Abstract

Evidence of chronic liver disease is found in 25% of patients with cystic fibrosis (CF) and is the cause of liver decompensation in 2–3%. Liver injury is secondary to bile duct plugging and secondary bile-acid-related toxicity; almost all cases present in the first two decades of life. The marked variation in the presence and severity of disease may be due to modifier genes. Most cases are detected on routine screening and only a small proportion present with variceal bleeding, ascites or persistent jaundice. Abnormalities of liver function tests have a low sensitivity and specificity and the presence of established cirrhosis will be diagnosed on imaging. There is some evidence that the biliary liver disease of CF responds to ursodeoxycholic acid, although the degree of benefit remains uncertain. Liver transplantation has been successfully undertaken in the presence of isolated liver decompensation with maintained pulmonary function. Specific complications of cirrhosis including variceal haemorrhage, ascites and encephalopathy are managed by standard techniques applicable to all types of cirrhosis. There is accumulating evidence that established compensated cirrhosis does not adversely affect the outcome from lung transplantation.

Liver involvement is well recognized in cystic fibrosis (CF) and may also be an occasional dominant manifestation. Estimates of the prevalence of liver disease depend upon the tools and definitions used, the earliest from post-mortems suggesting that in excess of 70% of adults in the third decade had some evidence of focal biliary cirrhosis (the pathognomic lesion of CF liver disease) [1]. Recent prospective studies suggest that approximately 20–25% of CF patients will develop liver disease but only 6–8% of these will have established cirrhosis [2, 3], the majority of which will present in the first 20 years of life. With the vast improvements in the care of pulmonary complications of CF as well as the availability of lung transplantation, it might have been anticipated that the prevalence of liver disease in a more elderly adult population would increase, but this does not appear to be the case.

Pathogenesis

The pathogenesis of chronic liver disease in CF is illustrated in figure 1. The characteristic hepatic lesion in CF is focal biliary cirrhosis consistent with that seen in partial biliary obstruction (fig. 2). The plugging of intra-hepatic bile ducts is similar to that seen in the pancreatic ducts of CF patients [4]. CF transmembrane conductance regulator (CFTR) has been localized to the apical membrane of the cells lining the intra-hepatic bile ducts [5]. The abnormalities of chloride transport inhibit the hydration of the canalicular-produced bile, resulting in increased viscosity. In addition, intra-hepatic biliary epithelial cells produce excessive mucus composed of proteoglycans, which increases the viscosity of CF bile [6]. The initial focal distribution of cirrhotic changes in CF can be explained by early patchy plugging of the intra-hepatic ducts; with increasing ductular involvement, the process becomes more diffuse, producing a fully established biliary cirrhosis with pan liver involvement. Whether biliary duct obstruction is alone sufficient to account for this process remains controversial.
A study of CF liver disease based on both light and electron microscopy demonstrated features more in keeping with a destructive bile duct lesion than obstruction alone [7]; the authors suggested a bile-related toxin as the most likely explanation for these findings. Changes in the composition of the bile acid pool have also been suggested as possible causes [8]. Although studies have shown no significant difference in the serum bile acid profile between those with and without evidence of liver disease, the crude measures used may not accurately reflect the exposure of the hepatocyte to potentially hepatotoxic bile acids. Bile salt output remains normal or modestly reduced in CF, although the total volume of bile is significantly decreased [8, 9]. Thus a high concentration of bile acid is generated within the intrahepatic bile ducts. If there is partial or complete ductal obstruction, bile acid reflux could occur, exposing the hepatocyte to a high concentration of potentially toxic lipophilic bile acids, either primary (chenodeoxycholic acid) or secondary (deoxycholic and lithocholic acids).

