Cystic fibrosis liver disease: A condition in need of structured transition and continuity of care

Julian Hercun MD¹, Fernando Alvarez MD², Catherine Vincent MD¹, Marc Bilodeau MD¹

ABSTRACT
Liver disease affects one-third of patients with cystic fibrosis (CF) and it is one of the major causes of morbidity and mortality in these patients. Historically considered a disease of childhood, its impact is now seen more often in adulthood. The heterogeneous pattern of CF liver disease and its rapid progression to cirrhosis remain a diagnostic challenge and new questions pertaining to the nature of liver involvement have recently been raised. Non-invasive measures to stratify the severity of liver involvement are increasingly used to predict clinical outcomes. A single treatment, ursodeoxycholic acid, has been used to slow progression of liver disease while recent advances in the field of CF treatments are promising. Management of portal hypertension remains challenging but outcomes after liver transplantation are encouraging. While many questions remain unanswered, a growing number of CF patients reach adulthood and will require care for CF liver disease.

KEYWORDS: biliary cirrhosis; cystic fibrosis; cystic fibrosis liver disease; portal hypertension; non-invasive diagnosis

Author Affiliation
¹Hepatology Department, Centre Hospitalier de l’Université de Montréal, Montréal, Québec, Canada; ²Gastroenterology, Hepatology and Nutrition Division, CHU Sainte-Justine, Montréal, Québec, Canada

Correspondence: Julian Hercun, Hepatology Department, Centre Hospitalier de l’Université de Montréal, 1000 Saint-Denis Street, Montréal, Québec H2X 0C1 Canada. Telephone: 514-890-8000. Fax: 514-412-7314. E-mail: julianhercun@gmail.com

Liver disease in cystic fibrosis (CF) represents the third leading cause of mortality in cystic fibrosis patients (1). Long thought to be primarily an issue of childhood, cystic fibrosis–associated liver disease (CFLD) has become a concern in adults due to recent advances in extending life expectancy in North American CF patients, who can now expect to live beyond 40 years of age (2). Historically the majority of the research in this field has been done in children with a relative paucity of data in the adult literature. Therefore, particular attention has to be paid to the transition of care from pediatric into adult medicine and to liver involvement in adult CF patients.

CF, an autosomal recessive disorder, is caused by mutations of the gene encoding the cystic fibrosis
transmembrane conductance regulator (CFTR). The most common mutation is the F508del, which is frequent in Caucasians; however, CF can affect all ethnicities. CFTR mutations are separated into classes according to their clinical impact. Classes I, II and III, often described as severe, are associated with CFLD. Besides mutations, it is known that pancreatic insufficiency, meconial ileus and younger age at diagnosis have been associated with the occurrence of CFLD (3,4). Liver involvement is thought to be more prevalent in individuals of Latin American origin (5).

While the most prominent clinical manifestations of CF are pulmonary, liver involvement has been described in about 30% of cases in prospective pediatric cohorts (4,6,7) with a similar prevalence in adult retrospective cohorts (7,8).

It remains unknown why certain patients develop severe liver involvement: in particular, no specific CFTR mutation has been clearly associated with CFLD (9,10). Non-CFTR polymorphisms such as SERPINA1Z allele of the α1-antitrypsin gene (11) have been associated with a greater risk of developing portal hypertension in CFLD. Environmental factors, while yet to be determined specifically, are thought to play a role as suggested by the discordance in the clinical expression of liver disease in siblings (12).

**DEFINITION**

The definition of CFLD is controversial and expert panels have highlighted that there is an ongoing need to clarify disease staging and to identify relevant biomarkers to assess disease severity (13). Variable definitions have been used throughout time and in the available literature, showcasing the difficulty in describing CFLD.

The diagnostic criteria proposed by Debray et al in 2011 (14) currently serve as the most commonly used definition, requiring the identification of at least two of the following: 1) evidence of hepato-megaly or splenomegaly (confirmed by ultrasound); 2) AST, ALT, or GGT elevation above the normal limit on three consecutive occasions over 12 months; or 3) ultrasonic evidence of liver involvement, portal hypertension, or biliary involvement. A liver biopsy is required if uncertainty remains and is judged to be clinically relevant, while keeping in mind possible sampling errors due to the non-uniform nature of CFLD. Recently, new data accumulated on the use of transient elastography or serum markers have challenged the Debray criteria (15).

