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Cystic Fibrosis Liver Disease

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1. Introduction

Cystic fibrosis (CF) is the most common fatal autosomal recessive disorder in the white population with a frequency of 1 in 2500 live births. Inherited defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene result in abnormal regulation of salt and water movement across membranes. The overall feature of CF is that secretions are dehydrated due to water deprivation of luminal surfaces. This is true for the sino-pulmonary tract, biliary tree and for reproductive tubes (vas deferens and fallopian tubes).

Lung involvement is the main cause of morbidity and mortality, but this abnormal gene results in a multisystem disease affecting the liver, pancreas, sinuses, bones and reproductive system. Since its recognition in 1938 when life expectancy was 6 months (Davis, 2006), advances in medicine and a multidisciplinary team approach to patient care have increased the life expectancy of this condition such that children born today could expect to reach their 50s (Dodge et al., 2007; UK CF Trust 2009; USCF foundation 2009). The changing course of the disease has resulted in increasing relevance of other organ systems such as the liver.

2. Epidemiology of CF Liver Disease

The incidence of CF liver disease (CFLD) varies significantly among previous studies ranging from 5-30%. This is probably due to variations in definition.

On the whole, CFLD can be classified into 3 stages:

1. Biochemical – manifested by impaired liver enzymes
2. Structural – as increased bile content in the liver tissues or fatty infiltration visualised on liver ultrasound studies
3. Decompensated liver disease – which includes portal hypertension, hypoalbuminaemia, ascites and impaired coagulation.

The authors of this chapter propose to call 'clinically significant disease' as hepatic abnormalities that necessitate treatment by pharmacological and non-pharmacological methods.

In one study by Nash et al (2008), 30% of CF patients were found to be affected by clinically significant CFLD. Clinically significant disease in this study was defined as biochemical

abnormalities manifesting with raised liver enzymes and ultrasonographic evidence of structural changes, but not necessarily liver cirrhosis.

Post mortem analysis suggested that focal abnormalities in the liver tissues are commoner than was previously thought occurring in 25-50% of CF patients (Gaskin et al., 1988; Nagel et al., 1989).

The prevalence of CFLD changes with age. Unlike most CF-related complications, CFLD appears to decrease with age. The reason for this is not clear. In one study by Scott-Jupp et al (1991) on 1100 CF patients in the South and West of England, the prevalence of CFLD - as judged by the presence of an enlarged liver or spleen (or both) - was 4.2%. The age-related prevalence rose to a peak in adolescence, and then fell in patients over 20 years old. The authors concluded that the decrease in prevalence was not due to drop-out of those who died of CFLD as the proportion of fall in incidence was much greater than the expected mortality rate from CFLD.

Other studies have also found increasing prevalence with age through childhood to mid-adolescence with no significant increase thereafter (Colombo, 2007).

The prognosis of patients with a well-established CFLD also varies. Herrmann et al (2011) reported that 7.9% of patients over the age of 40 have portal hypertension. But with a 7 year median follow up, only 28% went on to develop ascites or variceal bleeding, and liver failure was a late event. Median survival after a first variceal bleed is 8.4 years. This favours well when compared to the general cirrhotic population where 1 year survival is only 34%. Hence in the absence of other markers of decompensated liver disease, bleeding may not necessarily be a marker of poor prognosis (Colombo, 2007).

Older studies suggested a much more benign course, but it is now the 3rd most common cause of death after ventilatory failure and organ transplant complications. It is therefore an important cause for concern. The overall mortality rate is reported to be 2.5% (Moyer and Balistreri, 2009), and is associated with a higher risk of overall mortality when compared to CF patients without liver disease (Gallagher et al., 2011).

3. Pathophysiology of CFLD

CFTR is expressed in the epithelial cells of the biliary tract, but not in the hepatic cells. The main feature of CFLD is destruction in the biliary duct. The impaired viscosity of bile, albeit expected, was not consistently reported in studies.

Factors that enhance destruction of the biliary tree may lie in the epithelial toxicity of retained bile salt (Westaby, 2000). Other factors leading to the development of steatosis (fatty liver) are not related to defects in the CFTR gene and remains poorly understood. It has been attributed to malnutrition, essential fatty acid deficiency, carnitine or choline deficiency or insulin resistance (Moyer and Balistreri, 2009). Another presumed factor is the impairment of the architecture of the pancreas that shares a common exit with the common bile duct (Westaby, 2000).

Development of CFLD, including portal biliary cirrhosis and multilobular cirrhosis, is attributable to the abnormal CFTR gene. This results in abnormal transport of Cl^- , HCO_3^- and H_2O at the apical membrane of cholangiocytes such that the regulation of fluid and

electrolyte content of bile is altered. As a result, bile is more viscous in CF patients than in non-CF individuals as with other mucous secretions.

