Journal of Cystic Fibrosis 16 (2017) S50–S61

www.elsevier.com/locate/jcf

Cystic Fibrosis-related cirrhosis

Daniel H. Leung [a,*], Michael R. Narkewicz [b]

[a] Division of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin St, Houston, TX 77030, United States

[b] Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Colorado SOM, Digestive Health Institute, Children's Hospital Colorado, 13123 East 16th Ave, Aurora, CO 80045, United States

Received 1 May 2017; revised 1 July 2017; accepted 3 July 2017

Abstract

While liver involvement is common in cystic fibrosis, the major liver disorder with impact on the clinical outcome of individuals with CF is the development of multilobular cirrhosis with progression to portal hypertension. Interestingly, this is a disorder primarily of children and adolescents. We review the proposed pathogenesis, clinical presentation, diagnostic work-up, medical and surgical management, and complications of CF cirrhosis.
© 2017 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Liver disease; Cirrhosis; Portal hypertension

1. Background

Liver involvement in cystic fibrosis is common. The spectrum of liver involvement and the reported prevalence ranges is shown in Table 1. In the liver, CFTR is localized to the apical surface of bile duct epithelium and not found in hepatocytes [1]. CFTR in biliary epithelium increases apical biliary chloride secretion primarily increasing bile acid independent bile flow. The most commonly espoused theory for the development of liver disease in CF is abnormal biliary chloride transport leading to lack of alkalinization and dehydration of bile [2]. This in turn may lead to inspissated bile in the small bile ducts with plugging, inflammation and subsequent fibrosis. This is consistent with the histopathologic lesions of biliary fibrosis in CF (Fig. 1A).

While liver involvement is common, the major liver disorder with impact on the clinical outcome of individuals with CF is the development of multilobular cirrhosis (Figs. 1B, C, and 2) with progression to portal hypertension [3,4]. Interestingly, this is a disorder of children and adolescents. In the largest series of 561 individuals with CF and cirrhosis and portal hypertension, 90% presented by 18 years of age with a mean age of diagnosis of 10 years [5]. This suggests that this is a disorder that presents early in the disease course of CF. The reason so few adults with CF are newly diagnosed with multilobular cirrhosis is unclear. In contrast, there is increasing recognition of hepatolithiasis, often associated with stricturing biliary disease and sclerosing cholangitis in adults with CF which require multiple procedures to clear stones from the liver [6].

CF associated liver disease is generally not the determinant of outcome in CF. However, multilobular cirrhosis with portal hypertension does impact outcome [7]. The main complications associated with cirrhosis are GI bleeding (10–40% in 5–10 years after diagnosis of cirrhosis), malnutrition and ascites, which are all related to portal hypertension [3,8]. Although synthetic dysfunction is rare in CF liver disease, liver disease remains the third leading cause of death but only accounts for 2–3% of deaths annually. Close to 300 individuals with CF have undergone liver transplantation in the US with about 75% occurring in children [9].

* Corresponding author at: Baylor College of Medicine, Gastroenterology, Hepatology, and Nutrition, Texas Children's Liver Center, Viral Hepatitis Program, 6621 Fannin St, CCC 1010, Houston, TX 77030, United States.

E-mail addresses: dhleung@texaschildrens.org (D.H. Leung), michael.narkewicz@childrenscolorado.org (M.R. Narkewicz).

http://dx.doi.org/10.1016/j.jcf.2017.07.002
1569-1993/© 2017 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Table 1
Spectrum CF liver involvement with reported prevalence.

Abnormality	Prevalence and/or frequency
Elevated AST and ALT	Persistent abnormalities >1.5 × ULN at well visits (>6 months apart), 30% by 20 years of age [23] 2/100 person months [16]
Elevated GGT	Persistent abnormalities >1.5 × ULN at well visits (>6 months apart), 20% by 20 years of age [23] 0.8/100 person months [16]
Hepatic Steatosis	Imaging US: 5% [12] Liver Biopsy: 23–75% [24]
Imaging abnormalities on US	18% [12]
Focal biliary cirrhosis	11–50% (autopsy studies) [33,34]
Multilobular cirrhosis	7% [13]
Neonatal cholestasis	<1%, usually associated with meconium ileus
Cholangiopathy	Increasingly recognized in adults with CF [6]

2. Clinical presentation and differential diagnosis

As mentioned above, the term cystic fibrosis related liver disease (CFLD) has been used to describe a wide spectrum of manifestations ranging from neonatal cholestasis, elevation of liver transaminases, steatosis (Fig. 1D), and gallbladder abnormalities to the development of biliary cirrhosis with or without portal hypertension [10]. Biliary cirrhosis secondary to CF (referred to as CF cirrhosis from this point forward) with portal hypertension is the most clinically important manifestation of CFLD. The most common physical exam findings of CF cirrhosis are an enlarged firm liver with or without splenomegaly. While persistent elevations greater than two times the upper limit of normal for aspartate aminotransferase (AST), alanine transaminase (ALT), or gamma-glutamyl transpeptidase (GGTP) should prompt further evaluation for subclinical CF cirrhosis, these biochemical parameters may be normal in patients with cirrhosis [11] and the specificity of these abnormalities for CF cirrhosis is poor. In patients with CF, a relative and consistent drop in platelet count over a finite period of time may also be concerning even if limits for thrombocytopenia are not met. An ultrasound revealing an abnormal heterogeneous pattern of increased echogenicity or nodularity should spur further investigation, but its prognostic value remains to be validated in a multi-center fashion [12]. Interestingly, the clinical hallmarks of advanced liver disease such as ascites, thrombocytopenia, splenomegaly, and caput medusa are often subtle, asymptomatic, or do not present until very late into the disease course in patients with CF cirrhosis, when it is irreversible and liver transplantation is indicated. While CF cirrhosis is understood to have a hepatobiliary etiology, patients rarely present with jaundice or icterus until end-stage liver disease has developed. Unfortunately, unexpected hematemesis from an esophageal variceal bleed or gastropathy secondary to advanced hepatic fibrosis and subsequent portal hypertension is often both a sentinel event and a declaration of CF cirrhosis [8]. Nearly all patients with CF cirrhosis will suffer from significant malnutrition due to a combination of anorexia and increased catabolism from chronic liver disease, early satiety due to organomegaly, and chronic liver disease. Noteworthy organomegaly and physical deconditioning also predisposes to constipation, though interestingly in CF, cirrhosis is often not characterized by hard or painful bowel movements. Rather, stools may remain soft but infrequent,

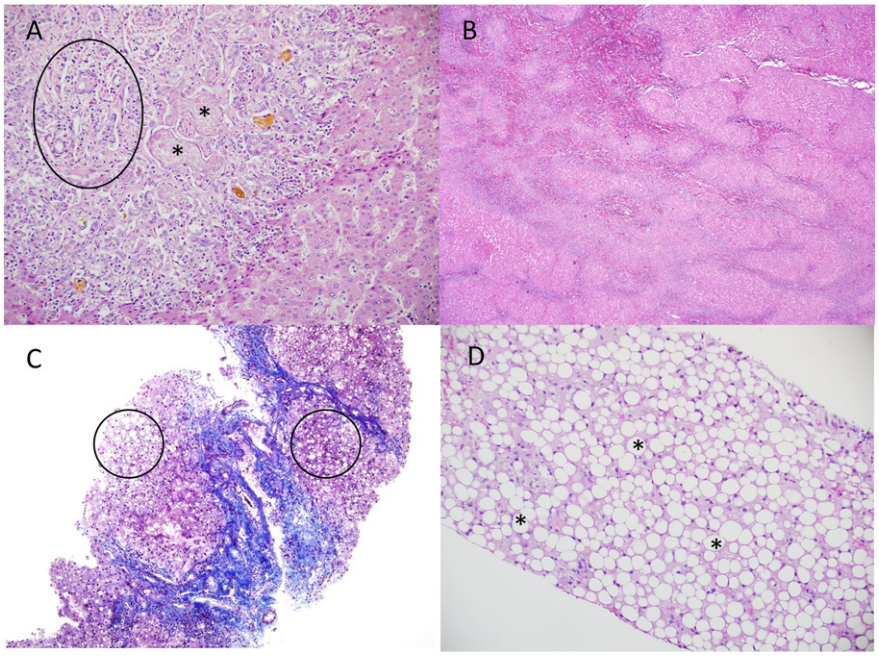

Fig. 1. Histopathology of cystic fibrosis liver disease. A-Portal fibrosis (outlined), eosinophilic concretions (*), and bile plugs (brown) adjacent to relatively unremarkable hepatic parenchyma, 20×. B-Micronodular pattern on H&E with replacement of hepatocytes with fibrosis, 20×. C-Trichrome stain highlighting thick bands of fibrosis (blue) representing cirrhosis as well as patchy steatosis (outlined), 10×. D-Liver parenchyma with diffuse macrovesicular steatosis (*) with microvesicular steatosis, 20× Images courtesy of Dr. Deborah Schady and Dr. Kelley Capocelli.