**PATHOGENESIS**

The pathogenesis of CFLD remains poorly understood. CFTR is expressed in the bile duct cells as well as in the gallbladder, but not in hepatocytes. The CFTR protein is present on the apical membrane of cholangiocytes (16), where it serves as an ATP-dependent channel for the transport of chloride ions. It is thought that the abnormal function of CFTR impacts the secretion of bile and its alkalization, leading to obstruction of biliary ductules by hyperviscous bile. This then leads to inflammation and duct injury (17). Subsequently, periportal fibrosis develops and, eventually, focal biliary cirrhosis appears. The progression to multifocal cirrhosis, at which stage diffuse liver involvement takes place, represents the final stage of CFLD. Multifocal cirrhosis has been described as a predominantly pediatric disorder, affecting 5%-10% of patients with most cases presenting in the first decade of life (3,4,6,18). However, autopsy series performed more than 50 years ago reported incidence of cirrhosis in up to 25% of cases in children (19).

Another aspect of the pathogenic process lies in the observation of higher serum concentrations of toxic bile acids, such as cholic and chenodeoxycholic acids in patients with CF (20). Furthermore, decreased ileal expression of fibroblastic growth factor 15 has been observed; this could contribute to increased biliary toxicity (21). However, data is lacking on the mechanisms of hepatocellular injury secondary to bile acids in CF (22). In fact, the primary role of bile acids in the pathogenesis of CFLD remains controversial, as histological findings do not correlate well with bile toxicity (13).

The gut-liver axis theory has gained ground as the contribution of dysbiosis in CFLD is suspected due to prolonged transit times and bacterial overgrowth (13). Patients with CFLD have indeed a higher prevalence of bowel mucosal lesions and slower transit time (23).

Recent findings suggest that some forms of liver disease are in fact separate from the continuum described above: indeed, some patients present with clear findings of portal hypertension despite showing no evidence of cirrhosis (24,25). Evidence of non-cirrhotic portal hypertension (NCPH) has been recognized in diagnostic liver biopsies as well
as in explanted livers. The pathogenesis of this form of CFLD remains hypothetical (26).

DIAGNOSIS
Considering the drawbacks previously mentioned, the diagnosis of CFLD still rests on a combination of abnormal liver tests or imaging (which includes transient elastography) in an individual with an underlying diagnosis of CF.

Individual clinical or biochemical parameters do not correlate with the severity of liver disease (27). No correlation between gastrointestinal symptoms and CFLD has been found, either (28). Furthermore, up to 25% of CF patients develop elevated liver enzymes without associated CFLD (29). Although abnormal serum aminotransferases and GGT are a common finding (30), other causes for elevated liver tests should be looked for. For example, idiosyncratic reactions due to antibiotics are a common cause of elevated liver enzymes in this population (31). Furthermore, it is well recognized that cirrhosis can be diagnosed despite the presence of normal serum transaminases and GGT. Even in cases of cirrhosis with portal hypertension, liver enzymes were less than twice the upper limit of the normal range in 63% of cases (32). However, in a pediatric cohort, elevated GGT on multiple occasions was predictive of the diagnosis of cirrhosis within the subsequent two years (33).

Liver imaging is important as it can reveal evidence of steatosis, hepatomegaly or stigmata of liver disease, and portal hypertension. Ultrasound has been shown to be more sensitive than liver enzymes for diagnosis of CFLD (14). Ultrasound can demonstrate pseudomasses that correspond to lobulated areas of steatosis (34). Ultrasound can also reveal periportal hyperechogenicity in cases of focal biliary cirrhosis (35). However, there is no correlation between ultrasonographic and histologic findings (36). Steatosis is a common finding, particularly in up to 23%–67% of pediatric patients, where it has been associated with malnutrition or essential fatty acid deficiency (37,38). This finding has not been observed consistently in adults.