Bile flow is reduced and the obstruction of intrahepatic bile ducts causes damage to hepatocytes and cholangiocytes through periductal inflammation, bile duct proliferation and fibrosis in portal tracts. This also results in activation of hepatic stellate cells, production of collagen, and stimulation of bile duct epithelium to produce TGF- β which is profibrogenic (Moyer and Balistreri, 2009).

Why some patients with early manifestations of CFLD go on to develop liver cirrhosis and why some do not remains unclear. Understanding these factors in longitudinal studies will help design strategies for management of early liver disease with the aim of halting its progression and obviating its complications.

4. Genetics of CFLD

More than 1500 CFTR gene mutations have been described (O'Sullivan and Freedman, 2009), but there is no evidence of a phenotype relationship with specific mutations in the CFTR gene. In one study, (Duthie et al., 1992) they did not identify a difference in the frequency of Delta F₅₀₈, G551 or R553X mutations and the presence of CFLD.

However the same group found that several human lymphocyte antigens (HLA) subtypes were more prevalent in patients with CFLD compared to those without (Duthie et al., 1995).

Genetics was assumed to play a role not only in the emergence of CFLD but also in its prognosis. However despite several studies reviewed by Moyer and Balistreri (2009), it remains unclear why only a small proportion of CF patients might develop liver disease, or why there was such variability in severity.

Genetic modifiers may be one way to answer this question. Modifier genes have shown to play a role by increasing susceptibility to the development of CFLD by up-regulating inflammation, fibrosis or oxidative stress. Identifying these genetic modifiers may allow identification of CF patients at risk of developing CFLD and thus allow early use of prophylactic measures (Colombo, 2007). ACE, SERPINA, CSTP1, MBL2, TGF- β 1 have all been identified as potential gene modifiers but only the SERPINA 1 Z allele has been found to be strongly associated with CFLD and portal hypertension (Bartlett et al., 2009).

5. Hepatic manifestations in cystic fibrosis

There is a broad spectrum of hepatic manifestations in cystic fibrosis as described in Table 1 (Colombo, 2007). Of those described the most clinically relevant in CF is focal biliary cirrhosis which may extend into multilobular biliary cirrhosis.

The incidence of impaired liver enzymes is high, affecting around 65% of patients with CF (Bhardwaj et al., 2009). Frequently these abnormalities may be transient and could relate to drug treatments or intercurrent infections (Moyer and Balistreri, 2009). The majority will not progress to clinically significant disease despite elevations of serum alanine aminotransferase, aspartate transferase or gamma-glutamyl transferase of up to 2.5x the upper limit of normal (Herrmann et al., 2010).

Type of lesion	Clinical manifestation	Frequency (%)
Specific alterations ascribed to the underlying CFTR defect	Focal biliary cirrhosis	20–30
	Multilobular biliary cirrhosis	10
	Portal hypertension	2–5
	Neonatal cholestasis	Rare
	Sclerosing cholangitis	Rare
	Micro-gallbladder	30
	Cholelithiasis	15
Lesions of iatrogenic origin	Liver steatosis	23–67
	Drug hepatotoxicity	Undefined
Lesions reflecting the effects of a disease process that occurs outside the liver	Hepatic congestion	Rare
	Common bile duct stenosis	Rare

Table 1. Major hepatic manifestations in cystic fibrosis (adapted from Colombo, 2007)

Steatosis is currently considered benign in cystic fibrosis with no evidence of progression to cirrhosis, portal hypertension or hepatic decompensation (Debray et al., 2011), while gallbladder abnormalities such as microgallbladder and cholelithiasis are frequently asymptomatic and detected on ultrasound requiring no intervention (Moyer and Balistreri, 2009). These hepatic manifestations can however contribute to post prandial abdominal discomfort, abdominal pain and fatigue in CF patients. Abdominal pain and fatigue are highly common in CF patients occurring in 77% (Jarad, 2009) and 87% (Sarfaraz et al., 2010) of patients respectively in the authors’ unit.

Development of liver cirrhosis is less common, occurring in up to 30% of patients. This includes focal biliary cirrhosis with around 10% of CF patients developing multilobular biliary cirrhosis. Fewer still progress to liver failure and portal hypertension which can be associated with hypersplenism and gastro-oesophageal varices (Colombo, 2007).

Variceal bleeding in well established CFLD occurs in 30% of all cases. However it should be regarded as a rare complication in the adult CF population.

This cohort with cirrhosis and established portal hypertension are also at increased risk of developing hypoglycemia, malnutrition, hepatic osteodystrophy and worsening pulmonary status through hepato-splenomegaly and ascites-induced diaphragmatic splinting and intrapulmonary shunting (Colombo, 2007).

