified [21, 38].

As prevention of sepsis is paramount with PN, such patients should be managed in specialist nutrition centres, where multidisciplinary staff are experienced in the use of PN administration and where better outcomes are achieved [39]. Awareness of bacterial overgrowth and subsequent bacterial translocation and sepsis is also important and should be considered in prevention of IFALD. Antibiotics are used to reduce the occurrence of small bowel micro-organism overgrowth and such inhibition of anaerobic bacteria in the intestine also decreases the rate of cholelithiasis [40].

Continuous PN use, when compared with cyclic administration, appears to show increased rates of cholestasis [41]. However, a recent review published in 2013 cast doubt on this, with studies showing no significant difference between continuous and cyclic PN, when adjusted for confounding factors [42]. Cyclic use has been suggested to have psychological, physical and metabolic advantages over continuous PN administration and is often given over 10–16 h nocturnally rather than over 24 h [43]. This gives patients more freedom during the day, but does mean they usually have to get up during the night to urinate.

Gallstones

It is felt that the lack of enteric gallbladder stimulation leads to decreased motor activity, promoting the formation of bile sludge and increasing the risk of acalculous cholecystitis [3]. Prolonged storage of bile salts and haem metabolites in the gallbladder and reduced bile salt synthesis leads to decreased bile acid secretion [44].

A function of the gallbladder is the acidification and concentration of bile which helps protect against gallstone formation through prevention of calcium salt precipitation [45]. The predominance of calcium-based gallstones in patients on PN differs from the general population where cholesterol stones account for the majority of cases [46]. Approximately one quarter of patients on long-term PN develop gallstones and sludge develops in almost all of those on such treatment. In this study, 4 weeks after the withdrawal of PN, there was no evidence of sludge in the gallbladder [47].

Due to the high rates of gallbladder disease related to long-term PN, it has been suggested that prophylactic cholecystectomy should be performed in those on long-term PN with benign conditions and otherwise good predicted long-term survival [48].

Other important factors

Many nutritional deficiencies have been linked with IFALD. A small study published in 2005 demonstrated that administration of choline caused increased liver density and resolution of steatosis using abdominal CT for assessment. Of the four patients assessed in the trial, one patient had recurrence of steatosis 10 weeks after cessation of choline-supplemented PN [49]. The reason for choline depletion is thought to be due to impairment of the hepatic transsulfuration pathway, which converts methionine (contained in PN solution) to choline, taurine and carnitine [20, 50]. The choline deficiency leads to triglyceride accumulation, secondary to deficient very low-density lipoproteins, causing structural membrane changes and hence hepatocyte death [50].

In addition, lecithin supplementation has been shown to increase the plasma free levels of choline, thus reducing steatosis [51]. Cysteine has also been linked with decreasing steatosis and intra-hepatic lipid concentrations either on its own or in combination with choline [52].

The amino acid taurine is important for bile salt conjugation [20]. Deficiency can be attributed to a combination of reduced hepatic transsulfuration (as mentioned above) and an increased loss of bile acids following ileocolonic resection [20]. Increased glycolythocholic acid is produced through the glycine amidation of bile acids which can lead to cholestasis and damage to bile canaliculi [3]. Taurine has been shown to be depleted in malnourished patients (as well as in post-operative surgical patients) to levels of less than 50% of a control population. One study found that following only 14 days of taurine-supplemented PN, patients returned to having normal serum levels of taurine [53]. The general consensus, however, is that the evidence of benefit from supplementary taurine is limited [54].

Glutathione deficiency caused by oxidative stress has been postulated to play a role in hepatic dysfunction caused by PN. Following only 8 days of PN administration in a rat population, glutathione levels were 16% of the level of the control population and serum alanine aminotransferase (ALT) and cholylglycine levels were elevated, with steatosis evident [55]. Although a deficiency in carnitine is known to favour lipid metabolism and exchange which could lead to steatosis, it appears that L-carnitine has no beneficial effects justifying its use in patients on long-term PN [3, 56].

