Journal of Cystic Fibrosis Volume 10 Suppl 2 (2011) S29–S36

Journal of Cystic Fibrosis

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# Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease

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**Abstract**

Approximately 5–10% of cystic fibrosis (CF) patients develop multilobular cirrhosis during the first decade of life. Most CF patients later develop signs of portal hypertension with complications, mainly variceal bleeding. Liver failure usually occurs later, after the paediatric age. Annual screening for liver disease is recommended to detect pre-symptomatic signs and initiate ursodeoxycholic acid therapy, which might halt disease progression. Liver disease should be considered if at least two of the following variables are present: abnormal physical examination, persistently abnormal liver function tests and pathological ultrasonography. If there is diagnostic doubt, a liver biopsy is indicated. All CF patients with liver disease need annual follow-up to evaluate the development of cirrhosis, portal hypertension or liver failure. Management should focus on nutrition, prevention of bleeding and variceal decompression. Deterioration of pulmonary function is an important consideration for liver transplantation, particularly in children with hepatic dysfunction or advanced portal hypertension.


*Keywords:* Cystic fibrosis; Liver disease; Liver biopsy; Esophageal varices; Ultrasonography; Ursodeoxycholic acid

## 1. Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease of the Caucasian population, with an incidence of approximately 1 in every 3000 live births worldwide [1]. It is a multiorgan disease affecting mainly the lungs, pancreas, sweat glands, and in males the Wolffian ducts. Liver Disease associated with Cystic Fibrosis (CFLD) is a well known complication. Long-term follow-up of different cohorts of CF patients carefully monitored for hepatic involvement indicates a cumulative incidence of liver disease ranging between 27% and 35%, without incident cases after the age of 18 years [2,3]. In a prospective study, the incidence of CFLD was 2.5 per 100 patient-years during the first 10 years of life (95% CI: 1.8–3.3), declining sharply during the second decade [2]. Approximately 5 to 10% of all CF patients will develop multilobular cirrhosis during the first decade of life [2,3]. Most of these will develop signs of portal hypertension (PHT), and present with related complications during the second decade, mainly variceal bleeding [4,5]. Liver failure is usually a late event that occurs rarely in the paediatric age group [4]. Liver cirrhosis remains the single most important non-pulmonary cause of death, accounting for 2.5% of overall CF mortality [6].

The wide spectrum of hepatobiliary disease in CF patients includes specific alterations due to the underlying cystic fibrosis transmembrane conductance regulator (CFTR) defect, lesions of iatrogenic origin, as well as the effects of extra-hepatic disease [7] (Table 1).

The typical hepatic lesion of CF, related to the CFTR defect in cholangiocytes, is focal biliary cirrhosis, which results from biliary obstruction and progressive periportal fibrosis. This is the most clinically relevant CF-associated hepatic problem, since extension of the initially focal fibrogenic

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Table 1
Hepatobiliary manifestations in CF (modified from Kelly [8])

| Type of lesion | Clinical manifestation | Frequency (%) |
|---|---|---|
| Specific alterations ascribable to the underlying CFTR defect | Focal biliary cirrhosis | 20–30 |
| | Multilobular biliary cirrhosis | 10 |
| | Portal hypertension | 2–5 |
| | Neonatal cholestasis | <10 |
| | Sclerosing cholangitis | often silent |
| | Microgallbladder | 30 |
| | Cholelithiasis | 15 |
| Lesions of iatrogenic origin | Hepatic steatosis | 25–60 |
| | Drug hepatotoxicity | undefined |
| Lesions reflecting the effects of a disease process that occurs outside the liver | Hepatic congestion | rare |
| | Common bile duct stenosis* | rare |

*Might be part of sclerosing cholangitis disease.

process may lead to multilobular biliary cirrhosis, portal hypertension and related complications [9]. The reasons why the distribution of hepatic lesions is focal at least in the early stages and why a minority of CF patients develop overt liver disease (i.e. multilobular cirrhosis), remain unknown. No specific CFTR mutations have been associated with the presence and severity of liver disease. The liver phenotype in CF patients with the same CFTR genotype is variable, suggesting that environmental factors or modifier genes might be important in the development of CFLD. Of different candidate genes (*SERPINA1*, ACE, TGFB1, MBL2, GSTP1), only the *SERPINA1* Z allele was found to be strongly associated with CFLD and portal hypertension [10].