Although these hypotheses provide a possible aetiological basis for chronic CF liver disease, they fail to account for the absence of liver involvement in the majority of patients or the wide spectrum of severity in those in whom this does occur. Speculation that with time the vast majority of patients with CF will develop liver disease has not been substantiated [10] and attempts to correlate the CFTR genotype with development of liver disease have been unsuccessful [11]. It has been proposed that other factors such as environmental, nutritional or non-CFTR genetic influences may be important. Mutations in the alpha-1-antitrypsin, mannose-binding lectin (MBL) [12] and glutathione-S-transferase [13] genes may act as independent risk factors for CF liver disease (chapter 10). It has also been suggested that obstruction of the common bile duct as it passes through the diseased pancreas may contribute to liver disease as biliary cirrhosis is a recognized complication of long-term bile duct obstruction in chronic pancreatitis of other causes [14] although some studies have not confirmed this [15]. The presence of a sub-population of lymphocytes, cytotoxic to hepatocytes and directed towards the liver-specific lipoprotein, suggests that immune mechanisms might also be involved in the pathogenesis of CF liver disease [16].

**Clinical Features**

Deep cholestasis secondary to common bile duct obstruction with inspissated bile may be the earliest manifestation of CF [17, 18]. Fatty infiltration of the liver may sometimes produce massive hepatomegaly and abdominal distension, complicated by hypoglycaemia [19, 20]. Evidence of underlying cirrhosis may occur at any time, but new diagnoses are most frequently made during the first
two decades of life. Historically, many cases of established chronic liver disease were detected as part of routine follow-up in patients with an established diagnosis of CF [21], hepatosplenomegaly being the commonest presentation. Abnormal liver function tests are common in CF; they may be of no significance, but might also be the only indicator of underlying chronic liver disease. Many large centres have established routine surveillance including sequential ultrasound scanning (see below), which has identified a small proportion of patients with no other clinical or laboratory evidence of liver disease. Variceal bleeding may be the presenting feature of established portal hypertension and may occur in the absence of any other signs of decompensation. As in other types of biliary cirrhosis, portal hypertension may occur in a pre-cirrhotic phase because of the pre-sinusoidal component to portal vascular resistance. Signs of decompensated biliary cirrhosis (jaundice, ascites or encephalopathy) are very unusual presenting features. In general, the clinical picture is one of very slowly progressive liver disease (as seen in other biliary cirrhotic disease such as primary biliary cirrhosis or primary sclerosing cholangitis [22, 23]). The natural history is, in fact, usually interrupted by mortality related to pulmonary disease.

Controversy remains as to whether the adverse effect of liver disease in CF is restricted to the 2–3% of patients with overt liver decompensation and the 1–2% with variceal bleeding, or it confers an adverse prognosis per se. One large study showed a decline in the prevalence of liver disease in the third decade, raising the possibility of premature mortality in those with the complication [10]. A large time-dependent, multivariate analysis reported liver disease as an independent risk factor for mortality in addition to pulmonary function and nutrition [24], although the mechanism has not been fully explained. The systemic and pulmonary haemodynamic abnormalities seen in all types of cirrhosis are also present in patients with CF liver disease [25]; the low peripheral vascular resistance, high cardiac out-put and increased pulmonary shunting might adversely affect patients with advanced pulmonary disease, although prospective studies will be required to determine whether this is the case.

**Investigations**

**Liver Function Tests**

Standard liver function tests have reasonable sensitivity but poor specificity, which is not surprising as they may be influenced by many factors such as infection, hypoxemia and medications. This is particularly the case with amino transferase levels. Markers of a biliary component such as alkaline phosphatase and γ-glutamine transpeptidase may be more helpful, particularly when they are elevated by a factor of 3–4, sustained over a period of months [26]. However, it must be remembered that a small proportion of patients with established cirrhosis will have entirely normal liver function tests [10, 26]. The most important role for standard liver function tests is to initiate a search for possible underlying liver disease, specifically, liver imaging.

**Ultrasound Scanning**

The availability of high quality transabdominal ultrasound scanning has provided a means of detecting liver disease cheaply and readily. In experienced hands ultrasound can both diagnose diffuse cirrhosis and detect focal disease [27]. Splenomegaly, a dilated portal vein and collateral vessels are all important markers of portal hypertension [27]. The use of doppler studies allows the detection of portal or splenic vein thrombosis, the incidence of which is increased in CF, most commonly as a consequence of associated chronic pancreatitis. An ultrasound scoring system has been developed for the detection of chronic CF liver disease in adults (table 1) [28] based on irregularity of the parenchyma and liver edge and periportal fibrosis (fig. 3).