In hoping to find minimally invasive methods to quantify CFLD, the use of transient elastography (TE) has been proposed. TE can be difficult to interpret in some of these patients because of respiratory limitations (39). There is a lot of heterogeneity in cut-off values of TE in adult patients with CFLD (Table 1). Nevertheless, studies consistently report

<table>
<thead>
<tr>
<th></th>
<th>Cut-off CFLD</th>
<th>Cut-off PHT</th>
<th>Median value CFLD</th>
<th>Median value CF</th>
<th>Median values</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Kitson, 2013</td>
<td>6.8 (76% sensitivity, 84% specificity)</td>
<td>8.9 (87.5% sensitivity, 90.5% specificity)</td>
<td>8.1 (IQR 6.8–9.5)</td>
<td>5.0 (IQR 4.1–5.6)</td>
<td>&lt;0.001</td>
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<td>Karlas, 2012</td>
<td>5.9 (43% sensitivity, 97% specificity)</td>
<td></td>
<td>7.95+/–5.88 (stage of cirrhosis)</td>
<td>4.16+/–1.28</td>
<td>0.02</td>
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<tr>
<td>Van Biervliet, 2016</td>
<td>6.8 (91.5% sensitivity, 91.7% specificity)</td>
<td></td>
<td>14 (IQR 8.7–32.3)</td>
<td>4.6 (IQR 3.7–5.3)</td>
<td>0.0001</td>
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<tr>
<td>Lemaître, 2016</td>
<td>6.3 (67% sensitivity, 94% specificity)</td>
<td></td>
<td>7.85 (IQR 3.7–9.9) (Portal hypertension)</td>
<td>5 (IQR 3.4–7.5)</td>
<td>0.02</td>
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<tr>
<td>Rath, 2012</td>
<td>5.5 (55% sensitivity, 78% specificity)</td>
<td>11.5 (71% sensitivity, 98% specificity)</td>
<td>9.2</td>
<td>4.5</td>
<td>0.004</td>
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<td>Friedrich-Rust, 2013</td>
<td>7.1 (sensitivity 46%, specificity 91%)</td>
<td></td>
<td>6.7 (range 2.8–28.4)</td>
<td>4.3 (range 2.5–10.1)</td>
<td>0.049</td>
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<tr>
<td>Sadler, 2015</td>
<td>6.0 (56% sensitivity, 91% specificity)</td>
<td></td>
<td>6.4 (IQR 4.4–8)</td>
<td>3.9 (IQR 3.4–4.9)</td>
<td>0.0001</td>
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Abbreviations: CFLD = cystic fibrosis liver disease; PHT = portal hypertension; CF = cystic fibrosis
that CFLD patients have statistically significant higher values of liver stiffness compared with CF controls without liver involvement (40,41,42). TE values higher than 5.5 to 7.1 kPa are thought to be indicative of CFLD. Liver stiffness scores more than 6.8 kPa are most often reported (15,40,43). These cut-offs are lower than the ones observed in cases of cirrhosis due to other etiologies (39). In general, TE is considered as a good screening test and these values have been chosen to achieve optimal sensitivity. Although increasing TE values have been noted in patients developing liver disease during follow-up (43), the role of TE in identifying patients at risk of developing liver involvement has not been established prospectively.

Acoustic radiation force impulse (ARFI) imaging has also been studied in CFLD. By comparison to healthy controls, a cut-off of shear wave velocity of 1.27 m/s had a sensitivity of 56.5% and a specificity of 90.5% in detecting CFLD (45).

Serum biomarkers have also been used as screening tools for CFLD in a few studies: this includes the use of the aspartate aminotransferase-to-platelet ratio index (APRI) and the Fib-4 index. Both of these indirect markers of fibrosis have been studied in adults and children. APRI and Fib-4 scores higher than 0.264 and 0.358 have been found in 96% and 90% of CFLD patients, respectively; higher scores were observed in the sickest patients requiring liver transplantation (32). APRI predicted CFLD more consistently than Fib-4 when compared with liver biopsy in children (46). However, these indices were not considered as accurate as TE in assessing CFLD in adult patients (40).

Liver biopsy remains a useful test for establishing the diagnosis and evaluating the extent of liver disease. However, because of the patchy liver involvement found in CFLD, liver biopsy has a low diagnostic yield. Some have advocated for a dual-pass biopsy in order to increase detection of significant fibrosis (47).