Steatosis is a common hepatic lesion associated with CF that does not seem, however, to be directly related to the CF secretory defect (Table 1). Massive steatosis has become infrequent due to earlier diagnosis and to more appropriate nutritional care. Mild steatosis is more common and has been associated with selective nutritional deficiencies including specifically essential fatty acids and altered phospholipid metabolism in CF [3,11]. Steatosis has been considered a benign condition in CF, without a proven relationship to the subsequent development of cirrhosis. However, the available data on the role of nonalcoholic steatohepatitis as a cause of cirrhosis in adults may lead to reconsideration of this issue in CF patients [12].

Typical cholangiographic abnormalities of the intrahepatic bile ducts compatible with sclerosing cholangitis, have been reported in children [13] and in the majority of adult patients with CFLD [14]. Such lesions have been considered to be the expression of an inflammatory process involving the bile ducts, accumulation of proteins and mucus, and compression of intrahepatic bile ducts induced by fibrosis. Using magnetic resonance cholangiography (MR cholangiography), bile duct abnormalities have also been documented in a significant proportion of CF patients without clinically apparent liver disease [15].

Current evidence suggests that liver disease in CF results from bile duct obstruction related to the CFTR defect in cholangiocytes, toxic retention leading to peribiliary fibrosis [9,16] and increased amounts of sludge in the biliary tract, leading to the development of microgallbladder and variability of the biliary ductular lumen. Based on this pathophysiological hypothesis, ursodeoxycholic acid (UDCA), a hydrophilic and choleretic bile acid, has been widely used in CF patients and shown to improve liver function tests, biliary drainage, early ultrasonographic changes in the liver and even liver histology [17–21]. UDCA remains to date the only available treatment that may prevent or halt the progression of liver disease in CF patients. Therefore, asymptomatic patients with early stage liver disease are more likely to benefit from UDCA administration. No significant side effects related to the long-term use of this drug have been reported.

Neonatal screening for CF is now routine in many European countries. However, recognition of CF patients at risk of developing liver disease remains a major clinical issue. No genotype-phenotype correlation has been demonstrated [2,22]. Several factors have been recognized to be significantly associated with liver disease, including meconium ileus, the role of which as a predisposing factor to the development of CFLD remains controversial [2,3,22–24].

Therefore, regular screening for CFLD is necessary to detect pre-symptomatic signs of liver involvement in order to initiate UDCA therapy. In CF patients who develop cirrhosis, it is necessary to screen for complications related to PHT (e.g. esophageal or gastric varices, hepatopulmonary and portopulmonary syndromes) and for signs of liver failure. Management should focus mainly on nutrition, prevention of bleeding and variceal decompression.

## 2. Diagnosis of CF associated liver disease

Evidence of liver disease in CF patients is often subclinical until pathological changes are diffuse and pronounced.

Most often patients remain asymptomatic, without jaundice and pruritus, even when multilobular cirrhosis develops. The most common clinical presentation of liver disease is the finding of hepatomegaly on routine physical examination, often but not always associated with abnormalities of liver biochemistry. Hepatomegaly may also result from fatty infiltration of the liver or focal biliary fibrosis.

The rate of progression of liver disease differs markedly from one patient to another, but most often diagnosis of

multilobular cirrhosis becomes clinically evident at the end of the first decade of life, associated with signs of portal hypertension. The liver is firm and nodular and its enlargement may be limited to one lobe, particularly to the left lobe that protrudes centrally, often associated with splenomegaly that may cause abdominal discomfort or pain. Attention should be paid to the presence of peripheral signs of chronic liver disease, including spider naevi, palmar erythema, clubbing, jaundice, oedema, distension of abdominal wall veins and ascites, although these are late signs.

Since a sensitive and specific test to evaluate biliary cell function is not yet available, early diagnosis of CFLD requires regular clinical examination, biochemical tests and imaging techniques.