6. Investigations

No single reliable test is available to diagnose CFLD. Diagnosis thus relies on a combination of clinical assessment, liver biochemistry and other investigations. Table 2 gives proposed diagnostic criteria which incorporate these (Debray et al., 2011).

Hepatomegaly is often how CFLD is detected through routine examination, however, in isolation this is rarely associated with advanced liver disease. The slight enlargement of the liver size as well as the descending edge of the liver can be due to a combination of chronic

lung sepsis and lung hyperinflation both of which are common in patients with CF lung disease.

Consider CFLD if at least 2 of the following are present:
• Hepatomegaly confirmed by ultrasonography (US) • > 2cm below the costal margin below the midclavicular line • and/or splenomegaly on US • Abnormal liver function tests above the upper limit of normal • transaminases (AST and ALT) and GGT • on at least 3 consecutive occasions over 12 months • and other causes of liver disease excluded • US evidence of liver involvement, portal hypertension or biliary abnormalities • Positive liver histology (biopsy may be helpful where diagnostic uncertainty exist)

Table 2. Diagnostic Criteria for CFLD (Debray et al., 2011)

Each individual element of these criteria has their limitations when considered in isolation.

Abnormal biochemistry as previously discussed can occur frequently and often transiently. The chronic use of prophylactic oral antibiotics such as flucloxacillin in patients with chronic lung infection of Staphylococcus aureus may account for this. Also, the administration of beta-lactam antibiotics for acute pulmonary exacerbation is known to be associated with transient increases in liver enzymes. There is thus a low sensitivity for raised liver enzymes without abnormal radiology and abnormal histology. In addition some patients with multilobular biliary cirrhosis may have normal liver biochemistry (Colombo, 2007).

Ultrasonography is non-invasive and inexpensive. It can be useful in distinguishing between fibrosis, cirrhosis, ductal abnormalities and fatty infiltration (Colombo, 2007). The additional use of duplex scanning also allows detection of portal hypertension and portosystemic collaterals (Herrmann et al., 2010). Changes seen on US tests are more specific than clinical or biochemical abnormalities, with US abnormalities often preceding these changes. However, a normal scan does not exclude the development of future disease. The test is limited by both intra and interobserver variability in sonographic assessment with a positive predictive value of a normal US of only 33% and a sensitivity of 57% (Debray et al., 2011).

Williams et al (1995) devised and validated a scoring system for the severity of CFLD. The scoring system included the appearance of liver parenchyma, liver edge and periportal fibrosis. The score was found to distinguish transient liver disease from well established disease. The scoring system also identified sub-groups of patients who were regarded to have a pre-cirrhotic liver. A prospective prognostic evaluation of this scoring system has not yet been performed.

Magnetic resonance imaging (MRI) is emerging as an important investigation of the abdomen in CF patients (Figure 1). In a case-control study, we found that the pancreas was absent in CF patients with and without diabetes compared to age matched non-CF patients

with Type I diabetes mellitus (Sequeiros et al., 2010). In another study we also reported that the spleen size, as measured on MRI, is reduced in patients with CF-related diabetes compared to those without and compared to age-matched patients with type I diabetes without CF (Jarad et al., 2010).

