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BAPEN / BIFA Guidelines on the Diagnosis and Management of Intestinal Failure Associated Liver Disease (IFALD)

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Aims of the Guidelines

1. To review the aetiopathogenesis and risk factors of IFALD
2. To understand methods of diagnosing IFALD, in particular the role of liver biopsy
3. To review management strategies for IFALD, including when to refer for intestinal transplantation

Background

Intestinal Failure Associated Liver Disease (IFALD) is a major consequence of long term parenteral nutrition and chronic intestinal failure (CIF). It was first described in 1971[1] and was previously called Parenteral Nutrition Associated Liver Disease (PNALD) but was subsequently renamed when it became understood there were contributions from more than just the PN.

The initial pathology can be predominantly cholestasis, steatosis/steatohepatitis, or a mixed picture[2], ductopenia has also been described[3]. Regardless of the initial pathology, progressive fibrosis leading to cirrhosis can also occur and therefore one of the goals of intensive intestinal rehabilitation is to prevent progression of IFALD so all members of the multiprofessional Intestinal Rehabilitation teams should be aware of diagnosis and management of this condition.

Whilst there is no standard definition of IFALD, a summary of previously published diagnostic criteria used in clinical studies[4–8] are given in table 1.

Who is at risk of IFALD?

Any patient with chronic intestinal failure receiving parenteral support is considered at risk of developing IFALD. The development of disease is likely multifactorial[9]. PN related factors include amount of energy, glucose, lipid (including type) delivered parenterally vs enterally, and delivery rate (and whether this exceeds the glucose oxidation rate). Certain nutrient excesses (including phytosterols, copper, manganese and aluminium) or deficiencies (choline, taurine, carnitine and essential fatty acids) have been linked to the pathogenesis of IFALD[10]. Non-PN factors include the frequency of catheter related bloodstream infections (CRBSI) episodes, the residual gut length (though this may just be a surrogate for

the proportion of energy delivered parenterally), the presence of a colon, gallstones, bacterial overgrowth and drugs[11–17]. In the paediatric population, the predominant histological finding is of cholestasis, as infants and young children have immature bile ducts vulnerable to injury. Hence, children can present with jaundice in early IFALD and this can be reversible with changes to the PN[18], weaning to enteral nutrition and growth. In adults, the main histological finding tends to be steatosis with or without steatohepatitis and fibrosis, though cholestasis often co-exists and ductopenia has been described. Differentiating IFALD from non-alcoholic fatty liver disease (NAFLD) can be challenging and requires review by an experienced pathologist in the context of the appropriate clinical history[2].

The significant risk factors for developing IFALD are ultra-short bowel (generally defined as ≤20cm of residual small bowel from the duodenojejunal flexure in adults, or ≤10cm in children), co-existing alcohol consumption, diabetes or other pathology associated with liver damage[19]. A small proportion of home parenteral nutrition (HPN) patients will have chronic viral hepatitis, biliary disease (particularly those with underlying inflammatory bowel disease) or autoimmune/metabolic liver disease. An under-recognised group is probably those patients with CIF following complications of bariatric surgery. The prevalence of steatosis, non-alcoholic steatohepatitis and cirrhosis in patients undergoing bariatric surgery is 91%, 37% and 17% respectively[20]. These patients may subsequently develop a combination of NALFD and IFALD. Patients with a second insult to the liver, whether it be NAFLD, alcohol or other intrinsic hepatic or biliary disease, should be considered at higher risk, though there is insufficient data at the moment to quantify this.

Table 2 provides a summary of the evidence for risk factors for IFALD

How does IFALD progress?