### *2.1. Diagnostic work-up: evidence and limitations*

#### *2.1.1. Liver function tests*

Biochemical abnormalities (serum liver enzymes) are frequently mild or intermittently present and have low sensitivity and specificity; abnormalities usually do not correlate with histological findings [25]. Common findings include intermittent rise in serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) and/or increased serum levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT). Not infrequently, CF patients with multilobular biliary cirrhosis may have completely normal liver biochemistry. Isolated elevation of transaminases with normal concentrations of enzyme related to cholestasis (GGT and AP) may suggest the presence of steatosis, which should be adequately recognized and followed-up, after correction of nutritional deficiencies, if present. An isolated increase of ALP with normal GGT and transaminases is not specific to liver disease in growing children. In addition, non-specific biochemical abnormalities are very common during the first year of life and have been documented in more than 50% of infants with CF, with complete normalization in most cases within 2–3 years of age. A minority of infants may even present with neonatal cholestasis, particularly those with meconium ileus, and other conditions enhancing the risk of cholestasis, i.e., total parenteral nutrition or abdominal surgery. However, cholestasis generally resolves spontaneously over the first months of life and has no impact on future development of liver disease [26].

Occasional biochemical abnormalities may also occur as a result of drug treatment or infection. Other causes of acute or chronic cytolysis should be excluded (Table 2).

New and potentially useful tests have been proposed, including serum markers of fibrogenesis (e.g. collagen VI and prolyl hydroxylase) [27]. However, their use remains limited and their diagnostic value needs to be further evaluated.

#### *2.1.2. Ultrasound scan*

Ultrasonography (US) of the hepatobiliary system with Doppler measurements of hepatic flow is non-invasive and inexpensive. Evidence has been provided that US is more sensitive for CFLD than clinical and biochemical abnormalities [28,29]. Abnormal echogenicity frequently precedes clinical and biochemical manifestations of liver disease, suggesting that routine US may be a valuable marker of early liver disease in CF. A simple echographic scoring system based on coarseness of liver parenchyma, nodularity of the liver edge and increased periportal echogenicity has been proposed for the identification of patients with pre-cirrhotic liver disease and their follow-up [30]. However, there is clearly intra and interobserver variability in sonographic assessment of hepatic echostructure. The positive predictive value of a normal ultrasound has been shown to be only 33%, with a sensitivity of 57% [31]. Although US diagnosis of fatty infiltration of the liver, of cirrhosis and portal hypertension is most often accurate, a normal ultrasound does not preclude significant liver fibrosis [31]. Therefore, diagnosis of early liver disease cannot reliably be made on the basis of ultrasound alone.

Table 2
Causes of acute or chronic liver disease in CF patients showing hepatic abnormalities

| Condition | Investigation |
|---|---|
| Acute/chronic viral hepatitis | Serology for HAV, HBV, HCV, EBV, CMV, adenovirus, HHV 6, parvovirus |
| $\alpha_1$ antitrypsin deficiency | Serum $\alpha_1$ antitrypsin level, including phenotype |
| Autoimmune hepatitis | Non-organ specific autoantibodies (SMA, anti-LKM1, LC1) |
| Celiac disease | Total IgA, IgA anti-tissue transglutaminase |
| Wilson disease | Ceruloplasmin, serum copper, 24 h urinary copper |
| Genetic hemochromatosis (adults) | Iron, Ferritin, Transferrin binding capacity |
| Other causes of steatosis | Malnutrition, diabetes, obesity |

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV6, herpes hominis virus type 6; SMA, smooth muscle antibody; LKM1, liver kidney microsomal type 1, LC1, liver cytosol type 1.

#### *2.1.3. Liver biopsy*

Histological assessment represents the gold standard in the diagnostic work-up of many chronic liver diseases. In CF, it may provide important information on the predominant type of lesion (steatosis or focal biliary cirrhosis) and the extent of portal fibrosis [25]. However, because of the patchy distribution of lesions in CFLD, liver biopsy may underestimate the severity of lesions and is not a routine investigation in many units.

#### *2.1.4. Transient elastography (Fibroscan)*

Fibroscan is a new medical device that measures liver stiffness in a non invasive, rapid, and reproducible way [32]. Liver stiffness has been shown to be closely related to liver fibrosis and validated for staging of fibrosis in patients with chronic liver diseases, especially hepatitis C [33]. Studies in CF patients are in progress to confirm its usefulness in

diagnosing CFLD at an early stage and assess progression of liver fibrosis [34].