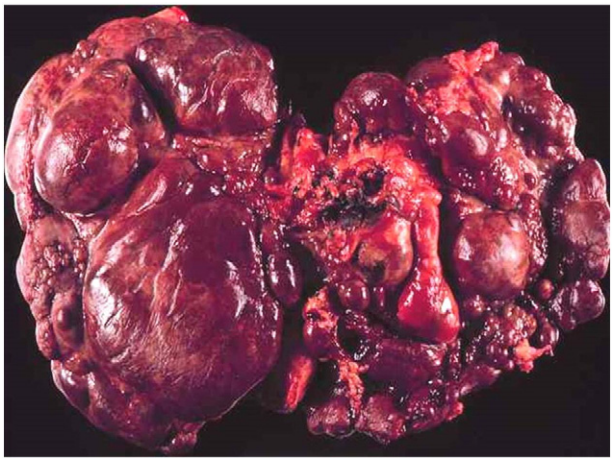

Fig. 2. Explant liver of an individual with CF cirrhosis. Image courtesy of Dr. Kelley Capocelli.

leading to chronic cramping pain. Eventually, some patients will progress to decompensated cirrhosis, heralded by ascites, liver failure with synthetic dysfunction (coagulopathy and hypoalbuminemia), or hepatic encephalopathy. Cutaneous manifestations such as palmar erythema and spider hemangiomata develop late in the disease course. This form of severe CFLD almost exclusively develops during childhood or adolescence, with no new cases beyond the age of 18 years [13,14]. However, it is possible that with increasing life expectancy, more cases of CF cirrhosis will be identified of slowly progressive CFLD that evolves to symptomatic portal hypertension, and an increasing proportion of individuals with compensated pediatric CFLD will be transplanted as adults.

3. Differential diagnosis

Recognizing various forms of CFLD can inform the provider how aggressively to pursue alternative diagnoses. Neonates with CF are uniquely vulnerable to developing cholestasis due to bile plugging/precipitation secondary to dysfunctional CFTR and altered bile composition but also their immature enterohepatic circulation, risk for meconium ileus, and variable bile acid transporter expression (i.e. BSEP, MDR3). Prior to universal newborn CF screening, infants with CFLD and elevated conjugated hyperbilirubinemia could be confused with biliary atresia (BA), a fibroinflammatory condition leading to atresia of the extrahepatic bile ducts with complete obstruction of bile flow to the duodenum [15]. Patients with BA classically present with a diminuative or absent gallbladder and acholic stools. While neonatal CFLD may present with jaundice, icterus, poor weight gain, and hepatomegaly, their hepatobiliary tree is usually fully intact.

During early childhood, elevated AST, ALT, and alkaline phosphatase without cholestasis are common [16] and transient in CF patients [17,18], often prompting further diagnostic testing and sonographic imaging. The role of ultrasound will be discussed in greater detail under Diagnosis and Management. Prolonged or chronic elevation of liver transaminases (>6 months), however, warrant additional thoughtful and targeted investigation. Children from high risk countries (i.e. Asia, E. Europe), families (i.e. IV drug use, tattoos, piercings) or communities (i.e. Burmese, Pakistani), where hepatitis B or C prevalence is high, should be screened for infectious hepatitis [19]. Patients with CF are commonly on multiple medications including antibiotics which can lead to drug induced liver disease (DILI). Ivacaftor alone or in combination with lumicaftor has also been associated with elevated liver transaminases [20]. Other potential causes for chronically elevated transaminases include autoimmune hepatitis, Wilson disease, alpha-1-antitrypsin deficiency and celiac disease. Heterozygotes for the alpha 1 antitrypsin z allele are at 7-fold increased risk for developing CF cirrhosis [21]. Nutritional deficiencies, particularly essential fatty acid deficiency and carnitine deficiency can also lead to prolonged elevation of aminotransferases [22]. In the setting of a prescribed high fat diet, PERT and limited physical activity, patients with CF may be prone to developing steatosis of the liver but this is thought to be distinct from the traditional non-alcoholic fatty liver disease (NAFLD) due to the obesity epidemic in children. While longstanding NAFLD may lead to non-alcoholic steatohepatitis (NASH) in the non-CF population, now the 2nd most common cause of cirrhosis in the United States, fatty liver that is not related to obesity does not appear to increase risk for fibrosis or cirrhosis in CF [12]. Fatty liver can also be seen in malnutrition and in poorly controlled CF related diabetes. Biliary tract disease, particularly cholelithiasis and choledocholithiasis which are part of the spectrum of CF hepatobiliary disease can lead to chronic elevation of aminotransferases. Abnormalities in GGTP are slightly less common but appear to be more common in individuals eventually found to have CF cirrhosis [23].

4. Diagnostic workup

The goal of clinical evaluation is to detect CFLD prior to the development of CF cirrhosis, distinguish it from other benign CF liver abnormalities (i.e. steatosis [24], mildly elevated aminotransferases), and exclude other hepatic diseases. Annual screening for CFLD is recommended for all children with CF (<18 years of age) and begins with a thorough physical exam. As the development of CF cirrhosis is a pediatric phenomenon, the role of routine screening of liver transaminases or ultrasound in adult patients without prior or current signs or symptoms of progressive liver disease is uncertain. Development of intrahepatic biliary stones is more common in adults but the utility of screening has not been studied.

4.1. History

In patients with persistently elevated liver aminotransferases, a careful history, specifically addressing the neonatal course, history of jaundice, change in activity level, change in stool pattern or color, abdominal pain, weight loss, medication intake including over-the-counter medications and supplements, exposure to blood transfusions, and family history of liver disease should be conducted.

4.2. Physical exam

Patients with CF should be carefully examined for hepatomegaly and splenomegaly, noting contour, liver span, and texture by both palpation and percussion. Hepatomegaly in CF may be asymmetric due to focal regenerative nodules and palpable in the subxiphoid region, rather than the traditional right intercostal spaces. Splenomegaly, while most commonly felt below the left costal margin, may also be detected along the flanks or deep in the pelvis, depending on severity.

4.3. Laboratory testing

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP), and platelet count should be measured at least annually. As mentioned before, elevation of AST, ALT, and GGTP are common in CF and admittedly have low sensitivity and specificity for early detection of CF cirrhosis. AST is found in high concentrations in skeletal muscle, kidney, heart, and liver, so is less specific for liver injury. Elevation in AST is often seen in muscular dystrophy, dermatomyositis, acute pancreatitis and high performance athletes. On the other hand, ALT is present primarily in hepatocytes and its elevation indicates parenchymal liver disease characterized by varying degrees of necrosis. A large pediatric National Health and Nutrition Examination Survey (NHANES) study by Schwimmer et al. that compared sensitivity and specificity of ALT thresholds currently used by children's hospitals with study-derived and gender-specific cut-offs for a variety of pediatric chronic liver diseases concluded that the upper limit of ALT varies greatly and is set too high to reliably detect chronic liver disease in children [25]. As such, many pediatric liver centers now recognize ALT >25 U/L for boys and ALT >22 U/L for girls as the threshold for abnormal ALT. Elevated GGTP can be seen in any form of liver disease, although typically represents biliary obstruction at either a canalicular or duct level. It is rarely accompanied by cholestasis or an elevated conjugated bilirubin in CF until cirrhosis is end-stage. A GGTP value of <50 U/L is widely considered as normal [26], although pediatric studies have suggested this threshold to be as low as 25 U/L in younger children. In a small single center case-controlled study by Bodewes et al., GGTP was a marker of CFLD (defined as splenomegaly and macronodularity on imaging) and persistent "high-normal" GGTP (>35 U/L) was highly associated with a future diagnosis of CF cirrhosis within 2 years [27]. Of note, GGTP can be inducible by drugs such as phenytoin and phenobarbital. Lastly, alkaline phosphatase (ALP) is present in a number of tissues including bone, intestine, and liver. While increased ALP levels may suggest hepatobiliary disease or obstruction, it is often elevated in conditions associated with increased osteoblastic activity, such as hyperparathyroidism, rickets, fractures, or accelerated bone growth which is common in children.