There is very limited data on how quickly IFALD progresses, and which factors affect this process. Serial biopsies are very rarely performed and there are only a few reports of this. Two very early case reports (one in a young adult[21] and one in an infant[22]) demonstrated progression from fibrosis to cirrhosis on serial biospies. In a recent French study[19] three patients underwent more than one biopsy, and all showed progression of fibrosis stage whilst continuing HPN. One 24-year-old patient had stage 1 fibrosis (Kleiner/Brunt score) after 9 months of HPN and stage 3 at 54 months; a 62 year old moved from stage 2 at 18 months to stage 3 at 41 months; finally a 36 year old progressed over 30 months from stage 2 to 3. In a case series of patients undergoing intestinal transplant, 1/3 showed progression of fibrosis stage between their baseline/assessment biopsy and an intraoperative biopsy at the time of transplant, after a median of just 191 days[23] on PN.

It is acknowledged that the development of clinical jaundice is a very late sign in IFALD and prognosis after this is poor. One older small series showed that death occurred within a median of 10.8 months after the initial bilirubin rise[24] and transplant centres do continue to see patients with jaundice deteriorate very rapidly. Mortality on the waiting list for combined liver/intestine transplant has always been high, reflecting the poor physical condition of patients with two organ failures. In the period 1987 to 2005, 29.8% of candidates listed in the US for a combined liver and intestine transplant died on the waiting list, compared to 8.8% of those awaiting intestine only[25]. The most recent report from the US[26] shows the absolute numbers are better, but the disparity is just as stark, with a mortality of 2.72% of those awaiting an isolated intestine graft versus 10.3% of those awaiting combined grafts. Wait times are longer for combined liver/ intestine grafts – median 190 days in the UK versus 139 days for isolated small bowel graft[27].

How is IFALD diagnosed?

Abnormalities in liver biochemistry are commonly seen in the early phase of PN and usually reflect pre-existing liver disease, drugs or sepsis, rather than an early form of IFALD[9]. True IFALD takes years to develop, though this can be a short number of years in those at very high risk.

Clinical manifestations of decompensated liver disease in non-IF patients include splenomegaly, ascites and varices. These signs develop as a consequence of portal hypertension. However, patients with CIF, especially short bowel, do not exhibit these features even with very advanced liver disease, due to the

general reduction in splanchnic blood flow[28]. The development of jaundice in an adult with IFALD is an end-stage sign and patients often die within months of this[25].

Intestinal Rehabilitation teams often see abnormalities in liver biochemistry in patients receiving PN. In the acute hospital setting it is mainly due to drugs, sepsis, or pre-existing liver disease[9]. In a patient with CIF receiving HPN, a raised alkaline phosphatase is the most common abnormality[14], which may be related to metabolic bone disease in many cases, rather than liver disease. This same study showed a high proportion of patients had abnormal liver biochemistry but none developed overt liver disease by the end of the study (median follow up 18.5 months). In a study by a group in France, there was no correlation between moderate or advanced liver fibrosis and the liver function tests[19].

Non-invasive tests have gained popularity in other aetiologies of liver disease/cirrhosis, but none have been validated in IFALD. Transient Elastography (Fibroscan®) in particular seems an attractive method, but 2 studies have shown it is not reliable[29,30]. As the elastography component on Fibroscan relies on liver stiffness, which will be influenced by portal inflow, it is perhaps not surprising that it is unreliable in patients with CIF, who do not have normal mesenteric/portal haemodynamics.

Certain biochemical panels have been proposed as non-invasive methods to detect fibrosis, including Fibrosis-4 (FIB-4), Enhanced Liver Profile (ELF, which measures serum levels of 3 fibrosis markers) and APRI. The FIB-4 test uses a formula derived from patient age, alanine transaminase, aspartate transaminase and platelet count, and has been particularly validated in NAFLD[31], but can be used in other liver diseases too. In a 2020 IF registry based review, FIB-4 was associated with risk factors for IFALD, such as bowel length and time on HPN but no comparison with histology or other modalities were carried out[32].

