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Cystic Fibrosis Screening, Evaluation and Management of Hepatobiliary Disease Consensus Recommendations

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List of Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PwCF, people with CF; CFF, Cystic Fibrosis Foundation; PICO, population, intervention, comparison, and outcome; MeSH, medical subject heading; CFHBI, CF hepatobiliary involvement; aCFLD, advanced CF liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; APRI, AST-to-Platelet Ratio Index; FIB-4, Fibrosis-4; GPR, GGT-to-Platelet Ratio; US, ultrasound; TE, transient elastrography; SWE, shear wave elastography; MRE, magnetic resonance imaging with elastography; MRCP, magnetic resonance cholangiopancreatography; INR, international normalized ratio; CFRD, CF-related diabetes; OGTT, oral glucose tolerance testing; EGD, esophagogastroduodenoscopy; HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; RCT, randomized controlled trials; UDCA, ursodeoxycholic acid; FEV_1, forced expiratory volume in 1 second; ERCP, endoscopic retrograde cholangiopancreatography; NSBB, non-selective beta-blocker; EVL, endoscopic variceal ligation; LAS, lung allocation score; AUROC, area under receiver operator curve.

Graphical abstract

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ABSTRACT

Background and Aims: Cystic fibrosis (CF) may cause a spectrum of hepatobiliary complications, including portal hypertension, multilobular cirrhosis, and liver failure. Current guidelines on the detection and monitoring of hepatobiliary complications in CF were published in 1999. The CF Foundation assembled a committee to evaluate research advances and formulate revised guidelines for CF-associated liver disease.

Approach: A committee of hepatologists, gastroenterologists, pulmonologists, pharmacist, nurse, dietitian, individual with CF, and parent of a child with CF devised “population, intervention, comparison, and outcome” (PICO) questions regarding hepatobiliary disease in CF. PubMed literature searches were performed for each PICO question. Recommendations were

voted on with 80% agreement required to approve a recommendation. Public comment on initial recommendations was solicited prior to formulation of final recommendations.

Results: 31 PICO questions were assembled, 6,401 manuscripts were title screened for relevance, with 1,053 manuscripts undergoing detailed full text review. Seven recommendations were approved for screening, 13 for monitoring of existing disease, and 14 for treatment of CF-associated hepatobiliary involvement or advanced liver disease. One recommendation on liver biopsy did not meet the 80% threshold. One recommendation on screening ultrasound was revised and re-voted on.

Conclusions: Through a multidisciplinary committee and public engagement, we have assembled updated recommendations and guidance on screening, monitoring and treatment of CF-associated hepatobiliary involvement and advanced liver disease. While research gaps remain, we anticipate that these recommendations will lead to improvements in CF outcomes through earlier detection and increased evidence-based approaches to monitoring and treatment.

INTRODUCTION

Cystic fibrosis (CF), caused by pathogenic autosomal recessive mutations in the *CFTR* gene, may result in a host of hepatobiliary pathologies, ranging from cholelithiasis, hepatic steatosis, and liver fibrosis to multilobular cirrhosis, portal hypertension, and in a subset of individuals, liver failure necessitating liver transplant or even liver-related death.[1] In 1999, the CF Foundation published recommendations for the diagnosis and management of CF-associated liver disease.[2] Since that time, research on hepatobiliary disease in CF has advanced, expanding our insights on the pathogenesis of disease, appreciating the range of complications, investigating the use of new technologies for diagnosis and monitoring of disease, and the introduction of new therapies such as the cystic fibrosis transmembrane regulator (CFTR) potentiators and correctors. While collectively these have enriched our knowledge and tools to address hepatobiliary disease in CF, they have also introduced many questions about how to care for persons with CF (PwCF) that have suspected or confirmed hepatobiliary disease. To address these questions, the CF Foundation established a committee to generate new consensus guidelines and recommendations for the diagnosis, monitoring, and treatment of CF-associated hepatobiliary complications based on published literature and expert opinion. Public comment on recommendations were also obtained. We anticipate that these new guidelines will improve early diagnosis and care for children and adults with CF-associated hepatobiliary disease, and ultimately improve the morbidity and mortality of PwCF. Through this process, we have identified gaps that need additional research, which we hope will further inform research priorities for clinical care advancements for CF patients with hepatobiliary disease.

METHODS

The CF Foundation (CFF) assembled a committee of multidisciplinary CF care team members including: hepatologists, gastroenterologists, pulmonologists, pharmacist, nurse, dietitian, an individual with CF, and the parent of a child with CF. The committee included members from the United States, United Kingdom, Netherlands, Canada, Italy, and France. The committee met virtually in August 2020 to develop their PICO (Population, Intervention, Comparison, and Outcome) questions. The committee divided into three workgroups to focus on

screening, monitoring, and treatment. The workgroups conducted literature searches in PubMed for each PICO question between March and October 2021, with a final query in April 2023, using the medical subject heading (MeSH) terms provided in Supplemental Methods, http://links.lww.com/HEP/I76 and Tables 1-3[kr1]. The committee systematically reviewed the results of these searches. The committee met multiple times between January and March 2022 to discuss and vote on recommendation statements. An *a priori* threshold of 80% agreement was required to advance a recommendation. Following the initial draft, the manuscript was posted on the CF Foundation's website and individual public comments were solicited via various communication mechanisms from individuals with interests in hepatology, GI, and CF for a 2-week period from September 14, 2022 to September 28, 2022, after which the committee evaluated the feedback. Based on public feedback, language of some recommendations were clarified (without major changes in intention) and a re-vote on modification of one recommendation was performed.