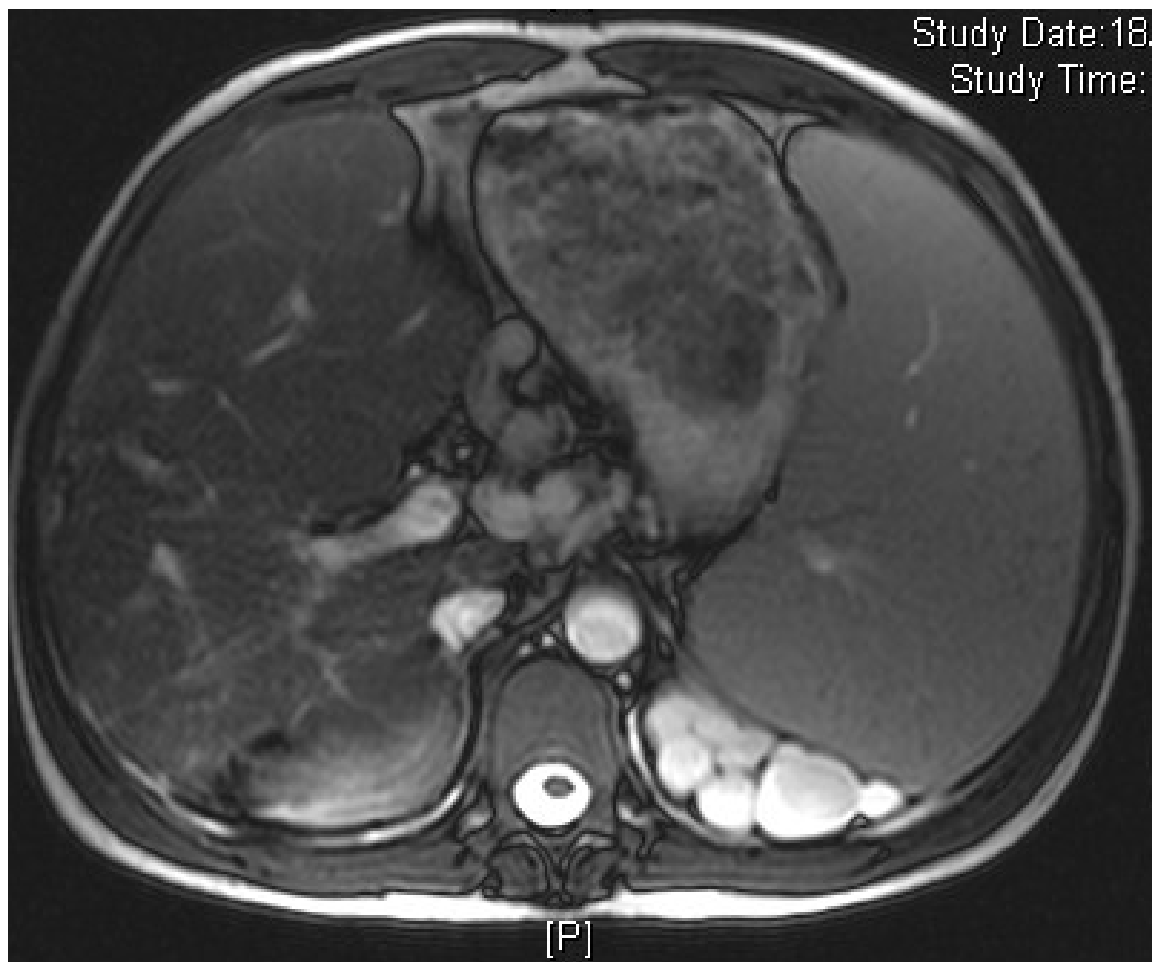


Fig. 1. MRI scan in a 24 year old lady with CFLD demonstrating liver cirrhosis, splenomegaly and tortuous veins on the spleen surface.

As for the liver, MRI scan is both a sensitive and a specific diagnostic test for CFLD. MRI can characterize the architecture of the liver structures (Westaby, 2000). A further delineation of the portal and splenic vascular bed and further enhancement of the definition of the liver architecture could be made through magnetic resonance cholangio-pancreatography (MRCP).

MRI and MRCP are non-invasive and well tolerated procedures, but the imaging remains too costly for the tests to become a screening procedure or to be used for follow-up purposes of all CF patients.

The presence of fibrosis on liver biopsy is both diagnostic and predictive of development of future portal hypertension and significant liver disease (Lewindon et al., 2011). However, the patchy distribution of lesions found in CFLD mean this invasive test can underestimate

severity which limits its use (Colombo, 2007). It is thus not a routine test in many units unlike in chronic liver disease that is not linked to cystic fibrosis.

These limitations mean that CFLD often remains undetected until advanced stages prompting the need for other investigations. Both MRI and CT imaging can be useful in discriminating steatosis from fibrosis. MRCP and hepatic scintigraphy may help detect extra and intrahepatic biliary tree abnormalities in patients without clinically apparent disease and aid assessment of biliary drainage (Herrmann et al., 2010). These may play an important role in the future of CFLD. Other potential methods include transient elastography (fibroscan), which measures liver stiffness in a non invasive manner, which correlates closely with fibrosis and biochemical markers of fibrosis. Their value in CF remains to be determined (Debray et al., 2011).

A suggested approach to investigating CFLD and its initial management is shown in Figure 2.

Diagnosis of liver failure is similarly problematic due to the maintenance of liver function until the terminal phase. Clotting factors and prothrombin time should be monitored at least annually as this may give an indication. Liver failure should be considered if PT remains prolonged or if factors VII, X and II remain decreased despite vitamin K supplementation (Debray et al., 2011).

7. Management of CFLD

The mainstay of treatment for CFLD currently is optimisation of nutritional status and bile acid therapy - ursodeoxycholic acid (UDCA). The aim of the former is to avoid vitamin deficiency and malnutrition, though a proven benefit in CFLD is lacking (Herrmann et al., 2010).

UDCA is a bile acid that was shown to increase bile flow (Renner et al., 1980) and probably protects the hepatocellular structures from the harmful effects of hydrophobic bile ducts (Hoffman et al., 1990) by displacement of toxic hydrophobic bile acids, cytoprotection and stimulation of biliary bicarbonate secretion (Moyer and Balistreri, 2009).