If serum biochemistries are abnormal (<2× ULN) but physical exam does not confirm hepatosplenomegaly, it is reasonable to observe and repeat the screen in 6 months. Simple biomarkers such as APRI (aspartate aminotransferase-to-platelet ratio index) and FIB-4 (Fibrosis-4) were designed to be convenient markers of liver fibrosis that incorporate standard of care laboratory data (i.e. AST, ALT, platelet count, age) and have performed well as surrogates of significant fibrosis in a variety of pediatric and adult liver diseases, including viral hepatitis, biliary atresia, and CFLD [28–30]. In a liver biopsy-validated study of children with CF, APRI appears to predict CFLD (AUC 0.75) and significant hepatic fibrosis among those with known CFLD (AUC 0.81) with good accuracy, thus providing, at a minimum, reason for increased vigilance in screening for worsening CFLD in patients with elevated values [29]. In a large international study of patients (n = 497) with CFLD and portal hypertension, Stonebraker et al. found that APRI and FIB-4 values could differentiate patients who developed secondary complications of portal hypertension, APRI and FIB-4 scores exceeded the diagnostic thresholds reported by Leung et al. (APRI > 0.264 and FIB-4 > 0.358) in 96% and 90% of their patients with portal hypertension and were significantly different in CFLD patients with and without known varices (APRI = 1.27, FIB-4 = 1.47 vs APRI = 0.9, FIB-4 = 0.7, $p < 0.0001$ for both) as well as in those who had or had not undergone liver transplantation (APRI = 1.59, FIB-4 = 1.96 vs APRI = 1.06, FIB-4 = 1.05, $p = 0.001$ for both). Combinations of serum biomarkers such as collagen/matrix markers (i.e. TIMP-1 and PH, AUC = 0.85) and more recently microRNAs (i.e. miR-122, miR-21, and miR-25, AUC = 0.78) have also been studied as surrogates of liver fibrosis in pediatric CFLD, but are not yet readily available in the clinical setting and may be cost prohibitive [31,32].

A large decrease in platelet count from a prior value or baseline should be vigilantly monitored, even if values do not meet laboratory criteria for thrombocytopenia, as the trend may be due to early splenic sequestration from progressive portal hypertension. A platelet count $<150 \times 10^3/\mu L$ is concerning for the presence of CF cirrhosis. Low albumin (<3 g/dL) is always concerning, particularly if prealbumin is normal. Importantly, serum albumin represents one of three "liver function" tests. Coagulopathy, reflected by an elevated prothrombin time (PT, >15 s), elevated partial thromboplastin time (PTT, >34 s), or elevated international normalized ration (INR, >1.2) is another sign of synthetic compromise and decompensated cirrhosis [26]. Lastly, persistent hypoglycemia (serum glucose <70 g/dL) is a harbinger of liver dysfunction as the liver both produces and stores glycogen and glucose.

4.4. Imaging

If the biochemical and hematological tests remain persistently abnormal (>6 months) or hepatosplenomegaly is detected on exam, a complete abdominal ultrasound with Doppler to visualize the liver, spleen and biliary tree and measure both direction and intensity of portal and hepatic blood flow is recommended. Gray scale ultrasound may detect subclinical findings suggestive of cirrhosis which include coarseness of liver parenchyma, nodularity of the liver edge, and increased periportal echogenicity and can exclude cholelithiasis (gallstones) or choledocholithiasis (common bile duct stones) as a cause of intermittently elevated

GGTP. Alternatively, cirrhosis may be obvious (Fig. 3A and B) or only found at autopsy [33,34]. Doppler measurements can detect reversal of blood flow in the portal vein (hepatofugal) or a recanalized umbilical vein, which may be seen in both cirrhotic and noncirrhotic portal hypertension. Large collateral veins and or gastroesophageal varices may also be visualized on ultrasound [35]. Traditional ultrasound has difficulty differentiating fat from fibrosis, thus magnetic resonance imaging (MRI) is becoming increasingly utilized to help confirm disease when there is clinical suspicion of CF cirrhosis [36]. The utility of traditional and newer ultrasound technologies including shear wave elastography (SWE) and transient elastography (TE) which measures liver stiffness (LSM) as an indirect measure of fibrosis in isolation or combination with other laboratory or clinical parameters to predict progression to CF cirrhosis is currently being explored in a multicenter study in collaboration with the National Institutes of Health (NIH) (NCT01144507) and CF Foundation (CFF). Early findings have confirmed that abnormalities in ultrasound patterns are present in 18% of children with pancreatic insufficient CF and a nodular pattern on ultrasound consistent with cirrhosis was found in 3.3% of subjects who had no clinical evidence of portal hypertension or thrombocytopenia [12]. In a single center study of 150 children and adolescents, TE demonstrated an AUC of 0.97 to detect CFLD (defined as having 2 of the following: hepatomegaly ± splenomegaly OR Increased transaminases or GGTP >1.5 × ULN × 3 over 12 months OR Abnormal US or signs of pHTN on duplex US) during a 6 year study period when using a LSM cut-off of >6.8 kPa (91.5% and 91.7% sensitivity and specificity). This study reported a median LSM of 16.4 kPa in children <14 years of age with CFLD vs 4.4 kPa without CF liver disease. However, currently, few pediatric centers have access to this technology which has only recently been approved for use in children with the appropriate pediatric probes. In a Italian pilot study of 75 children and adolescents using SWE, median sheer wave velocity (SWV) increased progressively from 1.02 m/s (95%, Confidence Interval, CI, 0.92–1.136) in patients with no evidence of CFLD on ultrasound (N = 16), to 1.12 (95%CI 1.05–1.19) in patients with CFLD without portal hypertension (N = 23), and ultimately to 1.25 (95%CI 1.14–1.36) in those with CFLD and PHT (N = 28). Lastly, SWV was 1.63 (95%CI 1.26–1.99) in patients with esophageal varices (N = 8) ($p < 0.0001$). This suggests SWE may also be a rapid, simple, non-invasive tool for the clinical follow-up of patients with cystic fibrosis associated liver disease, though was not validated by liver biopsy. However, these options may be limited by operator variability, lack of pediatric or disease-specific standards and accessibility.

4.5. Diagnosis

A diagnosis of progressive CFLD is made if two or more of the following findings are present, as suggested by experts from the joint NIH/CFF CFLD Clinical Research Workshop [37] and Europe [17].

- Hepatomegaly (e.g., liver edge palpable >2 cm below the costal margin) and/or splenomegaly, confirmed by ultrasonography.
- Abnormalities of ALT, AST, and GGTP above the laboratory upper limits of normal for >6 months, after excluding other causes of liver disease.
- Ultrasonographic evidence of coarseness, nodularity, increased echogenicity or portal hypertension, as described above.
- Liver biopsy showing focal biliary cirrhosis or multilobular cirrhosis (if performed).

Alternative terminology for liver involvement in CF was presented by Flass and Narkewicz [7], summarizing recommendations from a Williamsburg conference in 2006 (Table 2) in which the term “liver disease” was reserved for cirrhotic patients with or without portal hypertension while “liver involvement without cirrhosis” characterized all other abnormalities.