**Magnetic Resonance Imaging**

A recent study has investigated the use of magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) in the documentation of CF liver disease [29]. These techniques have produced excellent definition of the cirrhotic liver and the collateral circulation associated with portal hypertension (fig. 4). The MRCP technique has allowed visualization of the biliary tree required in the detection and management of common bile duct stones. With improving resolution, MRCP may also define the intra-hepatic biliary tree and the abnormalities of calibre characteristic of CF-related liver disease [30].

**Radionuclide Imaging**

Derivatives of iminodiacetic acid (IDA) labelled with technetium-99m provide an alternative means of assessing
the biliary tree [31]. IDA, when injected systemically, is taken up by hepatocytes and then cleared rapidly into bile. In established cirrhosis there are documented delays in hepatocyte uptake and excretion, at the levels of both the intra- and extra-hepatic biliary trees, which may be one of the earliest abnormalities seen in those susceptible to the development of the biliary cirrhosis [32]. The advent of quantitative IDA imaging raises the possibility of monitoring objectively the degree of hepatocyte and biliary impairment and response to therapy [33].

**Invasive Techniques**

The characteristic intra-hepatic bile ductular change associated with established CF cirrhosis is irregularity of calibre caused by areas of stricture and dilatation and is similar to the picture in primary sclerosing cholangitis (fig. 5) [15]. These changes were first detected by trans gall bladder or endoscopic contrast cholangiography [15, 32] and are highly specific for established chronic liver disease, not being described in patients without this on the basis of ultrasound evidence [15]. Endoscopic retrograde cholangiography (ERCP) is an invasive procedure which is no longer considered an appropriate investigative technique for evaluating CF-related liver disease. With the increasing resolution of MRI/MRCP there is every expectation that these intra-hepatic ductular changes will be adequately delineated by this non-invasive technique. Endoscopy has a role in the management of common bile duct stones and a small proportion of patients in whom there is evidence of common bile duct obstruction at the level of the head of the pancreas. Histological assessment forms a fundamental basis for most aspects of hepatology. However, in CF liver disease the initial focal nature of the changes may result in considerable sampling error. Ultrasound-guided biopsy may reduce this risk if focal nodularity can be detected.
There has been understandable reluctance to carry out liver biopsy in patients with CF on the basis that management was seldom changed and it carries the risk of pneumotho-rax. The imaging techniques described above, carried out in experienced hands may well provide sufficient diagnostic information for the vast majority of patients. Liver biopsy can then be reserved for a very small proportion of patients in whom other possible causes of liver damage need to be excluded.

**Management**

**Bile Acid Therapy**

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid, comprising 3% of the total bile acid pool in humans, which has been used extensively in cholestatic disorders [34], although the mechanism of action is unclear and is probably multi-factorial. Evidence points towards protection of cholangiocytes against the cytotoxic influence of hydrophobic bile acid [35]. In patients with primary biliary cirrhosis and primary sclerosing cholangitis there has also been evidence of reduced inflammatory reaction around the intra-hepatic bile ducts with UDCA therapy [36, 37]. UDCA has been shown to have a stimulatory effect upon biliary secretion by increasing the number and activity of carrier proteins in the apical cell membrane [38] and it may protect the hepatocyte against hydrophobic bile-acid-induced apoptosis [39]. A possible immunomodulatory effect has been proposed related to the reversal of aberrant expression of HLA class-1 molecules on hepatocytes [40]. A number of studies have evaluated UDCA in patients with CF liver disease. Initial uncontrolled data suggested both bio-chemical and clinical improvement [41, 42] and the optimum dose appeared to be between 15 and 20 mg/kg [43, 44]. Attention has been paid to the need for taurine supplementation as part of UDCA therapy. Taurine deficiency is frequently observed in patients with CF secondary to malabsorption and faecal loss of taurine-conjugated bile salts and increases the proportion of glycol-conjugated bile acids, which are potentially hepatotoxic. However, a single study showed no additional effect upon liver function, but there was a degree of nutritional benefit [42]. A small unblinded controlled trial was the first to report both benefits in liver biochemistry and improvement in biliary excretion of IDA derivatives with UDCA [45]. A further placebo-controlled trial has also confirmed improvement in biochemistry and a general illness score [46]. However, neither of these trials has been of sufficient power or duration to allow assessment of the risk of decompensated liver disease, need for liver transplantation or associated mortality. A small study has evaluated the effect of UDCA on liver histology [47]. Using a scoring system based on bile duct proliferation, fibrosis, inspissation of bile and inflammatory changes, a significant histological benefit was confirmed after 1 or 2 years. There are clearly insufficient data upon which to base clear management guidelines [48]. It is highly unlikely that this drug is capable of reversing advanced liver disease and as such there is considerable justification for focusing further studies on the introduction of this drug in patients with early imaging evidence of liver disease [26]. More objective therapy may evolve as risk factors predicting the development liver disease are identified. In the meantime it is likely that treatment with UDCA will continue as the drug is well tolerated with very few adverse effects.