The Enhanced Liver Fibrosis (ELF) score likewise can be used in many chronic liver diseases[33], and is now recommended in the NICE diagnostic criteria for NAFLD and combines a score from serum levels of 3 fibrosis markers (Tissue Inhibitor of metalloproteinases-1, amino terminal propeptide of type III procollagen and hyaluronic acid). In a recent study of paediatric patients with CIF[34], ELF did not correlate with any known IFALD risk factors (duration of PN, proportion of energy delivered enterally, number of CRBSI episodes). Adding to this, a study of HPN patients from Southampton[35] showed ELF, FIB-4 and elastography were unreliable for diagnosing IFALD. There is an opportunity for intestinal rehabilitation centres to work together in further evaluation of these potential diagnostic tools.

AST Platelet Ratio Index (APRI) is particularly used in chronic hepatitis C and can be easily calculated from these two blood parameters. It did correlate with some IFALD risk factors in the previously mentioned 2021 study[34], but there was no 'gold standard' comparison. The only other method to show correlation with IFALD risk factors is the LiMAX test[36], a dynamic test that measures metabolism of ^{13}C labelled methacetin, but this measures liver functional capacity rather than the degree of fibrosis. However, it is useful in predicting outcome after liver resection and may be worth further evaluation.

Current best practice for diagnosing IFALD, certainly among transplant centres, involves a liver biopsy. A review of the technique, criteria for establishing adequacy of histology samples and for reporting provides useful practical tips [37]. There is limited published information available on how well a biopsy represents the entire liver in IFALD and the histology must always be correlated with the clinical scenario. IFALD can be difficult to distinguish from NAFLD, though there a few key histopathological differences (Table 3). Sequential liver biopsies whilst on HPN would be the most informative in determining the trajectory of liver disease, but are unlikely to be possible or palatable for all HPN patients.

The additional information provided by hepatic venous wedge pressures may justify undertaking this procedure in selected patients, particularly for those whose liver fibrosis appears to be borderline for recovery after isolated intestinal transplant. In the UK, current practice in CIF and transplant centres would place this 'point of irreversibility' at severe fibrosis (Ishak 4 or 5[38]). Some previous attempts to perform isolated intestinal grafts in patients with well compensated cirrhosis and/or absence of portal hypertension have resulted in acute liver failure and/or death[39], however, there are also case reports of good long term outcomes in this scenario[40].

What is the role of Transplant in IFALD?

The only treatment for established cirrhosis due to IFALD is a combined liver and intestine transplant. Historically, patients were only referred for consideration of transplant when they had developed overt cirrhosis. Unsurprisingly the mortality for this group of sick patients with advanced organ failure (both pre and post-transplant), was high. It has become apparent that for patients with pre-cirrhotic IFALD-related fibrosis an isolated intestinal transplant can halt progression or even reverse the degree of fibrosis[41,42,43.] Isolated intestinal transplants are technically easier, associated with shorter lengths of stay, fewer complications and greatly improved survival compared to combined liver and intestine grafts[24,41,42] (Figure 1). If we can diagnose IFALD at these earlier stages, we can also optimise organ utilisation.

Hence, intestinal transplant centres have been trying to promote earlier referrals for IFALD, but the only way to currently diagnose those with early IFALD is with a liver biopsy, an invasive test with a small but definite risk of complications. We therefore need to think about which patients are at highest risk for IFALD and consider when to perform liver biopsies on this group of patients.

Who, When and How to biopsy?

Liver biopsies are usually carried out using ultrasound guidance, via a percutaneous approach with a 16 gauge needle. Two passes are generally adequate for sampling. Most are performed as a day case with minimal-mild post-procedural pain[37]. The main risk that clinicians and patients are wary of is bleeding. A UK-wide audit in 2013[45] demonstrated that only 0.4% of patients had clinically significant bleeding following a liver biopsy (being defined as a drop in Haemoglobin, radiological evidence of bleeding or need for intervention for bleeding. The mortality rate related to bleeding was 0.11% and the deaths all occurred in patients having targeted lesion biopsies.