5. Routine management

5.1. Referral

Patients suspected of having CFLD or CF cirrhosis based upon the clinical features described above should be evaluated by a hepatologist to assess for severity and/or other possible

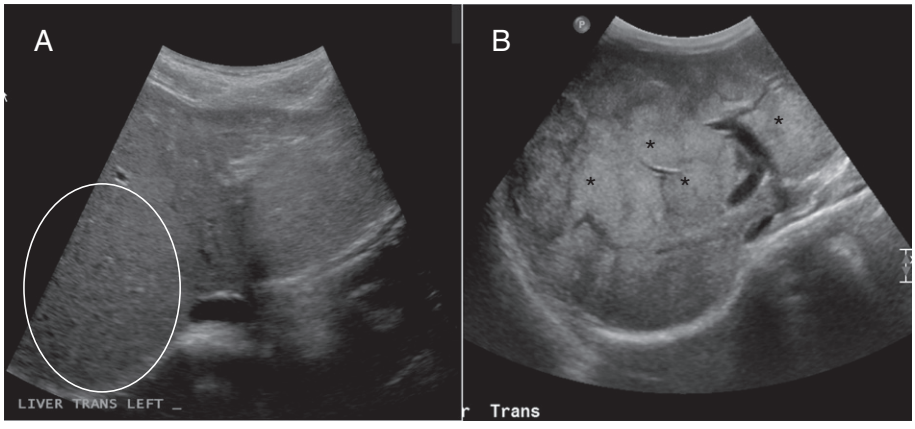

Fig. 3. Gray-scale ultrasound imaging of varying forms of CF cirrhosis. A-A focal area of micronodularity (circled) in the liver of a CF patient with focal biliary cirrhosis. B-Multiple and large nodules (asterisks) throughout the liver of a CF patient with multilobular cirrhosis. Images courtesy of Dr. Roger Harned.

Table 2
CF Foundation Hepatology Classification of CFLD

I. CF related liver disease WITH cirrhosis ± portal hypertension (based on clinical exam/imaging, histology, laparoscopy)
II. Liver involvement WITHOUT cirrhosis or portal hypertension consisting of at least one of the following:
a. Persistent AST, ALT, GGT >2 times upper limit of normal
b. Intermittent elevations of the above laboratory values
c. Steatosis (histologic determination)
d. Fibrosis (histologic determination)
e. Cholangiopathy (based on ultrasound, MRI, CT, ERCP)
f. Ultrasound abnormalities not consistent with cirrhosis
III. Preclinical: no evidence of liver disease on exam, imaging or laboratory values

causes of liver disease, in addition to future management. Liver biopsy is accepted as the gold standard for assessment of histologic staging of fibrosis [38], which is a strong determinant of CFLD outcome [39–41]. Unfortunately, liver biopsy has inherent risks and limitations, including discomfort, requirement of anesthesia in children, sedation complications, hemorrhage, infection, sampling error, and interpretive variability [42–46]. Due to the patchy or heterogeneous nature of CF cirrhosis, a liver biopsy may underestimate the severity of disease and many groups now recommend multiple passes to improve concordance [41]. As such, liver biopsy is not routinely recommended to assess the severity of fibrosis because the findings rarely affect decisions about clinical interventions, such as endoscopic variceal banding/sclerosis or timing of liver transplant evaluation. However, a liver biopsy may be helpful for select cases in whom the diagnosis of CFLD is confounded, particularly those suspected of having a concomitant liver disease (i.e., hepatitis C, alpha-1-antitrypsin deficiency, drug toxicity, or autoimmune hepatitis).

5.2. Nutrition

Fat malabsorption may be compounded in CF cirrhosis because of insufficient (canalicular cholestasis) or abnormal (composition altered due to CFTR dysfunction) bile acid pools in the gut, in addition to underlying pancreatic insufficiency. Optimal nutrition is imperative for all patients with progressive CFLD or CF cirrhosis, as chronic liver disease is a highly catabolic condition [47]. Daily caloric requirements may be 50% higher than the recommended daily allowance. As insulin deficiency and diabetes is common in CF, enteral supplemental nutrition via nasogastric (NG) or gastrostomy tube (GT) feeds may want to emphasize fat calories rather than carbohydrates. Rarely, parenteral nutrition may be necessary in cases of severe malnutrition, oral aversion, or anorexia secondary to organomegaly. Regardless of the presence of cholestasis, fat-soluble vitamins need to be monitored, replaced, and supplemented at large doses as needed [47].

5.3. Liver disease reduction

While recommended for all children, full immunization against hepatitis A and B is especially important for individuals with CF cirrhosis [48]. Avoidance of alcohol, herbal remedies and hepatotoxic prescription drugs, when feasible, is important in patients with progressive CFLD. Caution should be applied with non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen to minimize the risk of bleeding from portal hypertensive gastropathy or varices, and renal damage [49].

5.4. Ursodeoxycholic acid

The role of ursodeoxycholic acid (UDCA) in CFLD is controversial and its benefit has not been established. A gastroenterology or hepatology referral, particularly with CF expertise to consider the pros and cons of UDCA is recommended. UDCA is a nontoxic, naturally occurring secondary bile acid (metabolic byproduct of intestinal bacteria) thought to reduce liver injury in cholestatic liver disease by replacing cytotoxic bile acids, reducing the rate at which the intestine absorbs cholesterol molecules while breaking up micelles containing cholesterol, and inhibiting apoptosis. It also may have a direct cytoprotective and anti-inflammatory effect [50]. Despite these theoretical benefits, the clinical evidence supporting the use of UDCA is weak, and consists of low-quality or indirect clinical evidence [51]. Several observational studies and two small randomized trials suggest that UDCA may delay the progression of CFLD [52–54]. One of the randomized trials included 55 children and adults with CFLD, and reported improvements in GGTP and a global measure of CF severity after one year of treatment compared with placebo [52]. Another trial in at-risk children who presented with meconium ileus (MI) at birth concluded that treatment with UDCA reduced the likelihood of developing CFLD as early as nine years of age [55]. Most importantly, a Cochrane review found insufficient evidence to determine whether UDCA is effective for treatment or prevention of CFLD primarily due to the lack of adequate studies [51]. This review highlighted 3 studies, which included nearly 120 subjects, and the majority of whom were defined as having CFLD based on criteria similar to those outlined above. Subjects were treated with UDCA doses ranging from 10 to 20 mg/kg/day for up to 12 months. The review found no significant difference in weight gain or improvement in biliary excretion. There were also no data available for analysis for long-term outcomes, such as death or need for liver transplantation.

Further, indirect evidence suggests possible adverse effects of UDCA in high doses. In a randomized trial in adults with primary sclerosing cholangitis (PSC), chronic treatment with high-dose UDCA (20 to 30 mg/kg per day) was linked to improvement in liver biochemistries, but also was associated with higher rates of serious adverse events (including colonic adenocarcinoma [56]) and did not improve survival or reduce need for liver transplantation [57]. In light of this and a >2-fold increased risk for death, transplantation, or minimal listing criteria ($p = 0.038$) this study was discontinued prematurely [57]. Expert opinion differs regarding UDCA use for all patients with CFLD, or in select cases where cholestasis and fibrosis are prominent [58,59]. European guidelines suggest early use of UDCA in CFLD and studies by Colombo et al. have not found evidence for enhanced toxicity at standard doses (20 mg/kg/day) [60]. Gallstones in CF are not responsive

to therapy with UDCA, most likely because their main component is not cholesterol.

A finite course (2–3 months) of UDCA may be considered in children who have established cholestasis (e.g., conjugated bilirubin >1 mg/dL), particularly those with a history of meconium ileus or currently on or recently weaned off parenteral nutrition. A dose of 10–20 mg/kg body weight per day given in two divided doses appears to be safe. As noted above, there is inadequate data to make a recommendation for or against the use of UDCA as a treatment for children with subclinical or milder forms of CFLD.

6. Complications of CF cirrhosis and their management

The major complications related to CF cirrhosis are primarily due to the subsequent development of portal hypertension (PHTN). The three most common complications of PHTN are variceal hemorrhage, ascites and hypersplenism. Rarer complications include hepatic encephalopathy, hepatopulmonary syndrome and hepatopulmonary hypertension. Hepatic synthetic failure is rare in CF cirrhosis [17].

6.1. Gastrointestinal bleeding

The most dramatic complication related to CF cirrhosis with portal hypertension is variceal hemorrhage. The prevalence is unclear. Older studies suggest that variceal hemorrhage occurs in up to 70% of patients with CF and cirrhosis in 8–10 years [17]. Recent analysis of the US CF Registry suggests that the prevalence may only be about 20% in 10 years [8]. The differences may be due to referral bias in the original French study.

6.2. Ascites

Ascites is a potentially much more ominous complication. Once ascites is present, malnutrition and pulmonary function decline are common. Our expert opinion is that the development of ascites should trigger an evaluation for liver transplantation in individuals with CF and cirrhosis. Treatment is focused on salt and water restriction and judicious use of diuretic therapy (namely oral spironolactone and furosemide) [61].