The terminology for CF hepatobiliary involvement is evolving. For these guidelines, we used the following terms to categorize CF hepatobiliary involvement based on the existing literature. Definitions of CF hepatobiliary involvement (CFHBI) and advanced CF liver disease (aCFLD) were adopted from the existing literature and are as follows:

- Advanced CF Liver Disease (aCFLD) refers to having one (or more) of the following: nodular liver, advanced fibrosis (F4), multilobular cirrhosis with or without portal hypertension or non-cirrhotic portal hypertension
- CF Hepatobiliary Involvement (CFHBI) refers to having one (or more) of the following without features of aCFLD: hepatomegaly, liver fibrosis (<F4), increased liver stiffness by elastography (<F4), hepatic steatosis, focal biliary cirrhosis, cholestasis, persistent (>3-6 months) elevated serum liver function tests (any level above upper limit of normal), abnormal liver imaging, cholelithiasis, sclerosing cholangitis or hepatolithiasis.

For the purposes of this document, children are defined as birth to 17 years of age and adults as 18 years of age and older.

The CF Foundation intends for this guideline to summarize evidence, and provide reasonable clinical recommendations based on that evidence, to clinicians, patients, and other stakeholders. The application of these recommendations should not be mandated. Care decisions regarding

individual patients should be made using a combination of these recommendations, the associated benefit-risk assessment of treatment options from the clinical team, the patient's individual, and unique circumstances, as well as the goals and preferences of the patients and families that the team serves, as a part of shared decision making between the patient and clinician.

SCREENING RECOMMENDATIONS

S1. The CFF recommends that annual labs (total bilirubin, AST, ALT, alkaline phosphatase, GGT, Platelet Count) should be performed, at a time of clinical stability, for identification of hepatobiliary involvement in all persons with CF starting at CF diagnosis.

CFHBI can manifest in childhood[3, 4] adolescence, and/or adulthood.[5, 6] Liver test abnormalities may precede imaging abnormalities[7] and correlate with fibrosis.[8, 9] Early identification of CFHBI affects care through staging, regular monitoring, and treatment. Common liver test abnormalities in CF may include elevations in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and/or alkaline phosphatase. Elevated conjugated bilirubin may occur in aCFLD or with biliary obstruction. Portal hypertension may also cause an absolute or relative thrombocytopenia if baseline thrombocytosis is present.[10, 11] Prior guidelines recommended further action at 1.5-2x upper limit of normal values for increased specificity.[2] However, this, coupled with use of high thresholds can contribute to delayed diagnosis. Therefore, it is important to use age and sex normative values[12,13] and we recommend further evaluation if any abnormalities are persistent (>3-6 months). Few studies have evaluated the optimal timing and frequency of lab testing;[14] however, the CFF recommends that these tests be performed on an annual basis beginning at CF diagnosis. Many persons with CF have transient elevation of liver enzymes during systemic inflammation or antibiotic treatment; however, CFHBI is characterized by persistent liver test abnormalities[15, 16] and annual screening should be performed during a time of relative clinical stability (e.g. no active treatment for acute pulmonary exacerbation or infection). Calculation of liver fibrosis indices based on routine laboratory tests, including AST-to-Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4), and GGT-to-Platelet Ratio (GPR) can detect advanced fibrosis and

portal hypertension and may be more specific than liver tests alone since they include platelet count. APRI is the most studied in CF and may be useful to identify aCFLD.[6, 5, 17, 18, 19] GPR may be particularly useful in detecting early biliary disease prior to significant hepatocyte injury.[20] Optimal thresholds have not been broadly accepted in CF for any of the fibrosis indices and therefore the utility of these indices in screening PwCF for possible CFHBI or aCFLD is uncertain.

S2. The CFF recommends annual abdominal physical examination for hepatosplenomegaly for identification of advanced liver disease in all persons with CF starting at CF diagnosis.

Persons with CFHBI and aCFLD may manifest abnormalities on physical exam.[2] These include hepatomegaly, defined as enlargement of the liver span below the mid-clavicular line, and/or splenomegaly, defined as a palpable spleen on abdominal examination. Of these, hepatomegaly is the most common [21] with some studies reporting this in up to 30% of PwCF.[22, 23] A study correlating physical exam with liver biopsy in CF reported a sensitivity and specificity of 60% and 44% for hepatomegaly, and 93% and 57% for splenomegaly in the detection of aCFLD.[24] While the specificity of abdominal examination is relatively low, it is non-invasive, easily repeatable, and requires minimal additional time and cost. During the examination, percussion and palpation of the entire liver and spleen with measurement of the liver span at midclavicular line should be performed. One longitudinal study evaluated physical examination for hepatomegaly and splenomegaly in children with CF,[25] finding an incremental detection of abnormalities through annual examination. There is a lack of objective evidence to recommend screening abdominal examination more frequently than annually in PwCF not known to have CFHBI or aCFLD.