*2.1.5. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI)*

Both CT and MRI are useful to discriminate fibrosis from steatosis and to appreciate the nature of focal lesions (i.e. focal steatosis, hemangioma, focal nodular hyperplasia, hepatocarcinoma). MRI tends to replace CT, especially in older children who do not need sedation, since it does not expose the patient to radiation and allows imaging of the biliary tree. MR cholangiography is not routinely performed in the CF paediatric population, but could be useful for early detection of intrahepatic biliary tract involvement that may contribute to the development of biliary cirrhosis, especially in children with symptoms (i.e. jaundice, abdominal pain) or signs (i.e. dilated bile ducts at US) suggestive of sclerosing cholangitis, distal stenosis of the common bile duct or choledocholithiasis. Indeed, the usefulness of MR cholangiography, which can substitute for endoscopic retrograde cholangiopancreatography (ERCP), has been highlighted in one study on CF adults, showing cholangitic lesions in all patients with liver disease and in half of those without apparent liver disease [15].

*2.1.6. Cholangiography*

Percutaneous transhepatic cholangiography and endoscopic retrograde cholangiography (ERCP) are invasive procedures not suitable for screening and diagnostic purposes.

*2.1.7. Hepatobiliary scintigraphy*

Hepatobiliary scintigraphy with iminodiacetic acid derivatives can document a typical picture of biliary drainage impairment, with dilation of intra- and extra-hepatic bile ducts and delayed biliary excretion and intestinal appearance of the tracer [35]. Scintigraphy can document time-related progression of liver disease and has been employed to monitor the response to treatment with UDCA [18].

*2.2. Diagnostic criteria of CFLD*

The presence of CFLD should be considered if at least two of the following variables are present (Fig. 1):

- Abnormal physical examination:
  - Hepatomegaly defined as an increased liver span relative to age or as a liver edge palpable more than 2 cm below the costal margin on the mid-clavicular line, confirmed by ultrasonography (Table 3). A prominent left lobe palpable in the epigastrium is often noted in cases of multilobular cirrhosis.
  - And/or splenomegaly, confirmed by US (Table 3).
- Abnormalities of liver function tests defined as an increase of transaminases (AST and ALT) and GGT levels above the upper normal limits at least at 3 consecutive determinations over 12 months after excluding other causes of liver disease (Table 2).
- Ultrasonographic evidence of liver involvement (increased and/or heterogeneous echogenicity, irregular margins, nodularity) or portal hypertension (splenomegaly, increased thickness of the lesser omentum, spontaneous splenorenal anastomosis, large collateral veins, ascites) or biliary abnormalities (bile duct dilatation).
- A liver biopsy may be indicated if there is diagnostic doubt.