**Liver Transplantation**

Liver transplantation has been an important strategy for advanced chronic liver disease with survival rates in excess of 80% at 1 year and as high as 60% at 10 years. The criteria for inclusion of patients for liver transplantation have gradually expanded with increased experience. As for other types of cirrhosis, features of advanced liver decompensation are standard including encephalopathy, poorly controlled ascites and progressive jaundice. The use of liver transplantation in CF was initially discounted based on fears that the required immunosuppression would increase the risk of overwhelming pulmonary sepsis. However, beneficial results in several small series of patients undergoing liver transplantation have encouraged wider application [49, 50] and in fact, many patients demonstrated significant improvements in pulmonary function after this procedure, possibly related to resolution of splenomegaly or ascites, which impair diaphragmatic function, reduction of intra-pulmonary shunting or the immunosuppressive agents used. However, a number of pulmonary contra-indications to liver transplantation remain, including severely compromised lung function or frequent exacerbations of pulmonary infection. Infection with organisms such as *Burkholderia cepacia* or other multi-resistant bacteria may be considered relative contra-indications. A persistently raised arterial CO₂ indicating underlying ventilatory failure would also represent an absolute contra-indication to single organ liver transplantation. In appropriately selected CF patients, survival following isolated liver transplantation in the short and medium term (up to 5 years) appears to be similar to that in other types of cirrhosis [51]. The importance
of portal hypertension and variceal bleeding as indicators for liver transplantation is controversial. There are a number of groups who use the presence of portal hypertension and the history of variceal bleeding as specific risk factors incorporated in scoring systems to identify those suitable for isolated liver transplantation [52]. However, in our large personal experience, we observed long-term survival following variceal bleeding to be comparable to that of the general CF population [author's unpubl. data]. This likely reflects the success of new endoscopic techniques for managing variceal bleeding (fig. 6) and the absence of other serious complications such as persistent ascites and encephalopathy. There remains a small but important group of patients with advanced liver disease and pulmonary disease of such severity that liver transplantation alone would not be feasible, in whom there are a number of reports of heart, lung, liver or lung/liver transplantation [51, 53, 54], one demonstrating 1-year survival of up to 70% [53], although medium- and long-term data are not available. With a shortage of donor organs there has been some reluctance to use those available in such a high-risk undertaking.

Management of Complications

Most CF patients with cirrhosis never develop specific complications and with the exception of UDCA, no specific therapy needs to be considered. However, some care should be taken with respect to nutritional requirements as patients with established cirrhosis have an increased resting energy expenditure [55] and may have deficiencies of micronutrients, fat-soluble vitamins and clotting factors [56], which may be further compounded by the contraindication to gastrostomy in patients with established portal hypertension and ascites.

Jaundice

Jaundice is occasionally seen as a consequence of bile duct obstruction in infancy and resolves when the plugging of the common bile duct is relieved. As a complication of cirrhosis it is unusual [15], is considered a poor prognostic feature and requires investigation to exclude other possible treatable causes, such as sepsis, drug toxicity or haemolysis. Trans-abdominal ultrasound scanning is essential to exclude bile duct obstruction, from either stones or a distal common bile duct stricture (see above). For those patients in whom jaundice represents the advanced stage of chronic liver disease UDCA has been shown to improve liver function and may lead to at least transient resolution of the jaundice.