Ultimately, the aim of UDCA is to delay progression of disease. There is evidence of improved liver biochemistry (Desmond et al., 2007) shortly after introducing UDCA and improved histological features of liver disease afterwards (Linblad et al., 1998). However, evidence of improved outcomes such as reduced need for transplantations or improved survival is lacking (Cheng et al., 2000). UDCA is widely used as it is the only available therapeutic agent and is generally well tolerated with few side effects. Recommended dosing is 20-30 mg/kg/day.

All patients with CFLD should receive annual liver assessment. The need for the yearly input of a gastroenterologist or hepatologist has been suggested (Debray et al., 2011). Though they may request intuitive tests and aid recognition of progression to cirrhosis, as well as complications such as portal hypertension, there is no evidence of superior outcome compared to a review by an experienced CF physician. This is important as CF patients are frequently seen in hospital and all receive an annual CF assessment. Adding an assessment by another discipline need only be introduced to a selected group of patients.

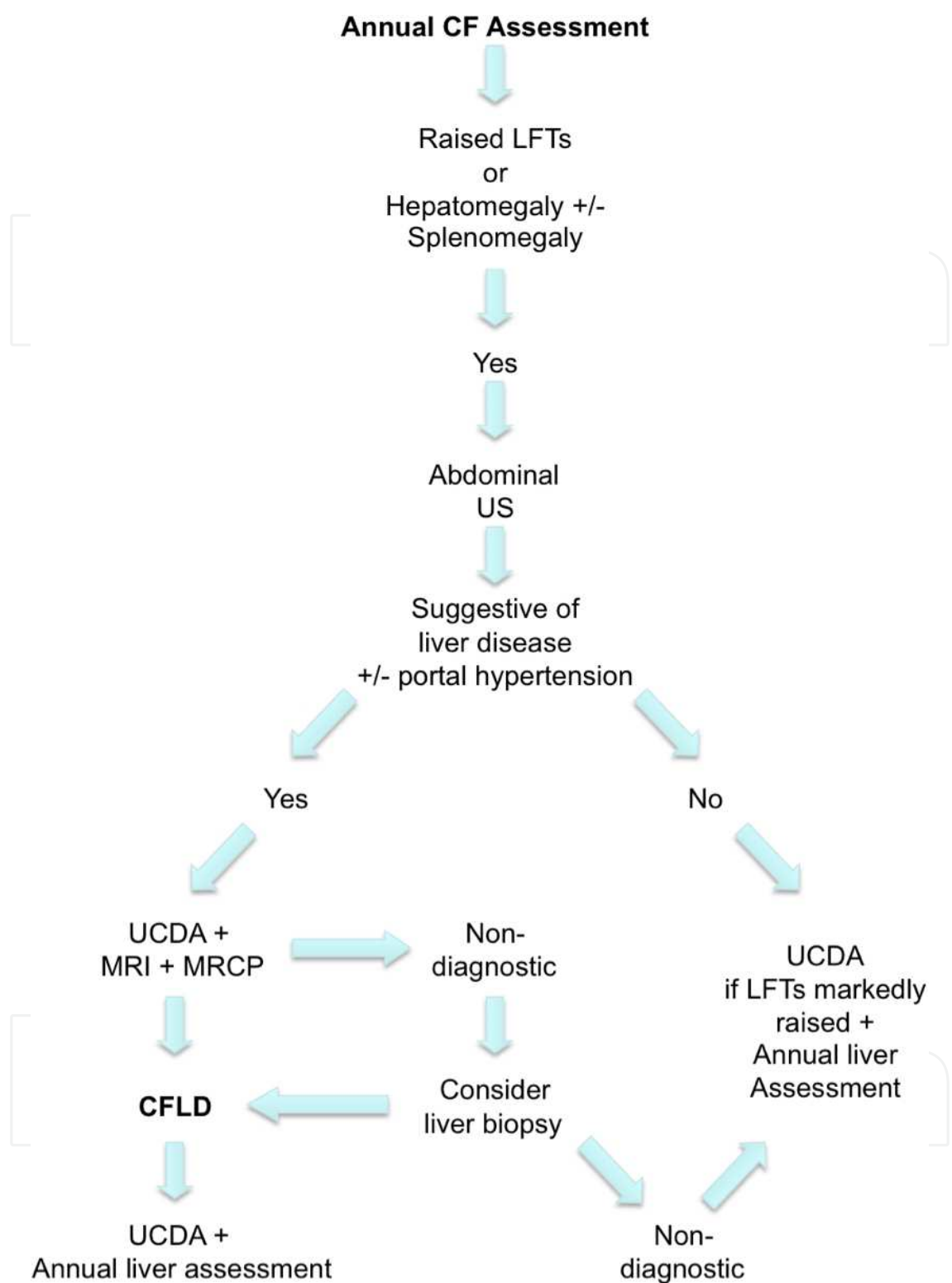


Fig. 2. Investigation and initial management of CFLD (adapted from Debray et al., 2011). Abbreviations: CF, cystic fibrosis; CFLD, cystic fibrosis liver disease; LFTs, liver function tests (i.e. liver enzymes including alanine transaminase, alkaline phosphatase; asparate transaminase and gamma glutamyl transpeptidase); MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; UCDA, ursodeoxycholic acid; US, ultrasound.