Transjugular biopsies are available in some hospitals and can be considered for patients with coagulopathy or ascites. However, such patients are unlikely to be undergoing a diagnostic biopsy outside of a transplant centre. It is critical that biopsies are reported by an experienced pathologist, especially as no standardised diagnostic criteria are available. The pathologist should initially comment on whether the sample is adequate for diagnosis. American Association for the Study of Liver Diseases (AASLD) guidelines state a sample with 12 or more portal tracts present should be sufficient for diagnosis[46]. The aim of histological examination is to confirm or refute the diagnosis of IFALD, stage IFALD and exclude co-existent liver pathologies. Descriptive reports as well as quantitative estimates of fibrosis (using Ishak or Brunt scores[38,47]) are helpful.

Considering who to biopsy, clearly not all HPN patients should undergo this procedure. If one of the aims of diagnosing early is to ensure a timely referral for intestinal transplant, the clinician should first consider whether the patient would be a candidate. There are no upper age limits for transplant in the UK, but the presence of major cardiorespiratory or neurological disease with poor prognosis, a history of metastatic cancer or serious psychological morbidity refractory to treatment should be regarded as contra-indications. If there is any doubt, Intestinal Rehabilitation teams can discuss with a transplant centre.

Thereafter, the individual patient risk must be considered – those who are ultra-short (residual small bowel length <20cm) are known to be very high risk[15] and should undergo early and possibly sequential biopsies. This document proposes the second high risk group are those with a second liver insult, as mentioned above (excess alcohol consumption, previous bariatric surgery or chronic viral, metabolic, autoimmune or biliary liver disease). These patients should have a baseline biopsy after a relatively short period of HPN, with further biopsies planned depending on the findings of the baseline sample and the ongoing presence of the ‘second hit’.

Management of IFALD

Comprehensive hepatoprotective strategies should be part of routine care for all patients with CIF. Clinicians should consider if their patient would be a candidate for intestinal (or intestine and liver) transplant, how to modify the HPN to be liver-sparing and which non-PN risk factors can be modified.

Routine IFALD preventative care should, based on the latest available evidence and expert opinion from BIFA, include the following:

1. Review of HPN script, with particular attention towards lipid type and amount and number of lipid-free days. Overall lipid intake should aim to be <1g/kg/day wherever possible mixed lipid emulsions should be used and lipid-free days maximised. Caution must be taken not to over-burden the patient with excess glucose energy which promotes de novo lipogenesis in the liver.

2. Review medication and stop or minimise all potentially hepatotoxic medications.

3. Restore intestinal continuity wherever possible. This may be of benefit in terms of normalising entero-hormonal and bile acid signalling as well as calorie-sparing. Along with this, encourage all patients to take some oral/enteral nutrition

4. Take all measures to reduce the incidence of CRBSI, including re-training, protective caps, single lumen catheters and antibiotic locks.

5. Counsel patients on their alcohol intake, including reminding them that it can be well absorbed and potentially toxic, even in patients with a very short bowel.

6. Consider patients who have undergone previous bariatric surgery to be at increased risk and establish baseline liver function/histology prior to surgery.

7. Screen at risk patients for co-existent liver disease.

Further guidance on management of IFALD is available at https://www.bapen.org.uk/pdfs/bifa/bifa-top-tips-series-3.pdf and https://pubmed.ncbi.nlm.nih.gov/30017241/

Figure 2 shows a schematic representation of a proposed management algorithm for patients deemed at high risk of IFALD.