Variceal Bleeding

This represents the commonest serious complication of chronic liver disease, but occurs infrequently, with a prevalence of under 2%. There is a well-recognized relationship between the severity of the underlying liver disease and the risk of first haemorrhage. Variceal bleeding should be managed using the same principles as in any other cirrhotic group of patients [57]. Initial resuscitation is critical. Replacement of blood loss is essential to maintain systemic haemodynamics and protect against renal impairment. There is a high risk of sepsis during an episode of variceal bleeding and prophylactic antibiotics covering a broad cross-section of gastro-intestinal-related bacteria are beneficial [58]. Injection sclerotherapy via fibre optic endoscopy was established as the first therapeutic technique to improve survival but has now been replaced by banding ligation (fig. 7) [59]. Success in controlling bleeding has been reported in 85–90% and in experienced hands the complication rate associated with banding ligation has been small [59]. Proton pump inhibitors [60] and sucralfate [61] are beneficial in the management of the mucosal ulceration associated with endoscopic therapy and also reduce the risk of early re-bleeding. There is a significant risk of early rebleeding (approximately 30%) and repeated banding ligation may be required. Both vasopressin and somatostatin analogues modulate portal blood flow and pressure by reducing splanchnic inflow and, in the case of somatostatin, by a direct effect on the portal circulation itself. The vasopressin analogue tri-glycyl-lysine vasopressin (glypressin) was the first pharmacological agent to be reported to produce a survival benefit in active variceal
bleeding [62]. This drug is easy to administer as an intravenous bolus and appears to have few cardiovascular side effects (the major drawback of vasopressin). Somatostatin and its analogue, octreotide, have benefit in active bleeding with few associated side effects although comparative studies suggest that glypressin is the most effective agent [63]. The major role for pharmacological agents is to buy time for endoscopic therapy. There is also some evidence that continuing these agents for 4–5 days after endoscopic therapy reduces the risk of early rebleeding [64]. In the presence of life-threatening bleeding, balloon tamponade [65] has been shown to be effective. It is at best a very uncomfortable and unpleasant experience for the patient and in the presence of significant pulmonary disease is associated with a high risk of complications, particularly aspiration. The most commonly used rescue procedure for persistent bleeding is the creation of a portal systemic shunt. Initial surgical shunts were highly effective at the expense of a marked reduction in liver blood flow and high morbidity and mortality from liver failure [66]. Over the last decade it has been possible to create a portal systemic shunt by a radiological technique termed a ‘trans-jugular intra-hepatic portal systemic shunt (TIPPS)’. Because this is a much less invasive procedure, operative morbidity and mortality are small and the benefits with respect to arresting bleeding and preventing re-bleeding were maintained [67]. However, hopes that this intra-hepatic shunt might maintain a higher level of blood flow to the liver as compared to shunt surgery have not been realized. Post-procedural liver decompensation, specifically encephalopathy, is well recognized and represents the major drawback. There is however a small but important rescue role for this approach in patients in whom there has been a failure to control bleeding following the endoscopic technique and this has been successfully applied in CF patients [68]. Non-selective β-adrenoreceptor blockade has been shown to be effective for preventing recurrent variceal bleeding as well as reducing the risk of the first variceal haemorrhage in those patients who are known to have high risk oesophageal varices [69]. Drugs such as propranolol and nadolol have been widely used in this setting. However, in the presence of pulmonary complications of CF there are concerns that these drugs might precipitate bronchoconstriction. Endoscopic techniques have also been evaluated to prevent the first variceal bleed in high risk patients and in the case of banding ligation there is some accumulating evidence of benefit [70].

Ascites
The accumulation of a transudate within the peritoneal cavity is a well-recognized complication of cirrhosis and portal hypertension and is a poor prognostic factor. In CF liver disease it is a feature of advanced disease and decompensation (which may not be the case for variceal bleeding). For those cases in whom clinically significant and

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Fig. 7. (a) A diagrammatic representation of banding ligation for oesophageal varices. (b) Endoscopic view of strangulated oesophageal varices after banding ligation.
Persisting ascites develops, the management is that applied in any case of underlying cirrhosis [71].