6.3. Hypersplenism

Thrombocytopenia is often the first clue to the presence of cirrhosis in CF, though a gradual decline in platelet count should alert the provider to progressive CFLD. The combination of a platelet count of <150,000/μL and leukopenia should trigger a search for cirrhosis and associated splenomegaly. Hypersplenism does not in and of itself require intervention and splenectomy is not a routinely recommended treatment for portal hypertension [62].

6.4. Encephalopathy

Hepatic encephalopathy is a rare complication in CF. It can be triggered by infections, excessive protein intake or GI bleeding. Treatment should include a search for triggers, provision of adequate calories to prevent catabolism and medical therapy including lactulose and/or antibiotics to lower ammonia and other potential toxins [63]. Like ascites, the presence of encephalopathy is a harbinger of poor hepatic synthetic function and should trigger consideration of evaluation for liver transplantation [63].

6.5. Hepatopulmonary syndrome

For the purposes of this focused article, diagnosis but not treatment of hepatopulmonary syndrome and portopulmonary hypertension will be briefly discussed as these highly morbid conditions require unique treatment considerations and confer a higher priority at the time of liver transplant listing.

Patients with CFLD and portal hypertension also may develop hepatopulmonary syndrome (HPS). HPS is characterized by progressive hypoxemia with no identifiable respiratory cause. It has been suggested that increased circulating pulmonary vasodilators secondary to the liver disease create intrapulmonary vascular dilatations. These cause hypoxemia by 1) intrapulmonary shunting (right to left), 2) alveolar capillary diffusion limitation, and 3) ventilation/perfusion mismatch [64]. A hallmark feature of hepatopulmonary syndrome is “orthodeoxia,” which refers to a decrease in oxygenation in the upright as compared with recumbent position [65]. Unique hemodynamic-gas exchange patterns of HPS enable it to be distinguished from cardiopulmonary disorders. Patients with portal hypertension should be evaluated for orthodeoxia by measuring oxygen saturation (using pulse oximetry) in the supine and upright positions. A significant decrease in oxygen saturation (5%) when moving into the upright position suggests hepatopulmonary syndrome, and should be further evaluated. In patients with CF, the characteristic lung disease may mask the presence of HPS. Therefore, respiratory symptoms or A-a gradient measurements, even if >15 mm Hg, are not as useful to detect HPS in patients with CF cirrhosis. The estimated 5-year survival of patients diagnosed with HPS is 23%, with worse estimated survival in patients with a PaO_2 < 50 mm Hg. If HPS is clinically suspected, a contrast enhanced echocardiography (CEE) with injected agitated saline to a peripheral vein or an IV 99mTc-labeled albumin scan are the next steps for the diagnosis of HPS. CEE is considered the gold standard, but a 99mTc-labeled albumin scan may determine the degree of the shunt, and has been shown to serve as a prognostic predictor in patients with HPS with other lung diseases [64]. The diagnosis of HPS in CF is complicated (also does not meet the classic definition-lack of known lung disease) due to the presence of underlying lung disease, potential shunting from intrinsic pulmonary disease, and likely significantly underdiagnosed given that both conditions present with hypoxia [66]. CF patients with early hepatopulmonary syndrome should be considered for liver transplantation and are eligible for higher priority based on this diagnosis. OLT has been shown to induce complete resolution of

HPS in >80% of patients, with an improved post transplant 5-year survival rate of 76% [67].

6.6. Portopulmonary hypertension

Portopulmonary hypertension (PPH) refers to pulmonary arterial hypertension (PAH) that is associated with portal hypertension, and is a well-recognized complication of chronic liver disease including CFLD. PAH is defined as having a mean pulmonary artery pressure (mPAP) >25 mm Hg at rest OR pulmonary capillary wedge pressure (PCWP) <15 mm Hg according to right heart catheterization [68]. The pathogenesis of portopulmonary hypertension (PPH) has not been elucidated, however the most widely accepted theory is that a humoral substance (i.e. serotonin, interleukin-1, vasoactive intestinal peptide) that is normally metabolized by the liver reaches the pulmonary circulation via portosystemic collaterals [69]. Similar to HPS determining that pulmonary hypertension is due to PPH and not pulmonary disease in CF can be difficult. CF patients with PPH should be considered for liver transplantation. They may receive priority on the transplant waiting list, similar to patients with hepatopulmonary syndrome. If PPH is present, eligibility for transplantation must be evaluated on a case-by-case basis because high pulmonary vascular resistance may be a relative or absolute contraindication to liver transplantation. Medical pharmacotherapy should be maximized.

6.7. Management of complications of CF cirrhosis

6.7.1. Pharmacotherapy

While nonselective beta-adrenergic blockers such as propranolol and nadolol are the mainstay of treatment of esophageal varices in adult patients without CF, these agents are generally avoided in patients with CF because of their risk of bronchoconstriction as seen in asthma. In addition, beta-adrenergic blockers and their titration and dosing have not been well studied in children with portal hypertension and may blunt the reflexive tachycardia needed for children to compensate (and for providers to monitor) for acute variceal bleeding. In the setting of an acute variceal hemorrhage, octreotide, a somatostatin analogue (only vasoactive drug available in the US for control of acute variceal bleeding) or terlipressin, a vasopressin analogue (primarily used in Europe as it is currently not approved for use in the US) may be used to decrease splanchnic flow, thus decreasing the tension and flow to gastroesophageal varices [70].

6.7.2. Endoscopy

Patients with clinical or radiographic signs of portal hypertension may benefit from screening upper gastrointestinal endoscopy to evaluate for esophageal varices and risk for gastrointestinal bleeding. However, the role of primary prophylaxis (before first variceal bleed) with endoscopic band ligation is controversial as its impact on clinical outcome and survival is unknown in children and adolescents [62,71]. In adults with CF cirrhosis and portal hypertension, guidelines suggest that screening endoscopy and primary prophylaxis with variceal band ligation is appropriate [72]. Once variceal hemorrhage has occurred, standard management for acute variceal hemorrhage with airway and hemodynamic stabilization, use of splanchnic vasoconstrictors (octreotide and others) and endoscopic variceal band ligation should be followed by secondary variceal prophylaxis with repeated endoscopy and variceal band ligation to eradicate varices [72].

6.7.3. Portosystemic shunts

Placement of a transjugular intrahepatic portosystemic shunt (TIPSS) through interventional radiology may be an appropriate option for patients CF cirrhosis and portal hypertension with recurrent variceal bleeding for whom endoscopic band ligation is no longer effective, or access is compromised (gastric fundus). Use of TIPS can be effective as primary therapy in select patients and as bridge therapy for CF patients up to 15 years with portal hypertension until liver transplantation [3,73]. Improvement in body mass index (BMI) and lung function after TIPSS is well documented. TIPSS and surgical portosystemic shunts (splenorenal) can be complicated by encephalopathy, stenosis or thrombus, although the use of new conduit material may decrease the incidence of occlusion.

6.7.4. Liver transplantation

Patients with uncomplicated CF cirrhosis likely do not benefit from liver transplantation (LT). GI bleeding alone is controversial as an indication for LT. In the French study, only 3% of patients with CF cirrhosis and GI bleeding went on to LT > Patients with complications aside from GI bleeding and hypersplenism should be referred promptly for liver transplant evaluation as wait times for an isolated liver may exceed one year and lung function may decline rapidly, impacting both eligibility and outcome. The established indications for liver transplant in CF would include cirrhosis with evidence for hepatic decompensation (Hypoalbuminemia (<3 g/dL and declining), persistent hypoglycemia, and/or worsening coagulopathy (INR > 1.5) that is not corrected by administration of intravenous vitamin K, ascites, and jaundice) or uncontrollable variceal bleeding that cannot be managed by a portosystemic shunt. Likely because of multiorgan involvement and the presence of chronic lung infection in CF, liver transplantation in CF is associated with suboptimal long-term patient survival compared to non-CF patients, though still quite good [74]. In a UNOS study by Mendizabal et al., which analyzed outcomes of 203 transplants performed in patients with CF (189 isolated liver, 13 combined lung/liver, 1 combined heart/lung/liver), 30-day and 5-year survival rates for children and adults were 94.6% and 85.8%, and 92.7% and 72.7%, respectively [75]. When compared to non-CF counterparts, children with CF who underwent transplantation had a lower survival rate at 30 days, while adults had similar short-term outcomes. Not surprisingly, by 5 years post-transplantation, both children and adults with CF had lower survival rates than non-CF patients. Despite this, a significant post-transplant benefit was observed in pediatric CF patients with 3 year survival rates of 91.3% among children transplanted vs 84.5% on the waiting list. This advantage was

even greater in adults, with 3 year survival rates of 81.2% in those transplanted vs only 61.2% on the waiting list. However, it is unclear if the survival rates were directly related to liver disease or multiorgan disease. At the time of liver transplantation, adult patients had a higher incidence than children of ascites (22.9% versus 10.8%), encephalopathy (36.3% versus 18.2%) and diabetes (54.5% versus 18.2%), suggesting benefits to early referral and liver transplantation in children with CF. In addition to those mentioned, other relative consensus contraindications to an isolated LT in CF include infection with multi-drug resistant organisms (Pseudomonas, Burkolderia), poor pre-transplant pulmonary function (FEV1 < 40% predicted), and irreversible pulmonary fibrosis on imaging [76,77].