Table 1: Frequency of IFALD according to various studies.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBili, conjugated bilirubin; GGT, gamma glutamyltransferase; LBx, liver biopsy; ULN, upper limit of normal

Citation	Number and type of patients	Diagnostic criteria	Population frequency according to these criteria	Comments
Beath 2008[4] (IRTA collaboration)	Adults and children	Early IFALD: ALP and GGT >1.5xULN for ≥6 weeks and Bilirubin <3 mg/dL. If LBx performed, up to 25% of parenchyma will show steatosis and 50% portal tracts will show fibrosis Established IFALD: ALP and GGT > 1.5xULN and Bilirubin 3-6 mg/dL. If LBx performed significant steatosis (25%) and up to 50% portal tracts will show fibrosis Late IFALD: ALT/AST and ALP >3x ULN and Bilirubin >6 mg/dL, INR >1.5 and clinical signs of PH. Biopsy "areas of intense fibrosis"		
Abi Nader[5]2016	N= 251 Paediatrics	ALT or AST or GGT or Bilirubin >1.5xULN	20%	86 Liver biopsies in 51 children Of which 52% had ≥ F2 fibrosis (18.7% of entire cohort)
Peyret[6] 2011	N=42 Paediatrics	ALT or AST or GGT or Bilirubin >1.5xULN for ≥ 2 months	57%	34 liver biopsies in 18 children reviewed: moderate or severe fibrosis in 23% of biopsies
ESPEN guidelines[7] (Lal et al) 2018	All patients	Liver injury as a result of one or more factors relating to IF including, but not limited to, PN and occurring in the absence of another primary parenchymal liver pathology		
Javid[8] 2018	N=191 Paediatrics	Conjugated bilirubin >2mg/dL	72% 38% Conj Bili >4mg/dL	All-cause mortality increased by 3-fold for baseline CBili 2-4 mg/dL (HR 3.25 [1.07-9.92], p=0.04) and 4-fold for baseline CBili >4 mg/dL (HR 4.24 [1.51-11.92], p=0.006)

Table 2: Summary of evidence for risk factors in IFALD

CB, Conjugated bilirubin; AST aspartate transaminase; ALT alanine transaminase; TAG, triacyl glycerol

*Complicated liver disease was defined as extensive portal fibrosis or cirrhosis, jaundice with a serum bilirubin level of 60μmol/L(3.5 mg/dL) or greater for at least 1 month, portal hypertension, liver encephalopathy, and liver failure

Contributory factor	Hypothesised link to IFALD investigated	Study type / patient details	Details / mechanism	Source
Sepsis	General link between sepsis and cholestasis (in all scenarios)	100 adult and paediatric in-patients with positive blood cultures	54% had elevated serum total bilirubin levels	Moseley 2004[48]
	Past incidence of catheter-related sepsis is associated with severe liver fibrosis	30 children on long term PN Patients stratified by liver biopsy into severe fibrosis (group A) or mild/normal (Group B)	Incidence of sepsis was significantly higher in group A than in group B (3.2 +/- 0.3/year vs 1.5 +/- 0.2/year)	Hermans[11] 2007
	Relationship between sepsis and hyperbilirubinemia	Post surgical neonates (n=74)	Episodes of sepsis associated with 30% increase in bilirubin	Beath[17] 1996
	Risk factors for developing CB >100μmol/L	Prospective study of 152 infants	Odds ratio 3.23 for septic episodes (95% CI 1.8-5.9)	Diamond[12] 2011
	Relationship between days to first infection and cholestasis / liver failure	Retrospective study of 42 inpatients	Mean age at 1st infection younger in those progressing to liver failure compared to those with cholestasis who recovered and those without cholestasis (28.5 +/- 5 days; 48.2 +/- 14.2; 167 +/- 43.2 days, p<0.01)	Sondheimer[13] 1998
Lipid in PN	Absolute amount of parenteral lipid given (soybean) in relation to	Prospective cohort study of 90 patients (adults and children)	Multivariate analysis: Parenteral lipid >1g/kg/day associated with a RR of 3.4 for developing	Cavicchi[15] 2000