8. Management of portal hypertension

Though clear recommendations exist for non-CF patients with cirrhosis, there is no agreed guidance for this very different cohort of patients. Non-selective β -blockade is recommended, for example, which has not been evaluated in CF where lung disease may mean this is contraindicated. We do however use propranolol in at least 2 patients in our unit without significant respiratory side effects.

Band ligation is more effective than sclerotherapy, which can also carry a risk of bleeding both during and following the procedure which may result in repeated general anesthesia to the detriment of the patient's lung function. There is however no long term efficacy data in CF patients.

In the absence of such studies, recent guidance (Debray et al., 2011) states that all patients with cirrhosis and splenomegaly and/or signs of hypersplenism should receive an oesophagogastroduodenoscopy (OGD) every 2-3 years to screen for oesophageal varices. If large varices are detected these should be treated with band ligation and repeated until eradicated. Frequency of screening may need to be increased to annually. As with non-CF patients an OGD may be required more urgently in the presence of GI bleeding.

Transjugular intrahepatic portosystemic shunt (TIPSS) procedures have been used to achieve portal decompression to treat recurrent bleeding both pre-transplant (Colombo, 2007) and to allow long term survival (Herrmann et al., 2010). Surgical portal systemic shunting has also been used to preserve liver function, but carries this risk of acute liver failure and hepatic encephalopathy (Debray et al., 2011).

Rarely extra-pulmonary bleeding can occur from tortuous splenic and gastric veins (Figure 3). The efficacy of splenectomy and partial splenectomy remains unclear, with some studies suggesting this could stabilize lung function and delay progression of portal hypertension (Herrmann et al., 2010). Other studies exist reporting accelerated decline in lung function and no reduction in variceal bleeding (Debray et al., 2011) and hence it is not recommended currently. Thrombocytopenia and leucopenia due to hypersplenism requires no specific therapy.

9. Liver transplantation

Liver transplantation in end-stage liver disease is a viable option with encouraging results. There is evidence of improved lung function, nutritional status and quality of life (Columbo, 2007). Analysis of data from the United Network for Organ Sharing (UNOS) database by Mendezibal et al (2011) also demonstrated a survival benefit of liver transplant in CF when comparing those that had received a transplant to those that were still on the waiting list. The difference in mortality was significant in both paediatric and adult populations. Further analysis from UNOS shows good survival at 1 year and 5 years post transplant of 84% and 76% respectively (Arnon et al., 2011). This represents the largest review of outcomes following transplants for CFLD and supports the findings of previous smaller studies (Friedell et al., 2003; Melzi et al., 2006; Nash et al., 2008). However, overall survival post liver transplant for CFLD is less than that seen in non-CF patients who receive liver transplants for other indications. The most common cause of long term mortality is progression of pulmonary disease (Friedell et al., 2003), though haemorrhage also represents an important cause of death (Arnon et al., 2011).