**Encephalopathy**

Hepatic encephalopathy is an extremely infrequent complication in patients with CF. It has only been described in patients with very advanced liver disease, often complicating some other adverse event such as ventilatory failure, sepsis, gastro-intestinal haemorrhage or persistent constipation. Where there is a clearly defined precipitating factor there may be expectation that the disturbed cerebration may revert promptly when the acute situation is resolved. More prolonged encephalopathy in the absence of a specific precipitant is an extremely poor prognostic factor. As with other complications of cirrhosis management is not different to that used more widely in the hepatological field [72].

**Splenomegaly and Hypersplenism**

Gross splenomegaly may occur in patients with CF related-cirrhosis. This may be the cause of abdominal pain, which on occasions may be severe (usually as a consequence of a splenic infarct). In most circumstances there is no indication for specific treatment, and simple non-opiate analgesia (avoiding non-steroidal inflammatory drugs) is sufficient. Pain alone is a very unusual indication for splenectomy. In the small proportion of patients with very large spleens there may be impairment of diaphragmatic function. Low platelet counts due to hypersplenism are frequently encountered, and in the rare instance in which spontaneous bleeding occurs is an indication for splenectomy [73] or partial splenectomy [74]. Alternative approaches have been to embolize the splenic artery to reduce splenic size. TIPPS has also been used as a means of reducing portal hypertension in this setting.

**Influence of Liver Disease upon Organ Transplantation**

There is now evidence from a small series that patients with well compensated cirrhosis tolerate lung transplantation without difficulty and have not presented problems with decompensation. Furthermore there is no evidence that variceal bleeding has been precipitated [75]. In our own series, 5 patients with established cirrhosis and portal hypertension have undergone heart/lung or lung transplantation without specific liver related complications. For those patients in whom there is evidence of liver disease but not fully established cirrhosis there should be no contraindication to lung transplantation.

![Fig. 8. A cholangiogram obtained at ERCP showing multiple stones in the biliary tree as well as in the gallbladder.](image)

**Extra-Hepatic Biliary Disease in Cystic Fibrosis**

Abnormalities of the extra-hepatic biliary system, the pathogenesis of which is similar to that of intra-hepatic biliary disease, are commonly observed in CF. Approximately 25% of patients have non-functioning gallbladders and at post mortem 30% have micro-gallbladders (<1.5 cm in length and <0.5 cm in width) [27]. Stenosis or atresia of the cystic duct is also a common finding. At post mortem 24% of adult CF patients were found to have gallstones [27] (fig. 8). A reduced prevalence in younger patients suggests increasing risk with age which is typical of the pattern seen in the general population. These stones are almost always radiolucent and the majority are of cholesterol origin [76]. Analysis of stones removed from patients with CF has shown a composition including calcium bilirubinate as well as proteinaceous material. The most likely stimulus for stone formation is the low volume, high viscosity bile that follows on from the failure to hydrate the canalicular-produced bile. Complications of gallstones are commonly seen...
in CF including biliary colic, cholecystitis and extrahepatic bile duct obstruction. The management of gallstones in CF is similar to that in the general population [77]. Laparoscopic cholecystectomy is generally well tolerated in CF even in the presence of quite severe pulmonary disease. The endoscopic approach offers a minimally invasive means of managing common bile duct stones and in our own experience this has been extremely well tolerated with a very low risk of complications. The use of UDCA to dissolve gallbladder stones has not been specifically reported in CF and it is likely that in the presence of a diseased gallbladder this would not be successful. However, in selected cases in which gallbladder function is still maintained this may represent an alternative approach.

### Hepatobiliary Malignancy

It is now well recognized that patients with CF have an increased risk of gut-related malignancy [78]. We have observed a single case of a gallbladder cancer in a patient presenting at the age of 40 with biliary colic. There has recently been another single case report of a hepatocellular carcinoma in a patient with CF-related cirrhosis [79].

### References