**BILIARY DISEASE**

CF is not limited to involvement of the liver parenchyma; magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) anomalies have been described in CFLD patients. MRI has been reported to be more sensitive than ultrasound (48). MRCP can reveal periportal fibrosis but can also demonstrate large ducts anomalies such as strictures and calculi. Such findings, which can be similar to sclerosing cholangitis, have been shown in up to 70% of patients (34,49,50). Symptomatic hepatolithiasis is a rare biliary complication of CF (51). Gallbladder involvement as well as bile duct obstruction have also been described in case reports (52).

**EVOLUTION**

The common belief is that CFLD is primarily a disease of childhood that develops in the first decade of life, and occurs more frequently in boys (32). Once the threshold of puberty is reached, most patients were thought not to develop severe liver disease (6). It was also considered that patients with CFLD presented with a more severe CF phenotype during childhood (53). However, recent data seem to show that CFLD does not run a benign course in adulthood.

Portal hypertension is one of the major complications of adult CFLD. In a single-centre study of adult patients with CF, liver involvement was found in 28% and portal hypertension in 19%. However, progression of disease was rare in this cohort, without any cases developing portal hypertension during follow-up, suggesting stability of CFLD during adulthood (8). An Australian cohort of 27 adult patients with CFLD with a median follow-up of 7 years reported a 67% prevalence for portal hypertension, liver decompensation episodes in 7%, ascites in 11%, but no liver-related deaths or liver transplantation (54). A case series of 18 patients with at least one episode of variceal bleeding had a survival that was not statistically different from a control group of CF patients, with only one fatal hemorrhage and a single patient requiring liver transplantation. This suggests that adequate control of portal hypertension is key to achieving optimal prognosis (55).

On the other hand, a more dramatic evolution has been observed in a French cohort, where CFLD patients with cirrhosis at baseline developed liver decompensation during follow-up, which was associated with death or lung transplantation (7). Portal hypertension has been found to be an independent risk factor for mortality in a cohort of CF children who were followed up into adulthood (56).

Expanded criteria for the diagnosis of CFLD that took into account TE were evaluated in a population of adult CF patients (15) and resulted in a larger number of new diagnoses of CFLD than with the originally proposed criteria. Furthermore, this study demonstrated that the prevalence of
CFLD in adults is higher than previously thought and that new diagnosis can be made outside the first decade of life.

**MANAGEMENT**

The only recognized treatment for CFLD is ursodeoxycholic acid (UDCA). UDCA stimulates bile flow in mice devoid of CFTR function and reduces bile salts hydrophobicity (57). A retrospective study established that high doses of UDCA 20 mg/kg can halt the progression of CFLD (58). UDCA therapy in CFLD leads to short-term clinical and biochemical improvement in liver tests (59). On the other hand, no long-term studies comparing UDCA with placebo have been performed. A 2014 Cochrane Review on the topic concluded that too few studies evaluated long-term outcomes and that formal recommendations on its use required more data (60). Nonetheless, because of its safety profile, a daily dose of up to 20 mg/kg is recommended as best practice guidance in pediatric patients (14).

Some have advocated starting UDCA prophylactically when risk factors (including meconial ileus) are present to prevent the development of CFLD (9,61), while others advocate starting UDCA only once criteria for CFLD are met. Progression of complications of liver disease, such as portal hypertension, has been shown to be prevented by UDCA in CFLD patients when compared with a historical cohort (62). A recent observational study found improvement in liver stiffness score with UDCA treatment in cases of mild liver disease at 1 year; on the other hand, no improvement was observed in patients already at the stage of cirrhosis (63). Some studies point toward favourable effects of UDCA therapy on the digestion and absorption of lipids in patients with exocrine pancreatic insufficiency. Furthermore, increased loss of bile salts causing diarrhea can also be avoided by the use of UDCA (64).

The negative outcomes associated with high-dose UDCA in adult patients with primary sclerosing cholangitis have been judged as concerning for its use in CFLD. However, a recent study in children and adult CF patients did not show evidence of enhanced transformation of UDCA into the putative toxic bile acids responsible for this observation (65).

New treatments that directly target the dysfunctional CFTR proteins and have been shown to be effective for lung disease have not been thoroughly investigated with regards to liver disease as patients with abnormal liver test were excluded from participation in major trials. No clinically apparent liver injury has been reported in the large clinical trials that have been performed with these agents although elevated liver tests have occasionally been observed with severe adverse events reported with Ivacaftor/lumacaftor (66,67,68). Case reports have described improvement in steatosis with the use of Ivacaftor (69). CFTR modulators and potentiators have the potential to improve bicarbonate secretion which could reduce the frequency of CFLD (70).