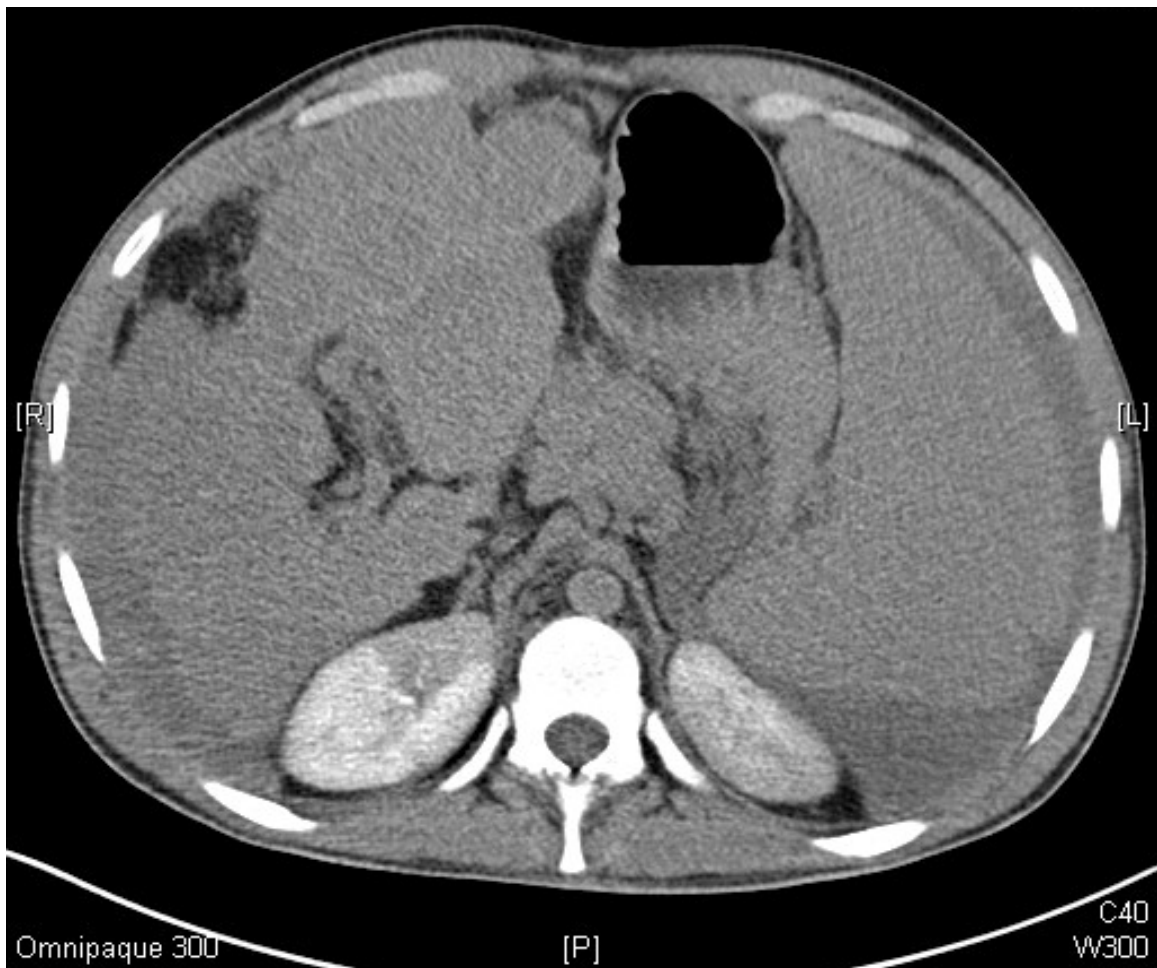


Fig. 3. CT scan in a 26 year old man with CF showing signs of liver cirrhosis, splenomegaly and haematoma around the spleen and within the abdominal cavity due to spontaneous splenic rupture. The patient died 1 week later.

The criteria and timing for liver transplantation remain uncertain. Although the criteria have widened with increased experience, inclusion of patients in liver transplantation needs to be evaluated on a patient-by-patient assessment. This is mainly because of concomitant lung disease, impaired nutrition (Figure 4) and of inability of some patients to withstand the rigor of transplant. One school of thought is that without signs of liver decompensation, survival is dependent on respiratory complications (Gooding et al., 2005). However, with other extra-hepatic benefits, earlier transplantation may be indicated. This needs to be weighed up against the risks associated with liver transplantation such as graft rejection and drug related complications (Debray et al., 2011).

Improved management options for the complications of portal hypertension may mean that transplantation ought to be considered in those with evidence of hepatocellular dysfunction in addition to portal hypertension, or those with rapidly deteriorating lung function. Other suggested indications include: the development of ascites and jaundice, intractable variceal bleeding, hepatopulmonary and portopulmonary syndromes, severe malnutrition unresponsive to intensive nutritional support, and deteriorating quality of life related to liver disease (Debray et al., 2011).