With increasing global experience, it is clear that severity of liver disease alone is not sufficient for determining optimal timing and candidacy of liver transplantation. Stage of lung disease must be strongly considered. CF patients in whom both lung and liver disease are advanced may be considered for dual liver-lung transplantation (LLT). In the United States between 1987 and 2009, combined liver-lung transplantation was only performed in 4% (8 of 210) of liver transplants for CFLD in children and adolescents [78]. However, despite expected increased morbidities of combined LLT in CF, one- and five-yr patient and graft survival are not significantly different in patients who undergo LT in comparison with patients who underwent LLT [9]. Among adults, combined liver-lung transplant was performed in 21 of 84 (25%) of liver transplants for CFLD. The frequency of combined liver-lung transplantation varies among institutions. As an example, at Texas Children's Hospital, two of the nine children with CFLD who received orthotopic liver transplant between 1998 and 2008 also had a lung or lung-heart transplant, without graft morbidity or patient mortality [79]. Between 2008 and 2016, two additional liver-lung transplants and three isolated liver transplant for CFLD were performed at the same institution. Single center series have reported both short-term, favorable [76,80] and unfavorable lung function outcomes after liver transplantation [81], however an analysis of the US CFF registry reveals no difference in the rate of decline in FEV1 in the 3 years following liver transplantation in CF subjects compared to CF patients without liver disease [82]. The impact of liver transplantation on the nutritional status of CF patients is also conflicting with reports of clinical improvement [83,84] and lack of improvement [82].

Due to a high prevalence of CF related diabetes (CFRD) in cirrhotic CFLD and the impact of diabetes on post transplant management, some centers have advocated for combined liver and pancreas transplantation in CF patients who require a liver transplant [85]. Despite the impact of subsequent diabetes with isolated liver transplantation, a recent review of the UNOS data found that pancreas transplantation is rarely used in CF [86]. In addition, there is now clear data that following liver transplantation in CF, lung function deterioration is neither more nor less rapid compared to case matched CF subjects [82].

Much of the progress in the management of cystic fibrosis has been made in centers that are dedicated specifically to the care of these patients. The few patients with cystic fibrosis who undergo liver transplantation would undoubtedly benefit from specialized centers dedicated to developing management strategies that take into account the profound metabolic alterations of cystic fibrosis and their multiple effects on post-transplantation outcomes.

7. Potential clinical trials endpoints

The early detection of hepatic fibrosis and significant CFLD is challenging as clinically available serum chemistries to measure liver damage can be normal even in advanced cirrhosis and can be elevated with no evidence of significant liver fibrosis [11]. The use of hepatic fibrosis scores such as APRI and FIB-4 and serum biomarkers have the potential to serve as non-invasive, reproducible, and sensitive screening tools to track development and reversal of fibrosis [5,29]. Empirically identified markers identified by genomic, proteomic, and metabolomic technologies, as well as targeted serum marker analysis, also offer new strategies to diagnose and predict outcomes in pediatric liver diseases, including CFLD [31,32,87–89]. Preliminary studies in children with fibrotic liver disease including CFLD have identified specific markers reflecting matrix re-modeling, hepatic stellate cell activation, collagen turnover, and chemoattractant expression [31,32,88–90]. Understanding the degree of injury and the stage of fibrosis in children with CFLD is essential in the complex decision-making of initiating novel medical therapies, monitoring of liver disease progression, and the timing of liver transplant evaluation. These biomarkers of liver disease, namely imaging and serum-based could serve as endpoints in interventional studies. Reversal of fibrosis captured by elastography based technology for example, would allow for validated and quantitative measures to be monitored and compared over a treatment period.

8. Future directions

Easily attainable and quantifiable high risk predictors of CF cirrhosis should continue to be an essential research pursuit should antifibrotics, modulators, correctors, or other chaperone therapies prove to be clinically beneficial for the liver. The safety and efficacy of bile acid analogues or derivatives such as obeticholic acid or norursodeoxycholic acid to prevent progression of or even reverse liver fibrosis in CF may merit investigation given promising findings in a range of cholestatic liver and bile duct disorders such as primary sclerosing cholangitis and primary biliary cirrhosis [91,92]. Given the proposed hepatobiliary pathogenesis of CF liver disease, multi-center clinical trials should be thoughtfully conceived and developed. Alternate theories that an overabundance of pathogenic microbiota and intestinal mucosal compromise could promote translocation of bacteria into the portal circulation, hence activating the classic pathways of hepatic inflammation and fibrosis, makes the intestinal microbiome a ripe area for study as a modifier of CF cirrhosis.

9. Clinical practice points

- In patients with CF, with or without elevation of ALT, AST, or GGT, the following should prompt consideration for vigilant monitoring, evaluation, or referral for CF cirrhosis: 1) a relative drop in platelet count over time, even if within laboratory normal limits; 2) heterogeneity, increased echogenicity or any nodularity on liver ultrasound; or 3) Palpable hepatomegaly/splenomegaly.
- Liver biopsy is not routinely recommended to assess the severity of fibrosis because the findings rarely affect decisions about clinical interventions.
- There is inadequate data to make a recommendation for or against the use of UDCA as prevention of or treatment for children with CF cirrhosis.
- While the impact of liver transplantation on the nutritional and pulmonary status of CF patients is unclear, 5-year survival rates for children and adults are >85% and 72%, respectively [75].

10. Summary

CF cirrhosis is a pediatric liver disease with an onset in children <18 years of age that carries high mortality that extends to adulthood. The pathogenesis of CFLD is likely multi-factorial. An altered bile acid pool due to CFTR dysfunction leading to bile plugging and an altered intestinal microbiome resulting in cytokine activation of hepatic stellate cells are recognized as potential mechanisms of fibrosis. It is unclear why so few patients with CF cirrhosis develop classic signs of cirrhotic liver disease such as jaundice, icterus, ascites, and variceal hemorrhage. Other than liver transplantation, there are no current medical therapies to reverse liver disease in CF, however with the advent of therapeutics that modulate or correct CFTR dysfunction to varying degrees, the future looks promising.

Conflict of interest

DHL: Research grants/trials support from Bristol Meyers Squibb, Abbvie, Gilead, Roche. MRN: Research Grant Support: Cystic Fibrosis Foundation, Gilead (viral hepatitis), Merck (viral hepatitis), AbbVie (viral hepatitis) Consultant: Vertex (CF related), AbbVie (CF related).

Acknowledgements

DHL received grant support through the Cystic Fibrosis Foundation, Developing Innovative Gastroenterology Specialty Training (DiGEST) Program (LEUNG14GE0). MN received grant support through the CFF as a faculty member of DiGEST and NARKEW07AB0.