Vaccination against viral hepatitis is an important aspect of the management of CFLD (71). Preventing additive liver damage by limiting alcohol consumption should be reinforced throughout life of CF patients.

**MANIFESTATIONS AND TREATMENT OF PORTAL HYPERTENSION IN CF PATIENTS**

A worldwide study of 561 patients, consisting of CF children and adults with cirrhosis and portal hypertension, reported the presence of splenomegaly in 99% of patients and varices in 71% (32). CFLD with portal hypertension has been found to be an independent risk factor of mortality, half of the causes of death being liver-related (56).

Splenomegaly caused by portal hypertension is often problematic in CFLD patients. Besides causing thrombocytopenia, which can increase the incidence and severity of the bleeding (in particular, hemoptysis), it is often reported as being the cause of abdominal distension and bloating. Some have reported the use of partial splenectomy in this setting (72).

Esophageal varices have been described in 30%–100% of CFLD patients with cirrhosis and, in published series, up to 42% of these patients developed variceal bleeding (18). Acute variceal bleeding is associated with a significant risk of mortality. This risk is probably increased in patients with CFLD, as suggested by Debray et al (73), because of the underlying lung condition. Prophylactic therapy to decrease the risk of bleeding has been advocated. Although the use of β-blockers in CFLD patients might be considered contraindicated because of lung disease, there is no available data to confirm this. Prophylactic variceal band ligation is usually the treatment of choice: careful attention to the use of sedation needs to be made because of
the underlying lung disease (13). In cases of active refractory or recurrent bleeding, interventional radiology techniques, such as a transjugular intrahepatic porto-systemic shunt (TIPS) or surgical portosystemic shunt are required. A small case series of TIPS performed in pediatric patients demonstrates adequate control of portal hypertension (74). Particular attention has to be given to CFLD patients in whom TIPS could lead to decreased pulmonary compliance, as an increase in right-sided cardiac pressures are expected following this procedure (75). Porto-caval and spleno-renal shunts are well described in the pediatric literature but are rarely used in adults (73,76).

Other manifestations of portal hypertension and liver disease, such as ascites and hepatic encephalopathy, can also be observed in CFLD. Treatment of these complications is not different in patients with CF. However, it is usually thought that these patients should not be salt-restricted because of a risk of normonatremic sodium depletion. This has become a challenge in pediatric patients with ascites who are prescribed a sodium-restricted diet, as normonatremic sodium depletion has been associated with poor growth in patients with CF (77). Hepatopulmonary syndrome has been reported in a few cases: this can be challenging to diagnose because of the coexistent pulmonary condition in CF (78).

TRANSPANTATION

Liver transplantation is considered when the complications of CFLD cannot be addressed medically. The two main indications for liver transplantation are liver failure and hepatocellular carcinoma. However, as more and more CF patients require lung transplantation, liver complications can occur in patients with cirrhosis that have otherwise good liver function. However, there are no established indications for liver transplant in CFLD and this decision is made on a case-by-case basis. One centre has based candidacy for liver transplant (in a context of combined transplant) on a portal gradient >10 mm Hg and biopsy proven cirrhosis (79) with allocation of the liver graft from the same donor of the lung graft. Furthermore, established allocation models such as the Model for End Stage Liver Disease (MELD) score do not discriminate well CFLD patients on the transplant list. As an example, the mean MELD score of 17 adult CF patients undergoing liver transplant at a single institution was only 11 (80). Therefore, special exemption points have been attributed to CFLD patients on the liver transplant waiting list. Some centres prefer to perform early or pre-emptive liver transplantation as determined by nutritional status or respiratory function. While it has been suggested that liver transplantation is contraindicated when FEV1 <50%, it has been performed in this situation without adverse events (80).

Melzi et al (81) reviewed pediatric liver transplants from multiple European transplant centres, noting that the 3-year survival post-liver transplant for CF of 81.4% which was comparable to the 79% survival in the European Liver Transplant Registry. Interestingly, lung function was found to be improved post-liver transplant, which has also been described in other studies. In adults, survival rates were 85% at 1 year and 65% at 5 years (80), similar to survival rates for other liver transplant indications.