Along with nutritional deficiencies, many medicines have been shown to have an impact on LFTs. Nearly all classes of medications can cause a drug-induced liver injury but the commonest classes are antimicrobials and antiepileptic medications [57]. If the medication is not essential, or there is a suitable alternative, it can be stopped and the LFTs be monitored for improvement. Should the medication be essential with no viable alternative, a risk-benefit decision needs to be made.

Assessment of liver structure

Liver enzyme abnormalities are very common with long-term PN use, and therefore, traditional liver function tests do not always help with monitoring progression of IFALD [58]. Unfortunately, IFALD may have progressed to an advanced stage by the time liver dysfunction becomes apparent through laboratory investigations or physical signs. Non-invasive techniques for liver assessment could be useful for monitoring therapeutic interventions or timing transplants [59]. Liver biopsies are not routinely performed for monitoring IFALD given the potential risks associated with the procedure [60]. As well as assessing liver structure, co-existent liver disease, such as viral hepatitis and autoimmune hepatitis, should be excluded as they could also be the causative factor causing derangement in LFTs.

Ultrasound scanning (USS) provides observer-dependent measurement of hepatic steatosis, as well as being used to exclude biliary pathology such as intraductal calculi, commonly found in patients on PN (as mentioned in the previous section) [59]. CT scanning provides a semi-quantitative measurement based on density, but given the radiation dose required with CT, sequential evaluation is not appropriate [59].

Magnetic resonance imaging (MRI) and spectroscopy (MRS) allow a degree of quantification of hepatic lipid deposition without the use of such ionising radiation and can quantify hepatic steatosis [59]. Depending on the particular spectrum used in MRS, quantification can be made of choline levels (^{1}H spectra) as well as the extent of fibrosis (^{31}P spectra) [61, 62]. A small study validated MRS for evaluating the liver-associated complications of intestinal failure, including the extent of cirrhosis, and therefore, this may help to predict the need for biopsy [59]. Magnetic resonance cholangiopancreatography (MRCP) is useful at assessment of intraductal calculi, with a greater sensitivity than abdominal USS (91 vs 38%) as well as greater diagnostic accuracy (97 vs 89%) [63].

Transient elastography (TE) is another non-invasive method for assessment of liver fibrosis by measuring liver ‘stiffness’ [64]. The liver volume measured during TE is 100 times greater than that obtained through liver biopsy and is therefore more representative of the liver parenchyma [65]. As TE is well tolerated by patients, it can play a useful role in monitoring for progression/regression of fibrosis [65].

A rapidly evolving field of research is serum-based markers to detect liver fibrosis. The Enhanced Liver Fibrosis (ELF) test is a useful non-invasive method which can be used to determine the potential level of fibrosis. It consists of an algorithm comprising three fibrosis markers: hyaluronic acid, amino-terminal pro-peptide of type-III collagen and tissue-inhibitor of matrix-metaloproteinase-1. It has been found to have no significant difference in assessing for significant fibrosis and cirrhosis compared to TE, with a sensitivity and specificity of over 90% [66, 67]. In the UK, the National Institute for Health and Care Excellence (NICE) advise considering the use of ELF for patients with NAFLD as a means of testing for the presence of advanced fibrosis [68]. Other serum-based markers of liver fibrosis exist; however, they are not currently NICE approved [69].

Prevention and treatment

Intestinal rehabilitation programs can prevent liver disease by promoting intestinal motility and discouraging bacterial translocation [70]. Elements of such programs include aggressive use of enteral nutrition, control of small intestinal bacterial overgrowth, early recognition and treatment of sepsis and prevention of venous catheter sepsis.

Enteral feeding, even in small amounts, can increase gallbladder contractility, decrease gallbladder size and improve bile flow, leading to lower levels of cholestasis [71]. Therefore, enteral feeding should be re-introduced as early as possible [35]. Initial research supports the use of intravenous cholecystokinin-octapeptide (CCK-OP) in restoring gallbladder contraction and stasis to normal whilst not affecting cholesterol saturation [72]..