References

[1] Cohn JA, Strong TV, Picciotto MR, Nairn AC, Collins FS, Fitz JG. Localization of the cystic fibrosis transmembrane conductance regulator in human bile duct epithelial cells. Gastroenterology 1993;105:1857–64.
[2] Feranchak AP. Hepatobiliary complications of cystic fibrosis. Curr Gastroenterol Rep 2004;6:231–9.
[3] Debray D, Lykavieris P, Gauthier F, Dousset B, Sarder A, Munck A, et al. Outcome of cystic fibrosis-associated liver cirrhosis: management of portal hypertension. J Hepatol 1999;31:77–83.
[4] Mileti E, Rosenthal P. Management of portal hypertension in children. Curr Gastroenterol Rep 2011;13:10–6.
[5] Stonebraker JR, Ooi CY, Pace RG, Corvol H, Knowles MR, Durie PR, et al. Features of severe liver disease with portal hypertension in patients with cystic fibrosis. Clin Gastroenterol Hepatol 2016;14:1207–15 [e1203].
[6] Durieu I, Pellet O, Simonot L, Durupt S, Bellon G, Durand DV, et al. Sclerosing cholangitis in adults with cystic fibrosis: a magnetic resonance cholangiographic prospective study. J Hepatol 1999;30:1052–6.
[7] Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros 2013;12:116–24.
[8] Wen Ye JM, Narkewicz M, Leung D, Karnsakul W, Murray K, Alonso E, et al. Frequency and risk factors for variceal hemorrhage in CF Foundation registry patients with cystic fibrosis cirrhosis. J Pediatr Gastroenterol Hepatol Nutr 2016;63:S195.
[9] Arnon R, Annunziato RA, Miloh T, Padilla M, Sogawa H, Batemarco L, et al. Liver and combined lung and liver transplantation for cystic fibrosis: analysis of the UNOS database. Pediatr Transplant 2011;15:254–64.
[10] Flora KD, Benner KG. Liver disease in cystic fibrosis. Clin Liver Dis 1998;2:51–61.
[11] Gobel T, Erhardt A, Herwig M, Poremba C, Baldus SE, Sagir A, et al. High prevalence of significant liver fibrosis and cirrhosis in chronic hepatitis B patients with normal ALT in central Europe. J Med Virol 2011;83:968–73.
[12] Leung DH, Ye W, Molleston JP, Weymann A, Ling S, Paranjape SM, et al. Baseline ultrasound and clinical correlates in children with cystic fibrosis. J Pediatr 2015;167:862–8 [e862].
[13] Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, et al. Liver disease in cystic fibrosis: a prospective study on incidence, risk factors, and outcome. Hepatology 2002;36:1374–82.
[14] Lamireau T, Monnereau S, Martin S, Marcotte JE, Winnock M, Alvarez F. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol 2004;41:920–5.
[15] Balistreri WF, Grand R, Hoofnagle JH, Suchy FJ, Ryckman FC, Perlmutter DH, et al. Biliary atresia: current concepts and research directions. Summary of a symposium. Hepatology 1996;23:1682–92.
[16] Mayer-Hamblett N, Kloster M, Ramsey BW, Narkewicz MR, Saiman L, Goss CH. Incidence and clinical significance of elevated liver function tests in cystic fibrosis clinical trials. Contemp Clin Trials 2013;34:232–8.
[17] Debray D, Kelly D, Houwen R, et al. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros 2011;10(Suppl. 2):S29–36.
[18] Gelfond D, Borowitz D. Gastrointestinal complications of cystic fibrosis. Clin Gastroenterol Hepatol 2013;11:333–42 [quiz e330-331].
[19] Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, et al. NASPGHAN practice guidelines: diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr 2012;54:838–55.
[20] Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med 2016;4:107–15.
[21] Bartlett JR, Friedman KJ, Ling SC, Pace R, Bell SC, Bourke B, et al. Genetic modifiers of liver disease in cystic fibrosis. JAMA 2009;302:1076–83.
[22] Innis SM, Davidson AG. Cystic fibrosis and nutrition: linking phospholipids and essential fatty acids with thiol metabolism. Annu Rev Nutr 2008;28:55–72.
[23] Woodruff SA, Sontag MK, Accurso FJ, Sokol RJ, Narkewicz MR. Prevalence of elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen. J Cyst Fibros 2016;16:139–45.
[24] Herrmann U, Dockter G, Lammert F. Cystic fibrosis-associated liver disease. Best Pract Res Clin Gastroenterol 2010;24:585–92.
[25] Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology 2010;138:1357–64 [1364 e1351-1352].

[26] Tietz textbook of clinical chemistry1st ed. WB Saunders Company; 1994.
[27] Bodewes FA, van der Doef HP, Houwen RH, Verkade HJ. Increase of serum gamma-glutamyltransferase associated with development of cirrhotic cystic fibrosis liver disease. J Pediatr Gastroenterol Nutr 2015;61:113–8.
[28] Grieve A, Makin E, Davenport M. Aspartate aminotransferase-to-platelet ratio index (APRi) in infants with biliary atresia: prognostic value at presentation. J Pediatr Surg 2013;48:789–95.
[29] Leung DH, Khan M, Minard CG, Guffey D, Ramm LE, Clouston AD, et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. Hepatology 2015;62: 1576–83.
[30] McGoogan KE, Smith PB, Choi SS, Berman W, Jhaveri R. Performance of the AST-to-platelet ratio index as a noninvasive marker of fibrosis in pediatric patients with chronic viral hepatitis. J Pediatr Gastroenterol Nutr 2010;50:344–6.
[31] Cook NL, Pereira TN, Lewindon PJ, Shepherd RW, Ramm GA. Circulating microRNAs as noninvasive diagnostic biomarkers of liver disease in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 2015;60:247–54.
[32] Pereira TN, Lewindon PJ, Smith JL, Murphy TL, Lincoln DJ, Shepherd RW, et al. Serum markers of hepatic fibrogenesis in cystic fibrosis liver disease. J Hepatol 2004;41:576–83.
[33] Blanc WA, Di Sant'Agnese PA. A distinctive type of biliary cirrhosis of the liver associated with cystic fibrosis of the pancreas; recognition through signs of portal hypertension. Pediatrics 1956;18:387–409.
[34] Vawter GF, Shwachman H. Cystic fibrosis in adults: an autopsy study. Pathol Annu 1979;14(Pt 2):357–82.
[35] Zhang CX, Xu JM, LI JB, Kong DR, Wang L, Xu XY, et al. Predict esophageal varices via routine trans-abdominal ultrasound: a design of classification analysis model. J Gastroenterol Hepatol 2016;31:194–9.
[36] Reeder SB, Cruite I, Hamilton G, Sirlin CB. Quantitative assessment of liver fat with magnetic resonance imaging and spectroscopy. J Magn Reson Imaging 2011;34:729–49.
[37] National Institutes of Health/Cystic Fibrosis Foundation. Clinical research workshop; 2009.
[38] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017–44.
[39] Lewindon PJ, Ramm GA. Cystic fibrosis-cirrhosis, portal hypertension, and liver biopsy: reply. Hepatology 2011;53:1065–6.
[40] Ovchinsky N, Moreira RK, Lefkowitch JH, Lavine JE. Liver biopsy in modern clinical practice: a pediatric point-of-view. Adv Anat Pathol 2012;19:250–62.
[41] Lewindon PJ, Shepherd RW, Walsh MJ, Greer RM, Williamson R, Pereira TN, et al. Importance of hepatic fibrosis in cystic fibrosis and the predictive value of liver biopsy. Hepatology 2011;53:193–201.
[42] Huang JF, Hsieh MY, Dai CY, Hou NM, Lee LP, Lin ZY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: an evaluation of 3806 biopsies. Gut 2007;56:736–7.
[43] Falck-Ytter Y, McCullough AJ. The risks of percutaneous liver biopsy. Hepatology 2001;33:764.
[44] Westheim BH, Ostensen AB, Aagebaes I, Sanengen T, Almass R. Evaluation of risk factors for bleeding after liver biopsy in children. J Pediatr Gastroenterol Nutr 2012;55:82–7.
[45] El-Shabrawi MH, El-Karaksy HM, Okahsa SH, Kamal NM, El-Batran G, Badr KA. Outpatient blind percutaneous liver biopsy in infants and children: is it safe? Saudi J Gastroenterol 2012;18:26–33.
[46] Lachaux A, Le Gall C, Chambon M, Regnier F, Loras-Durclaux I, Bouvier R, et al. Complications of percutaneous liver biopsy in infants and children. Eur J Pediatr 1995;154:621–3.
[47] Dodge JA, Turck D. Cystic fibrosis: nutritional consequences and management. Best Pract Res Clin Gastroenterol 2006;20:531–46.
[48] Shapiro AJ, Esther CR, Leigh MW, Dellon EP. Vaccine induced hepatitis A and B protection in children at risk for cystic fibrosis associated liver disease. Vaccine 2013;31:906–11.
[49] Imani F, Motavaf M, Safari S, Alavian SM. The therapeutic use of analgesics in patients with liver cirrhosis: a literature review and evidence-based recommendations. Hepat Mon 2014;14:e23539.
[50] Poupon R. Ursodeoxycholic acid and bile-acid mimetics as therapeutic agents for cholestatic liver diseases: an overview of their mechanisms of action. Clin Res Hepatol Gastroenterol 2012;36(Suppl. 1):S3–12.
[51] Cheng K, Ashby D, Smyth RL. Ursodeoxycholic acid for cystic fibrosis-related liver disease. Cochrane Database Syst Rev 2014:CD000222.
[52] Colombo C, Battezzati PM, Podda M, Bettinardi N, Giunta A. Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis. Hepatology 1996;23:1484–90.
[53] Nousia-Arvanitakis S, Fotoulaki M, Economou H, Xefteri M, Galli-Tsinopoulou A. Long-term prospective study of the effect of ursodeoxycholic acid on cystic fibrosis-related liver disease. J Clin Gastroenterol 2001;32: 324–8.
[54] Kappler M, Espach C, Schweiger-Kabesch A, Lang T, Hartl D, Hector A, et al. Ursodeoxycholic acid therapy in cystic fibrosis liver disease—a retrospective long-term follow-up case-control study. Aliment Pharmacol Ther 2012;36:266–73.
[55] Siano M, De Gregorio F, Boggia B, Sepe A, Ferri P, Buonpensiero P, et al. Ursodeoxycholic acid treatment in patients with cystic fibrosis at risk for liver disease. Dig Liver Dis 2010;42:428–31.
[56] Eaton JE, Silveira MG, Pardi DS, Sinakos E, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011;106:1638–45.
[57] Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50:808–14.
[58] Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulm Med 2007; 13:529–36.
[59] Sokol RJ, Durie PR. Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. J Pediatr Gastroenterol Nutr 1999;28(Suppl. 1): S1–13.
[60] Colombo C, Crosignani A, Alicandro G, Zhang W, Biffi A, Motta V, et al. Long-term ursodeoxycholic acid therapy does not alter lithocholic acid levels in patients with cystic fibrosis with associated liver disease. J Pediatr 2016; 177:59–65 [e51].
[61] Runyon BA, Committee APG. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49:2087–107.
[62] Shneider BL, de Ville de Goyet J, Leung DH, Srivastava A, Ling SC, Duche M, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex bypass: summary of the Baveno VI Pediatric Satellite Symposium. Hepatology 2016;63:1368–80.
[63] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60: 715–35.
[64] Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, et al. International Liver Transplant Society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation 2016;100:1440–52.
[65] Ho V. Current concepts in the management of hepatopulmonary syndrome. Vasc Health Risk Manag 2008;4:1035–41.
[66] Breuer O, Shteyer E, Wilschanski M, Perles Z, Cohen-Cymberknoh M, Kerem E, et al. Hepatopulmonary syndrome in patients with cystic fibrosis and liver disease. Chest 2016;149:e35-8.
[67] Cosardereliogluc, Cosar AM, Gurakar M, Dagher NN, Gurakar A. Hepatopulmonary syndrome and liver transplantation: a recent review of the literature. J Clin Transl Hepatol 2016;4:47–53.
[68] Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66.
[69] Panos RJ, Baker SK. Mediators, cytokines, and growth factors in liver-lung interactions. Clin Chest Med 1996;17:151–69.
[70] Bhutta AQ, Garcia-Tsao G. The role of medical therapy for variceal bleeding. Gastrointest Endosc Clin N Am 2015;25:479–90.
[71] Shneider BL, Bosch J, de Franchis R, Emre SH, Groszmann RJ, Ling SC, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v consensus workshop on methodology of diagnosis and therapy in portal hypertension. Pediatr Transplant 2012;16:426–37.