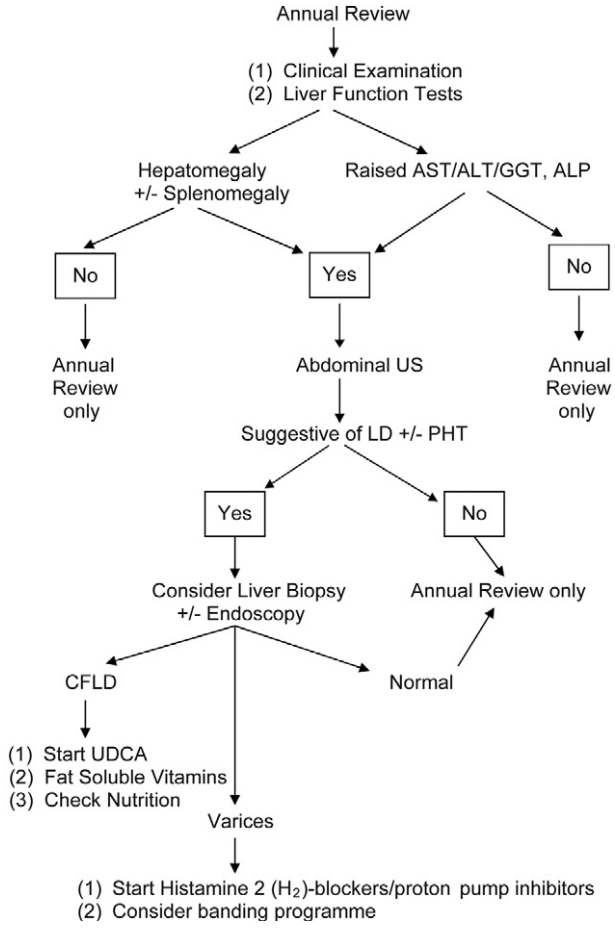


Fig. 1. Flow chart for the investigation and management of CF-associated liver disease. Abbreviations: ALT, alanine transaminase; ALP, alkaline phosphatase; AST, asparate transaminase; CFLD, Cystic Fibrosis-associated liver disease; GGT, gamma glutamyl transpeptidase; LD, liver disease; PHT, portal hypertension; UDCA, ursodeoxycholic acid; US, ultrasonography.

Some patients with CFLD only have persistent abnormal liver function tests with hepatomegaly and/or mild abnormalities on US (increased and/or heterogeneous echogenicity),

Table 3
Upper limits of liver span measured at midclavicular line and upper limits of spleen length measured at US in the longitudinal coronal plane according to age

| Age | Liver span (cm)* | Spleen length (cm)** |
|---|---|---|
| At birth | 5.5 | 6 |
| At 1 year | 6.0 | 7 |
| At 3 year | 7.0 | 9 |
| At 5 year | 8.0 | 9.5 |
| At 12 year | 9.0 | 11.5 |
| Adult | Up to 12 | Up to 13 |

*From Lawson et al. [36]; **from Rosenberg et al. [37].

while others have cirrhosis with or without portal hypertension. CFLD severity and related complications are clearly different between these groups. Therefore, both clinically and for study purposes, it might be useful to make a distinction between severe CFLD, i.e. those patients with cirrhosis and/or portal hypertension, and other patients with CF-related liver disease.

### *2.3. Recommendations*

#### *2.3.1. Screening for CFLD*

Annual screening is recommended with:

- Abdominal examination by a gastroenterologist;
- Biochemical evaluation (AST, ALT, GGT, ALP, Prothrombin time, platelets).
- Abdominal US with CT or MR imaging if concern exists about the nature of liver lesions or biliary tract involvement (such as sclerosing cholangitis).

#### *2.3.2. Recommendations for starting ursodeoxycholic acid*

The objective of UDCA treatment is to delay the progression of the disease and so treatment should be started as soon as the diagnosis of CFLD is made (Fig. 1), although there are no data on long-term outcomes such as death or need for liver transplantation [38]. A daily dose of 20 mg/kg is initially recommended [17]. A therapeutic schedule based on multiple divided doses (at least twice/day) seems to be more effective because of incomplete intestinal absorption [39]. Evaluation of indices of cholestasis and cytolysis should be performed 3 and 6 months from initiation of therapy to test for the efficacy of UDCA and the dose should be increased if necessary. Therapeutic drug monitoring for optimizing the dosage or to assess adherence to UDCA would require assessment of biliary enrichment with UDCA, which is not available on a routine basis. Although serum UDCA may be analyzed by gas liquid chromatography-mass spectrometry (GLC-MS), the target range level is not defined.

## 3. Follow-up of CFLD

All CF patients with CFLD need annual follow-up by gastroenterologists or hepatologists in order to evaluate the progression to cirrhosis, and screen for the development of portal hypertension and other complications.