	IFALD development		complicated liver disease*	
	Absolute amount of parenteral lipid given (soybean) in relation to IFALD development	Prospective study of 152 infants	10 fold increased risk of developing CB >100μmol/L after 60 days if parenteral lipid amount >2.5mg/kg	Diamond[12] 2011
	Reduction of parenteral lipid amount improves IFALD	Prospective study of 1g/kg/day lipid vs 3g/kg/day	Lipid reduction resulted in significant decline in bilirubin compared to controls	Cober[49] 2012
	Reduction of parenteral lipid amount improves IFALD	Retrospective cohort study of 82 infants receiving 1g/kg lipid per day vs 132 infants receiving 2-3g/kg/day	Multivariate analysis: standard lipid amounts 1.77 times more likely to develop IFALD than lipid-restricted infants	Sanchez[50] 2013
	Type of lipid influences risk - Phytosterols	Biochemical analysis of phytosterol levels in 29 children receiving PN (5 with severe liver disease) and 29 matched controls	Very high plasma levels of phytosterols in children with liver disease compared to those receiving PN without liver disease and controls	Clayton[51] 1993
	Type of lipid influences risk - Phytosterols	24 patients with short bowel and 21 controls	Significantly higher levels of phytosterols, cholesterol and 7alpha-hydroxy-4-cholesten-3-one Between short bowel patients and controls	Ellegard[52] 2015
	Type of lipid – fish oil reverses cholestasis	97 infants diagnosed with IFALD switched to fish oil lipid emulsion	86% survived with resolution of cholestasis	Premkumar[53] 2014

	Type of lipid – Mixed lipid emulsions lower risk than Soybean oil	Short term randomised, double blind study 34 adult patients receiving SMOF lipid vs 39 receiving intralipid	Significantly lower ALT, AST and bilirubin in SMOF group, significantly higher α-tocopherol in SMOF group	Klek[54] 2013
	Fish oil as a component of mixed lipid emulsion may be protective	5 year randomised open label trial of three intravenous lipid emulsions	Significantly lower bilirubin level in SMOFlipid group compared to formulations not containing fish oil	Klek 2021[55]
Parenteral energy	Proportion of calories delivered parenterally relates to IFALD risk	113 adults on HPN, of which 24% had biochemical chronic cholestasis (CC)	Higher parenteral calories intake associated with CC (OR 1.2 on multivariate analysis)	Lloyd 2008
	Influence of enterally vs parenterally delivered calories	29 patients with IBD randomised to isocaloric/isonitrogenous PN or EN	Incidence of deranged LFTs 61.5% in PN group vs 6.2% in EN group	Abad-Lacruz[56] 1990
Glucose amount	Fast glucose infusion exceeding Glucose Oxidation Rate leads to steatosis	Patients with burns injuries	>5mg/kg/minute glucose infusion leads to steatosis	Burke[57] 1979
Intestinal Anatomy	Residual Small Bowel length relates to IFALD risk	107 adults on HPN	SB length <100cm significantly associated with deranged LFTs on multivariate analysis	Luman[14] 2002
	Residual small bowel length relates to IFALD risk	Prospective cohort study of 90 patients (adults and children)	Multivariate analysis: Small bowel length <50cm associated	Cavicchi[15] 2000

			with Relative risk of 2.1	
	Presence of colon protects against IFALD development	113 adults on HPN, of which 24% had biochemical chronic cholestasis (CC)	Colon in continuity protective (Odds ratio 0.2 on multivariate analysis)	Lloyd[16] 2008
Nutrient Deficiencies	Choline deficiency impairs hepatic TAG export, promoting steatosis	41 adults and children receiving PN	Plasma free choline levels low in >90% of patients receiving HPN and levels correlate with LFT abnormalities	Buchman[58] 1993
	Supplementation of choline improved liver disease	15 adult patients receiving supplemental choline	Radiological improvement in steatosis after treatment, also improved ALT, AST	Buchman[59] 2001
	Lack of taurine reduces bile flow	32 adults receiving taurine-free HPN with 10 subsequently receiving taurine-enriched HPN	Reduction in AST following supplementation	Schneider[60] 2006
	Lack of taurine reduces bile flow	Randomised controlled trial of 236 neonates	Significantly reduced CB in certain groups	Spencer[61] 2005
Cycling PN	Cyclical vs continuous PN associated with better liver outcomes	Children with gastroschisis, comparison between continuous PN and cyclical	Children in continuous group 2.86 times more likely to develop hyperbilirubinaemia	Jensen[62] 2009
	Cyclical vs continuous PN associated with better liver outcomes	Prospective study of 65 patients with varying degrees of cholestasis, half switched from continuous to cyclical PN	Significant improvement in biochemical cholestasis after switching	Hwang[63] 2000

