Title	Cystic Fibrosis Related Liver Disease (CFLD)
Version	3

1. Introduction

Cystic fibrosis related liver disease (CFLD) is the third most frequent cause of death in CF after respiratory and transplantation complications, but accounts for only 2.5% of all CF related mortality. It is slowly progressive, starting around 9-10 years of age, with increasing prevalence through childhood to mid-adolescence, and with most patients stabilising thereafter. Up to 40% of all patients with CF will show abnormal imaging results. Multi-lobular biliary cirrhosis only affects 5-10% mainly causing portal hypertension but rarely liver failure.

The risk is not whether there is evidence of CFLD but whether cirrhosis and/or portal hypertension is present. Risk factors for CFLD include pancreatic insufficiency, male predominance, alpha-1-antitrypsin heterozygote for Z-allele (ie α1at disease carrier), meconium ileus and Hispanic race.

2. Screening

2.1. **Recognition of CF patients at risk** of developing CFLD is difficult. There is no clear genotypic-phenotypic link, though CFLD sits mainly in class I – III mutation groups (>2000 mutations). A combination of several tests is needed to reliably detect liver disease.

2.2. **The goals for screening** are to:

- Identify individuals at risk for cirrhosis prior to its development in order to institute therapy to prevent or reduce disease progression
- Detect patients who have developed clinically silent cirrhosis to allow monitoring and interventions to reduce or mitigate complications.
- Ensure prompt nutritional surveillance and management.

2.3. **Annual Screening for CFLD** is done at annual assessment and includes:

- Clinical examination looking for hepatosplenomegaly (large liver and spleen). In fact this should be done routinely at every clinic visit
- Blood tests (transaminases, coagulation, FBC)
- Abdominal ultrasound scan (probably the most sensitive method of early detection of CFLD) is performed annually from 5 years of age.
- Nutritional screening should form part of annual CFLD assessment. (body composition, fat soluble vitamin levels and Creon dosing)
- Optimisation of glycaemic control
- Screening for alcohol use and for excessive use.

3. Interpretation of Screening Test Results

- **Liver function test results** may be intermittently elevated and do not always correlate with the severity of hepatic lesions. Transient elevation of liver function tests may be seen with hypoxaemia,

antibiotic treatment and during pulmonary exacerbation. Liver disease should be suspected if any liver enzyme (AST, ALT, GGT) is above upper end of normal range on at least 3 consecutive occasions during a 12 month period after excluding other causes.

- **Abdominal ultrasound.** Steatosis (fatty deposits in the liver) is the most common hepatic abnormality associated with CF and is detected in up to 67% of patients of any age. Steatosis is a relatively benign condition but, in some, can progress to steatohepatitis and cirrhosis (similar to non-alcoholic fatty liver disease or NAFLD).
  Biliary manifestations of CFLD are seen in up to 33% of patients and include abnormalities of intra- and extrahepatic bile ducts, gallbladder thickening and contraction, microgallbladder and cholelithiasis.

4. Other Causes of liver disease

If there is suspected or evidence of CFLD other causes of liver disease should be excluded. Other causes include:

- α1antitrypsin deficiency
- those who are heterozygous (carrier status) or homozygous (have disease) for α1antitrypsin deficiency are at higher risk of developing more severe liver disease
- autoimmune liver disease
- Wilson ’s disease
- viral hepatitis
- hemochromatosis
- coeliac disease
- other causes of steatosis

5. CFTR Modulator Therapies and Abnormal Liver Function Tests

CFTR modulators commonly give rise to mild elevations of liver enzymes. Current recommendations from the drug manufacturer are 3 monthly liver function tests following initiation of therapy. These mildly elevated enzyme levels are commonly transient and in most cases do not necessarily mean the CFTR modulator needs to be discontinued but this should be decided on a case-by-case basis. The annual liver ultrasound scan can also be helpful when deciding.

6. Other Liver Tests

6.1. **Liver biopsy** is invasive but can be considered if there is diagnostic doubt. Be aware that CFLD is a focal disease and, as it is impossible to see on USS which part of the liver to target, the biopsy may be completely normal even if CFLD is present.

6.2. **Elastography (FibroScan)** is a non-invasive, rapid bed-side method to assess liver fibrosis by measuring liver stiffness. It uses both ultrasound and low-frequency elastic waves produced by a specialised ultrasound vibrator applied to the body wall. FibroScan has proved useful in adults but has not been formally validated in children with CFLD. It is acceptable though to extrapolate adult cut-off values to interpret paediatric results.

6.3. **Magnetic resonance cholangiography (MRC)** is a non-invasive procedure that provides a high quality picture of any abnormalities of the intra- and extra-hepatic bile ducts. Patients with CFLD show abnormal findings on MRC. However, MRC is not practical in paediatrics and is relatively expensive.

6.4. **Serum markers** of hepatic fibrogenesis may be useful. The ELF test (Enhanced Liver Fibrosis) is a marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease. However, it is not validated in children with CFLD, but again, as we are following individual value trends over time, it would be acceptable to use adult cut-off values for significant fibrosis.