A review of the United Network for Organ Sharing (UNOS) database from 1987 to 2009 reported survival rates of 80%, 74%, and 67% at 1, 3, and 5 years post-liver transplant in an adult CF population of 63 patients (82). There was no statistical difference in terms of survival when compared with outcomes of combined liver-lung transplantation. Another review of the UNOS database reported a similar 5-year survival rate of 72.7% in adults and 85.8% in children having undergone liver transplantation for CFLD (83). Increased mortality was noted when compared with other patients undergoing transplant, though mortality was not related to graft dysfunction (84). However, when comparing survival rates at 3 years, adult patients having received a liver transplant had a higher survival rate than those remaining on the transplant list (83).

The role of pancreatic transplant in CF patients with diabetes has yet to be determined, as it represents less than 1% of pancreatic transplants according to the UNOS database (13); case reports of combined liver-lung-pancreas transplantation have been reported (85). Post-liver transplant, Kuo et al have reported new-onset diabetes in CFLD patients, a complication that often affects CF as they grow older (86).

LUNG INVOLVEMENT IN CFLD

As already stated, liver disease has been linked with worse pulmonary outcomes in CF patients, notably treatment failure in cases of infections caused by Pseudomonas aeruginosa (87). CFLD has
been associated with concomitant colonization by *Aspergillus fumigatus* and *Stenotrophomonas maltophilia*, which are prevalent in the CF population (88). CF patients are also at higher risk for hepatotoxicity due to voriconazole post-lung transplant (89).

While short-term studies described improvement in lung function in pediatric patients undergoing liver transplantation, results in the adult population are not as consistent. Whereas Nash et al (90) described worsening in lung function post-liver transplant more rapidly than what would have been expected without transplant, Dowman et al (80) reported stable pulmonary function 4 years after liver transplant. Analysis of respiratory function in 52 adult patients undergoing LT in the United States revealed similar FEV₁ 3 years postoperatively and a slower decline in FEV₁ than in a control group of CF patients without CFLD (91).

Combined lung and liver transplants have been reported in a limited number of cases. A single centre reported eight combined liver and lung transplants performed, two on patients with CF, achieving excellent outcomes (79). Triple transplant, consisting of combined liver, heart, and lung transplantation, has been associated with high mortality rates (90).

The decision of whether or not to proceed to liver transplantation in patients with CFLD who need a lung transplant is a difficult one to make. The burden and risks associated with double versus single organ transplantation are increased. Therefore, it is generally considered better to perform lung transplantation alone whenever possible. On the other hand, it is probably better to perform liver-lung transplant if the liver disease is going to progress after lung transplantation. Predicting the evolution of CFLD after lung transplant is difficult because of the lack of data in the literature on this topic.

**HEPATOCELLULAR CARCINOMA**

Hepatocellular carcinoma (HCC) is a complication observed in patients with cirrhosis regardless of its etiology. However, there are currently only case reports of HCC complicating CFLD (92,93,94). Nevertheless, biannual surveillance is recommended in all cirrhotic CFLD patients. CF patients are also at an increased risk of digestive tract cancers, regardless of the presence or absence of CFLD (95).

**TRANSITION OF CARE**

The transition of care from pediatric to adult medicine occurs at a crucial moment in an individual’s life. The optimal approach to such a crucial task remains undetermined. A multidisciplinary approach is necessary, with communication between the adult and pediatric teams beforehand. Transition of care for CF patients as well as liver transplant patients has been previously documented. A major issue raised by these reports is that of reduced adherence to health care following transition (96). However, transition of care for CFLD and other hepatobiliary disease has not been well studied despite recent efforts to raise attention to this issue (97). With a growing number of patients reaching adulthood and better awareness of existing liver involvement or diagnosis during adulthood, a growing need for structured transition of care is becoming evident.

**CONCLUSION**

CFLD remains an aspect of cystic fibrosis that is not well studied. Long thought to be a disease of childhood, increased life expectancy and adult-onset cases have challenged this observation. Awareness of the possibility of liver involvement, the use of non-invasive diagnostic methods, transition of the cases identified in childhood and better follow-up are important aspects of the management of this condition. Portal hypertension remains problematic in pediatric as well as in adult cases, but therapeutic options, including liver transplantation, yield encouraging results.

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