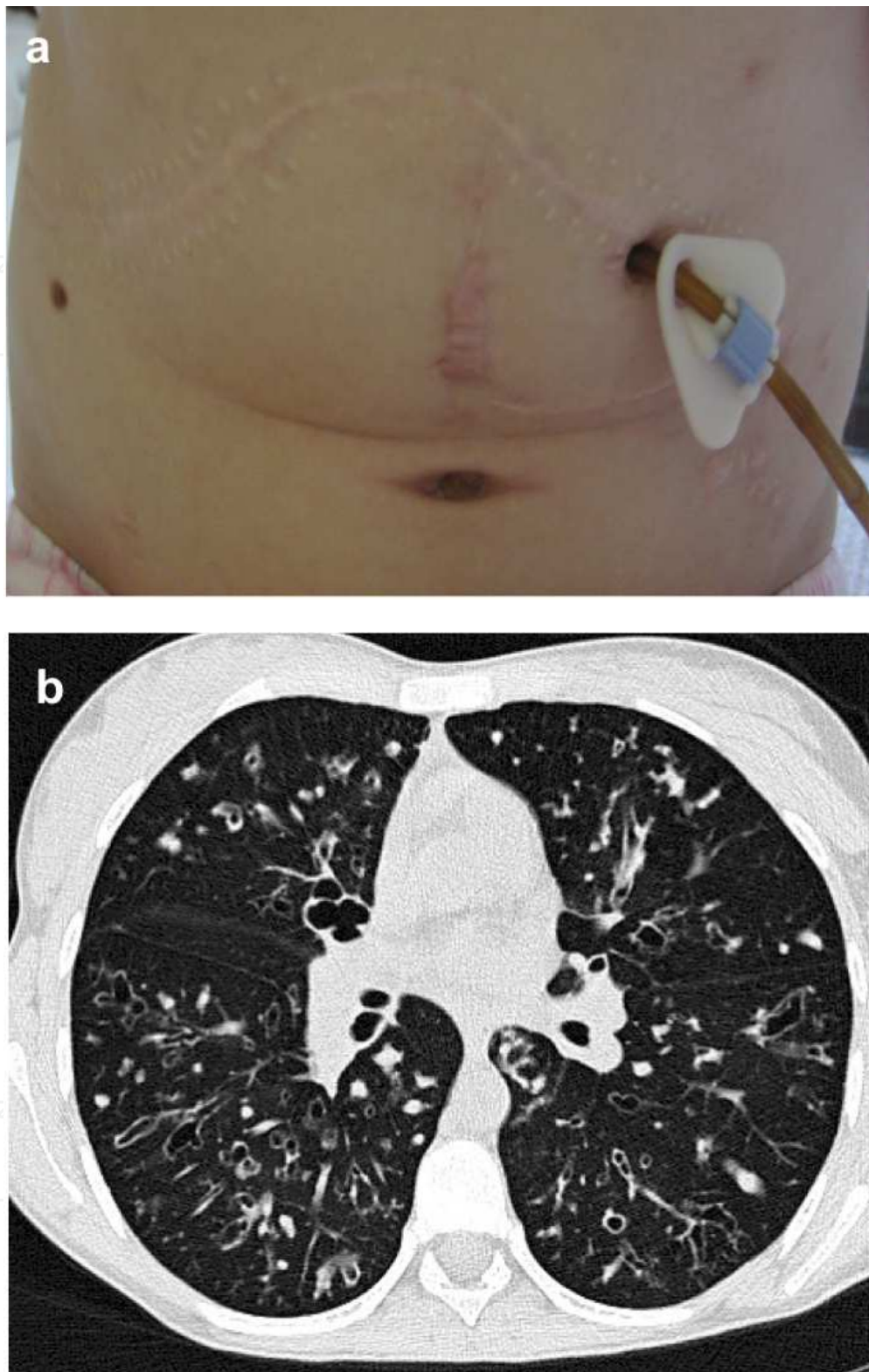


Fig. 4. a) A 21 year old female CF patient with liver transplant. Please note that the patient needed per entero-gastric (PEG) feeding due to concomitant malnutrition and low body mass index. b) Liver transplant was successful with little complication despite significant lung disease as seen by widespread bronchiectasis on her CT scan of the chest done several months after transplant.

In some occasions when patients may need both lung and liver transplant, it would be indicated to undertake transplantation of both organs. With the shortage of donated organs, this decision needs to be taken carefully. However, survival is comparable for combined liver and lung transplantation where this is indicated (Arnon et al., 2011).

10. Conclusion

CFLD occurs relatively frequently and is the most common non-pulmonary cause of mortality.

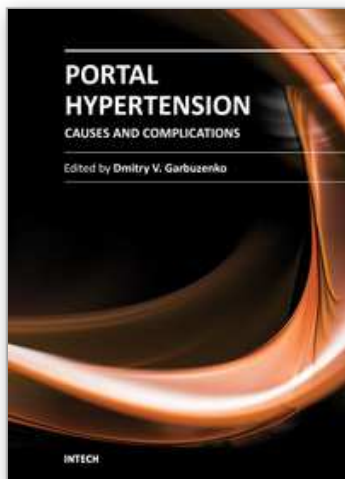
Improvements in the survival of cystic fibrosis patients mean that liver disease is likely to play an increasing role in long term morbidity and mortality. Current diagnosis relies on a combination of clinical examination and biochemistry, with old and new imaging techniques. UDCA is currently the only therapeutic option in CFLD, though its benefits on long term outcomes are not proven. Options addressing the complications of portal hypertension include TIPSS and OGD with variceal ligation. Orthostatic liver transplantation is also an option in end-stage liver disease with encouraging results.

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Portal hypertension is a clinical syndrome defined by a portal venous pressure gradient, exceeding 5 mm Hg. In this book the causes of its development and complications are described. Authors have presented personal experiences on conducting patients with various displays of portal hypertension. Moreover, the book presents modern data about molecular mechanisms of pathogenesis of portal hypertension in liver cirrhosis, the information about the original predictor of risk of bleeding from gastro-esophageal varices and new methods for their conservative treatment.

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