7. Management of CFLD

7.1. **Ursodeoxycholic acid (UDCA)** is the only therapy that may prevent or delay progression of CFLD. UDCA increases bile flow, possibly replaces toxic bile salts, acts as a cytoprotective agent and probably stimulates bicarbonate secretion in the biliary tract. The dose of UDCA is 15-20mg/kg/day. However there is significant disagreement about the use of UDCA in CF. Cochrane reviews in 2000 and 2012 concluded data are insufficient to justify routine use in CF. There are no long-term outcome data on UDCA impact on death or Liver transplantation. Also a recent study of higher doses of UDCA in primary sclerosing cholangitis was terminated early due to increased risk of death or liver transplantation in the UDCA group.

7.2. **Endoscopy** should be performed if there is significant evidence of portal hypertension to look for oesophageal varices and treat them by applying endoscopic band ligation if varices are large enough to band, thus reducing the risk of a future variceal bleed. A child with CFLD and cirrhosis has a significant risk of bleeding from varices. Patients with cirrhosis and early drop in platelet count may be at higher risk of variceal bleeding.

7.3. **Nutritional assessment for malnutrition** should include liver specific macronutrient and micronutrient assessment, body composition assessment (Mid Upper Arm Circumference MUAC, Mid Arm Circumference MAC, Tricep Skinfold TSF, Hand Grip Strength HG) Bioelectrical Impedance allows muscle mass to be monitored with serial measurements. Nutritional assessment should not solely focus on weight or BMI, these nutritional markers may be inaccurate as a result of fluid shift, organomegaly or ascites. If known cirrhosis or poral hypertension, nutritional assessment should be completed every 6 months.

7.4. **Nutritional Interventions** may include

- Regular review of Pancreatic Enzyme dosage (liver damage can complicate absorption)
- Additional monitoring of fat soluble vitamins may be required. Vitamin A levels should be interpreted with caution in advanced CFLD.
- Increased energy requirements, these may be 120-170% greater than compared to healthy individuals.
- Considerations to MCT fats (30%-70% of total fat) to aid absorption. (see ESPEN-ESPGHAN-ECFS guideline on nutrition care for cystic fibrosis 2023)
- Protein requirements would be assessed considering presence of encephalopathy.
- Early discussions about appropriateness of enteral nutritional support are encouraged to prevent a nutritional decline. Gastrostomy feeding should be avoided in patients with oesophageal varices and/or portal gastropathy for the risk of gastric haemorrhage.

8. Treatment of portal hypertension

8.1. **Trans-jugular Intrahepatic Porto Systemic Shunt (TIPPS)** should be considered if there is failure of banding programme, deteriorating lung function and need for repeat endoscopies and as a bridge to transplant. TIPPS reduces portal pressure and risk of bleeding. No surveillance endoscopies are needed but an annual TIPPS venogram is recommended and there is a risk of hepatic encephalopathy.

8.2. **Surgical porto-systemic shunting** can permanently reduce portal pressure and relieve portal hypertension in patients without progressive liver and lung failure. Complications include onset or worsening hepatic encephalopathy shunt thrombosis or occlusion. Operative shunts may also make eventual liver transplantation more difficult.

8.3. **Liver transplantation** is indicated for intractable variceal bleeding, progressive hepatic dysfunction, development of ascites and jaundice, severe malnutrition and deteriorating quality of life related to liver disease. Immunosuppression is required but despite concerns about the effects on respiratory infections successful outcomes have consistently been reported. Survival rates are comparable to other indications for liver transplantation. Children are more likely than adults to develop de novo CF related diabetes mellitus early post liver transplantation due to a combination or predisposition and additional risk factors (eg diabetogenic drugs).

9. New developments

9.1. **New bile acid (BA)** theories have come to light. BA are inherently cytotoxic. Serum BA levels in CFLD is higher compared to liver disease in non-CF and healthy patients. Higher serum cholic acid levels are associated with increased fibrosis and inflammation. There is higher faecal BA loss in CFLD suggesting defective enterohepatic BA reabsorption in the ileum.

9.2. **Farnesoid X receptor (FXR)** is expressed in the liver and gut. It is a major controller of BA homeostasis by regulating BA synthesis via a negative feedback loop. Impaired FXR signalling is associated with increased hepatocellular damage. This could be caused by reduced bile salt levels in the lumen of the ileum, acidic surface pH in the CF ileum, increased glucuronidation of apical bile salts and increased levels of natural FXR antagonists in relation to bacterial overgrowth (eg reduced lactobacillus). Treatment option is use of a synthetic FXR agonist (Obeticholic acid).

9.3. **Vitamin D receptor (Vdr)** may play a role in CFLD. Vitamin D binds to Vdr and indirectly may reduce the inflammatory reaction and reduce risk of fibrosis.

9.4. **Gut-Liver-Axis-Theory:** increased intestinal permeability can lead to bacterial overgrowth that can cause inflammation in the liver. CF patients have inherently different gut microbiota and alterations in gut permeability (likely secondary to high fat diet).