- All patients with cirrhosis and splenomegaly and/or signs of hypersplenism should be screened for esophageal varices (EV) at diagnosis by means of upper gastrointestinal (GI) endoscopy. If normal, it should be repeated every 2–3 years. Once EV have developed, it is prudent to perform an upper GI endoscopy once a year and treat large varices (see management of PHT below). Any sign suggestive of possible GI bleeding (anemia, microcytosis, chronic iron depletion) should also prompt an upper GI endoscopy. Some patients may develop rectal varices and present with rectal bleeding.
- Other complications related to portal hypertension also need annual screening:
  - Hepatopulmonary syndrome results from dilatation of intrapulmonary capillaries leading to a functional right to left shunt and hypoxemia. Oxygen saturation should be monitored in the supine and upright position: a significant decrease in oxygen saturation (>5%) when the patient moves from a supine to an upright position (called orthodeoxia) is suggestive of the diagnosis. Proof of intrapulmonary capillary dilatation may be obtained by means of contrast enhanced (bubble) echocardiography or technetium 99-labelled macro aggregated albumin scintigraphy [40].
  - Pulmonary arterial hypertension (i.e. portopulmonary syndrome) is easily detected by echocardiography [41].
- Thrombocytopenia and leucopenia resulting from hypersplenism do not require any specific therapy. There is no rationale for platelet transfusions unless there is intractable bleeding, invasive procedures or surgery, neither for the use of granulocyte growth factors in cases of severe leucopenia.
- Diagnosis of early signs of liver failure is more difficult as hepatic function is retained until the terminal phase. Prothrombin time (PT) and coagulation factors should be measured at least once a year to detect early signs of liver failure. A prolonged PT (above 13.5 seconds or decreased PT activity below 70% of normal) and a decrease in cofactors are however, non-specific markers of liver failure. A prominent decrease in coagulation factor V compared to other cofactors is often noted in patients with a large splenomegaly, possibly as a result of intrasplenic consumption. An isolated decrease in cofactors VII, X and II suggest vitamin K deficiency that should be corrected with oral or intramuscular vitamin K supplementation. Liver failure should be considered if PT and coagulation cofactors VII, X and II remain decreased despite vitamin K supplementation.
- In patients with cirrhosis, it is appropriate to perform an ultrasound scan of the liver and to measure alpha fetoprotein levels annually in order to monitor the possible development of hepatocellular carcinoma [42,43].

## 4. Management of esophageal varices

Whilst liver failure is uncommon in the paediatric population, management of long-term complications of cirrhosis should focus on control of bleeding and on variceal decompression.

Screening for and treating large varices in adults with cirrhosis without a history of bleeding is recommended by recent guidelines of the American Board of Gastroenterology, which are similar to European guidelines [44]. Recommendations suggest the use of non selective β-blockers as first step therapy in patients with grade 2 or 3 varices, band ligation in cases of β-blockade contraindication or failure (secondary prophylaxis) and the placement of a transjugular intrahepatic portosystemic shunt (TIPS) in cases of ligation failure (tertiary prophylaxis). No clear recommendations with respect to prevention of GI bleeding have been published in CF patients. CF patients clearly differ from others with respect to lung disease that may contraindicate β-blockers.

However, repeated general anaesthesia required for screening of therapeutic endoscopic procedures may also reduce lung function and predispose to infection unless managed with intravenous antibiotics and vigorous physiotherapy.

The efficacy and safety of β-blockade in preventing variceal bleeding has not been evaluated among CF patients. Sclerotherapy has for a long time been the only means of treating bleeding esophageal varices. Because sclerotherapy carries a risk of bleeding during or following the procedure and because repeated general anaesthesia might cause deterioration of lung function, it has not been recommended in CF patients as a primary prophylaxis. Band ligation is a more effective therapy to prevent GI bleeding in adults [45], but studies are needed in the CF population to assess the long-term efficacy and possible impact of repeated general anaesthesia on lung function.

TIPS has been employed for portal decompression in patients with recurrent bleeding, both as a long-term therapy for portal hypertension or as a bridge for liver transplantation [46].

Alternatively, surgical portal systemic shunting has been successfully performed in selected CF patients with preserved liver function and without severe lung insufficiency, allowing prolonged post-operative survival [4,47]. However, potential complications include development of hepatic encephalopathy and acute liver failure.

Partial splenectomy has also been advocated as a therapy for portal hypertension in CF patients who present with large splenomegaly and profound thrombopenia related to hypersplenism [48], but accelerated decline in lung function and unsuccessful prevention of variceal bleeding have been reported [4,49,50] and therefore this is not recommended.

Although practice differs among different centers, common recommendations are:

- Contraindication of salicylic acid and non-steroid anti-inflammatory drugs if there is evidence of CFLD, to prevent bleeding from portal hypertensive gastropathy and GI varices
- Vaccination against hepatitis A and B
- Treatment of large varices with red wale signs (grade 2 and more) to prevent bleeding: band ligation appears a preferable alternative to sclerotherapy to be indicated as first line therapy and should be repeated until varices are eradicated.