[72] Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–38.
[73] Pozler O, Krajina A, Vanicek H, Hulek P, Zizka J, Michl A, et al. Transjugular intrahepatic portosystemic shunt in five children with cystic fibrosis: long-term results. Hepatogastroenterology 2003;50:1111–4.
[74] Black SM, Woodley FW, Tumin D, Mumtaz K, Whitson BA, Tobias JD, et al. Cystic fibrosis associated with worse survival after liver transplantation. Dig Dis Sci 2016;61:1178–85.
[75] Mendizabal M, Reddy KR, Cassuto J, Olthoff KM, Faust TW, Makar GA, et al. Liver transplantation in patients with cystic fibrosis: analysis of United Network for Organ Sharing data. Liver Transpl 2011;17:243–50.
[76] Genyk YS, Quiros JA, Jabbour N, Selby RR, Thomas DW. Liver transplantation in cystic fibrosis. Curr Opin Pulm Med 2001;7:441–7.
[77] Melzi ML, Kelly DA, Colombo C, Jara P, Manzanares J, Colledan M, et al. Liver transplant in cystic fibrosis: a poll among European centers. A study from the European Liver Transplant Registry. Transpl Int 2006;19:726–31.
[78] Desai CS, Gruessner A, Habib S, Gruessner R, Khan KM. Survival of cystic fibrosis patients undergoing liver and liver-lung transplantations. Transplant Proc 2013;45:290–2.
[79] Harring TR, Nguyen NT, Liu H, Karpen SJ, Goss JA, O'Mahony CA. Liver transplantation in cystic fibrosis: a report from Baylor College of Medicine and the Texas Children's Hospital. Pediatr Transplant 2013;17:271–7.
[80] Colombo C, Russo MC, Zazzeron L, Romano G. Liver disease in cystic fibrosis. J Pediatr Gastroenterol Nutr 2006;43(Suppl. 1):S49–55.
[81] Nash KL, Collier JD, French J, McKeon D, Gimson AE, Jamieson NV, et al. Cystic fibrosis liver disease: to transplant or not to transplant? Am J Transplant 2008;8:162–9.
[82] Miller MR, Sokol RJ, Narkewicz MR, Sontag MK. Pulmonary function in individuals who underwent liver transplantation: from the US cystic fibrosis foundation registry. Liver Transpl 2012;18:585–93.
[83] Colombo C, Costantini D, Rocchi A, Romano G, Rossi G, Bianchi M, et al. Effects of liver transplantation on the nutritional status of patients with cystic fibrosis. Transpl Int 2005;18:246–55.
[84] Nightingale S, O'Loughlin EV, Dorney SF, Shun A, Verran DJ, Strasser SI, et al. Isolated liver transplantation in children with cystic fibrosis—an Australian experience. Pediatr Transplant 2010;14:779–85.
[85] Bandsma RH, Bozic MA, Fridell JA, Crull MH, Molleston J, Avitzur Y, et al. Simultaneous liver-pancreas transplantation for cystic fibrosis-related liver disease: a multicenter experience. J Cyst Fibros 2014;13:471–7.
[86] Usatin DJ, Perito ER, Posselt AM, Rosenthal P. Under utilization of pancreas transplants in cystic fibrosis recipients in the United Network Organ Sharing (UNOS) data 1987–2014. Am J Transplant 2016;16:1620–5.
[87] Feldstein AE, Nobili V. Biomarkers in nonalcoholic fatty liver disease: a new era in diagnosis and staging of disease in children. J Pediatr Gastroenterol Nutr 2010;51:378–9.
[88] Song Z, Dong R, Fan Y, Zheng S. Identification of serum protein biomarkers in biliary atresia by mass spectrometry and ELISA. J Pediatr Gastroenterol Nutr 2012;55:370–5.
[89] Nobili V, Alisi A, Torre G, De Vito R, Pietrobattista A, Morino G, et al. Hyaluronic acid predicts hepatic fibrosis in children with nonalcoholic fatty liver disease. Transl Res 2010;156:229–34.
[90] Nobili V, Marcellini M, Giovannelli L, Girolami E, Muratori F, Giannone G, et al. Association of serum interleukin-8 levels with the degree of fibrosis in infants with chronic liver disease. J Pediatr Gastroenterol Nutr 2004;39:540–4.
[91] Fickert P, Hirschfield GM, Denk G, Marschall HU, Altorjay I, Farkkila M, et al. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. J Hepatol 2017 [epub ahead of print].
[92] Erlinger S. Obeticholic acid in primary biliary cholangitis. Clin Res Hepatol Gastroenterol 2017;41:3–5.