Table 3: Distinguishing IFALD from NAFLD (adapted from Buchman et al[2])

IFALD	NAFLD
Cholestasis	No cholestasis
Macro- and micro-steatosis	Usually macrosteatosis
Zone 1 steatosis	Zone 3 steatosis
Ductopenia and features of biliary obstruction can be present	
Steatohepatitis rare (or mild)	Steatohepatitis common
Fibrosis pattern usually 'jigsaw' / biliary	Sinusoidal fibrosis
	Ballooned hepatocytes
	Mallory Denk bodies

Figure 1: Kaplan-Meier survival curves (uncensored) for transplantation with and without liver included (From Woodward et al[64])

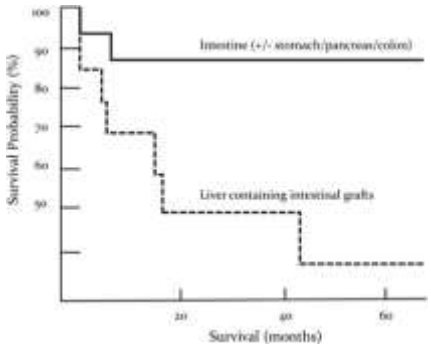
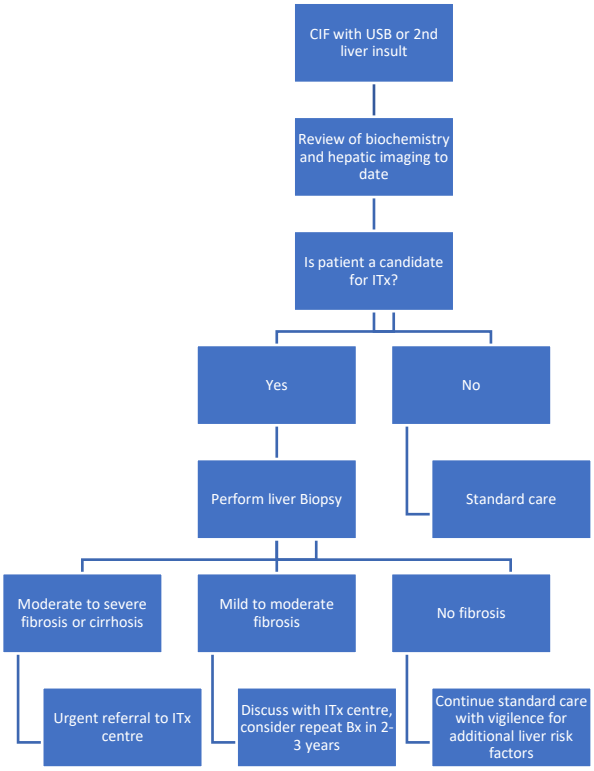


Figure 2: Management scheme for a patient deemed to be 'high risk' for IFALD.

'Standard care' includes review of PN script, consideration of alternative lipid source, review of hepatotoxic medications, counselling regarding alcohol intake, attention to other potentially modifiable hepatic risk factors (see text)

CIF, Chronic Intestinal Failure; USB, Ultra-Short Bowel; ITx, Intestinal Transplant



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