### *4.1. Nutritional support*

The development of liver disease may further exacerbate malnutrition, a common complication of CF, by increasing fat malabsorption and protein loss.

The following dietary management is recommended:

- Increase energy intake to 150% of Estimated Average Requirement (or Recommended Daily Allowance), which may be preferentially achieved by increasing the percentage of fat and only rarely by adding carbohydrate supplements, such as glucose polymers, due to the risk of developing CF-related diabetes mellitus [51].
- Increase the proportion of fat to 40–50% of the energy content of the feed or diet, with supplementation in medium chain triglycerides and special attention to polyunsaturated fatty acids.
- Provide protein supplements to ensure an intake of 3 g/kg/day in patients without signs of liver failure.
- Ensure that sufficient pancreatic enzymes are prescribed to allow optimal absorption of long-chain triglycerides and essential fatty acids.
- Avoid salt supplementation in CF patients with cirrhosis and PHT that may precipitate the development of ascites.
- Prescribe fat soluble vitamin supplements: high oral doses of vitamin A (5,000–15,000 international units daily), vitamin E (alpha tocopherol 100–500 mg daily) and vitamin D (alpha calcidiol 50 ng/kg to maximum of 1 μg). Vitamin K is sometimes required (1–10 mg daily). PT and cofactors need to be carefully monitored to prevent deficiency. Supplementation with vitamin A, vitamin E and vitamin D should be also carefully monitored with plasma levels to prevent toxicity or deficiencies.

In children in whom anorexia is a problem, enteral nasogastric feeding may be required to ensure adequate caloric intake when awaiting a liver transplant. Gastrostomy feeding is not recommended in children with advanced liver disease, varices or portal gastropathy because of the risk of gastric haemorrhage.

## 5. Recommendations for referral to a transplant center

Selection criteria for orthotopic liver transplantation (OLT) and timing in CF have not yet been established, however indications differ from other liver diseases in which chronic hepatic failure is the main indication. In CF, other extra-hepatic parameters are important considerations, which include progressive deterioration of nutritional status despite nutritional support, deterioration of pulmonary function and recurrent respiratory multi-resistant bacterial infections, leading to frequent hospital admissions. There is increasing evidence that poor growth and nutritional status are associated with deterioration of lung function and a high post-transplant mortality rate. The issue of timing is clinically relevant and two scoring systems evaluating the need for transplantation are available, both of which include parameters of nutritional status [52,53].

Clear indications for liver transplantation in CF liver disease are:

- progressive hepatic dysfunction (falling albumin $<30$ g/l; increasing coagulopathy, not corrected by vitamin K)
- development of ascites and jaundice
- intractable variceal bleeding which is not controlled by conventional means
- hepatopulmonary and portopulmonary syndromes
- severe malnutrition, unresponsive to intensive nutritional support
- deteriorating quality of life related to liver disease
- deteriorating pulmonary function ($FEV_1/FVC <50\%$).

The transplant assessment should evaluate pulmonary and

cardiac function in order to establish whether liver transplantation alone is required or a combined heart/lung/liver transplant is more appropriate [54].

A few patients benefit from early and elective OLT, before development of significant and irreversible pulmonary and nutritional deterioration [52,53,55]. Stabilization and even amelioration of lung function post transplantation has been reported, arguing in favour of early liver transplantation. Recently, a poll among European CF and Transplant Centers was carried out in order to obtain information on current practice and outcome for liver transplant in CF patients in Europe: in the majority of cases, transplantation was performed before development of end-stage liver disease [56]. Although patient and graft survival compare favourably with those of liver transplantation for indications other than CF, the risk of chronic liver graft rejection, lymphomas, renal dysfunction and diabetes should be balanced against the potential benefits of transplantation on lung function and nutritional status [57,58]. Indeed, recent studies suggest that OLT may not improve long-term survival in patients with CF and significant portal hypertension, but does improve quality of life [59]. Given improved management of the complications of portal hypertension, liver transplantation should be reserved for CF patients who have evidence of hepatocellular dysfunction in addition to portal hypertension or those with rapid deterioration of pulmonary function.

## Acknowledgements

This work was supported by the European Union Sixth Framework Programme (contract no. LSHM-CT-2005-018932, EuroCareCF).

## Conflict of interest

The authors state that there is no conflict of interest.

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