Ursodeoxycholic acid (UDCA) is used in several chronic cholestatic liver diseases as it decreases bile synthesis and secretion, increases the bile flow and solubilises cholesterol [73]. It has been used in children on long-term PN with good effect, but studies in adults show less consistent results, although it is well tolerated [74, 75]. UDCA has been shown to reduce liver enzymes in patients on long-term PN with liver dysfunction [24].

As mentioned previously, there are differing opinions as to whether cyclic PN regimes decrease the rate of cholestasis as a result of reducing total insulin levels compared with continuous PN [41, 42]. It has been suggested that long-term PN should be administered in a cyclic regime over 10–16 h rather than infused for 24 h continuously as it is better tolerated by patients and gives them more freedom, benefiting them psychologically, as well as the potential metabolic benefits [43].

IFALD with decompensation is an indication for consideration of transplantation, which in this setting may be liver and small bowel transplant (SBLT) or multivisceral transplant (MVT—intestine, stomach, pancreas and liver). Other

indications for transplant include frequent severe dehydration, frequent line-related sepsis, thrombosis of major central venous channels (≥ 2 sites), advanced desmoid tumours or poor quality of life that is thought likely to be improved by transplant [76, 77].

Optimal timing of transplantation remains a controversial subject and all patients in the UK are discussed at a national multidisciplinary meeting. Patients should ideally be considered for transplant prior to the development of end-stage liver disease [78]. Transplantation success rate continue to improve, with some centres quoting 1-year survival rates of up to 90%. Approximately 78% of patients are able to cease PN completely, with a further 12% having a decreased frequency of infusions following transplantation [77, 79]. However, given that outcomes for long-term PN patients remain very good (up to 96% 1-year survival), continuing on PN is the better option, should it be working well with good patient tolerance [77, 80] (Fig. 1).

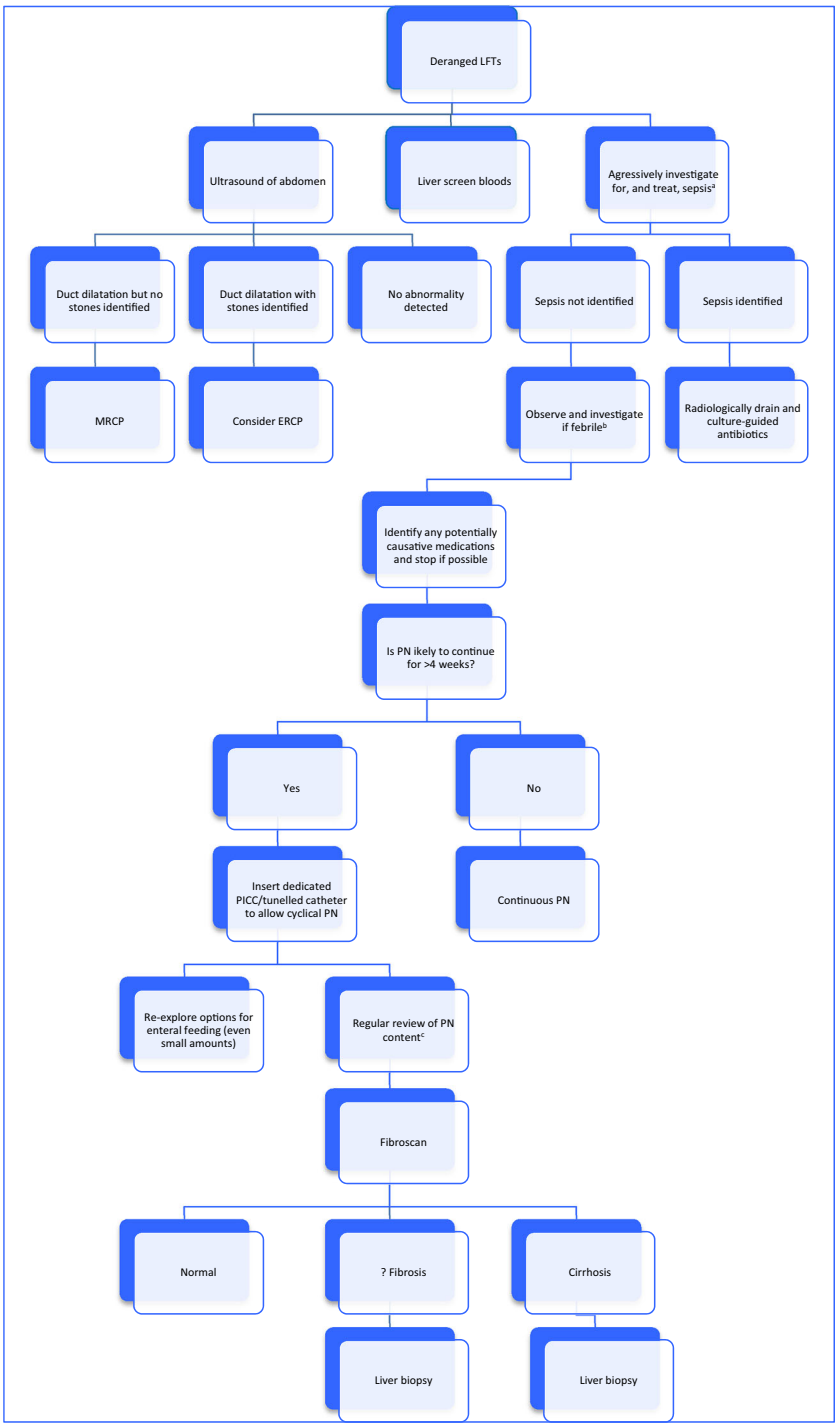

Fig. 1 An algorithm for the management of potential liver dysfunction in patients on parenteral nutrition. **a** Investigate sepsis—paired line cultures—for O&S as well as fungal cultures, CXR, urine culture, cross-sectional imaging (e.g. CT) if intra-abdominal sepsis likely. **b** If persistently elevated inflammatory markers, or suspicion of sepsis/unexplained positive blood cultures, consider further investigations—MRI skeletal survey/PET CT. **c** Reduce lipid content? Lipid-free PN can be considered (although lipid is essential so lipid-containing PN once weekly or fortnightly can be used as well as alternative lipid sources)

Conclusion

Both malnutrition and nutritional support have been shown to have the potential to cause hepatobiliary disease. With regard to hypoalimentation, most of the changes can be reversed with better nutrition in anorexia nervosa, controlled weight loss in obese individuals (which may involve the need for bariatric surgery) and management of co-existent liver conditions.

Abdominal ultrasound scanning remains first line-imaging modality for investigating abnormal liver tests given it has no radiation and is non-invasive. Transient elastography is a useful screening tool that is used to exclude the presence of fibrosis or cirrhosis and can thus reduce the need for unnecessary liver biopsies. This is of great importance, given the morbidity and risk associated with liver biopsy. There will, of course, be patients who require liver biopsy following an abnormal fibroscan.

PN is often associated with abnormal liver function tests. The origin of such abnormalities is often multifactorial and whilst PN can cause liver dysfunction through steatosis, cholestasis and formation of biliary system sludge/stones, a systemic approach to investigating such abnormalities is important. IFALD can be reduced through not exceeding the calorie requirements of the patient, limiting the lipid content to less than 1 g/kg/day and adding essential amino acids to the solution. There is also evidence that using alternative lipid sources with increased ω-3 PUFA content can improve LFTs in patients on PN.

The key management in IFALD is through prevention of sepsis, promoting intestinal health by re-introduction of enteral feeding, restoration of intestinal continuity where possible. Cyclic administration of PN through a dedicated PN tunnelled catheter can have both physical and psychological benefits to the patients. Most importantly, patients on PN for more than 28 days should be managed in a large centre with experience in managing intestinal failure to minimise the risk of such complications.

Early identification of liver dysfunction is essential and, should it progress despite the above measures, early discussion with an intestinal transplant centre should be encouraged.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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