S3a. The CFF recommends abdominal ultrasound to assess the liver and spleen at least every two years in persons with CF from childhood until late adolescence, starting at age 3 or at diagnosis, if diagnosed after age 3.

S3b. In adults with CF, there is value in baseline screening for CFHBI, but the optimal frequency of subsequent imaging for those with normal baseline findings is unknown and a specific recommendation cannot currently be made.

Together with laboratory tests and physical examination, periodic abdominal ultrasound (US) imaging to evaluate the liver and spleen is recommended for screening in all PwCF. US is a readily available, non-invasive test with modest cost which can identify abnormalities not detected by screening with physical exam or laboratory tests,[26, 27] such as the presence of echogenicity from steatosis, heterogeneous parenchyma and surface nodularity of the liver and findings suggestive of portal hypertension (ascites, mesenteric edema, splenic enlargement). Abnormal findings during screening can help in the characterization of CFHBI and evaluation for aCFLD.[11, 19] Dedicated vascular assessment by Doppler is not technically necessary to detect portal venous reversal of flow. However, centers should consult with local radiologists for local preferences on use of Doppler for this purpose. Since US abnormalities in PwCF can develop at any age, initiation of screening should occur starting at age 3, or at diagnosis, if diagnosed after age 3. While some studies have reported on annual screening abdominal US in PwCF,[28] there is insufficient evidence to recommend imaging on a yearly basis and defining the optimal frequency of US imaging is an important topic for future research. Specifically, studies to define risk stratification of individuals at high risk of developing CFHBI despite a normal baseline US will enable a more precise approach to US screening. Based in part on the PUSH Study of US imaging in pediatric populations with CF,[29] the CFF recommends US imaging every two years from childhood through late adolescence. In adults with CF, a baseline screening is recommended to detect abnormal US patterns. However, there is no data to define the frequency of subsequent US imaging if the initial screening results are normal. Therefore, a specific recommendation for follow up US imaging in adults with CF cannot be currently made.

S4. The CFF recommends that persons with CF who are found to have hepatobiliary involvement (abnormal physical exam, persistently elevated liver enzymes, or abnormal abdominal ultrasound findings), should undergo baseline liver elastography, when available, for the identification of advanced liver disease.

While persistent elevation of liver tests, abnormal physical exam (hepatomegaly and splenomegaly), and US abnormalities may be sufficient to detect aCFLD, these modalities are not sufficiently sensitive for detection of earlier stages of clinically relevant liver fibrosis. Differentiation of mild to moderate (stage F0-1) from more advanced liver fibrosis (stage F2-4) at baseline during diagnosis has been shown to impact prognosis and clinical care in many chronic liver diseases such as primary biliary cholangitis.[30] Liver stiffness measurement is ideal for this purpose as it is non-invasive and can be repeated over time. Modalities include transient elastography (TE), US shear-wave elastography (SWE) and magnetic resonance imaging with elastography (MRE), each of which have been tested in persons with CF liver involvement.[17, 5, 31] Among these modalities, TE and SWE are the most readily available and most studied in CF and other chronic liver diseases.[32, 33, 34, 35, 36, 37, 38] Published small cohort studies for TE and SWE thresholds for PwCF are variable but have been described (Table 1).

S5. The CFF recommends that persons with CF and hepatobiliary involvement should receive a standardized evaluation for other causes of liver disease.

PwCF, including those with CFHBI and aCFLD may also have unrelated causes of acute and chronic liver disease. Other causes of liver disease can mimic CFHBI and aCFLD. In addition, modifier genes such as the *SERPINA Z* allele (a cause of alpha-1 antitrypsin deficiency), can negatively impact the clinical course of hepatic injury in CF.[39] The growing epidemic of obesity and metabolic syndrome, associated with fatty liver disease, has implications for all PwCF since it can be concurrent with CF, particularly in adults.[40] Given this, all PwCF found to have CFHBI should undergo a standardized evaluation for additional causes of liver abnormalities. This should include testing for chronic viral hepatitis (e.g. chronic hepatitis B, C, and E if immunosuppressed or other risk factors present), cholestatic and autoimmune liver disease, alcoholic and non-alcoholic fatty liver disease, alpha-1 antitrypsin deficiency, Wilson disease, non-hepatic disorders such as celiac disease, and drug-induced hepatotoxicity from CFTR modulators and other forms of pharmacotherapy.[41, 1, 42, 43, 44, 45] Further testing can be tailored to individualized risk factors**.** Depending on the availability of local expertise, and familiarity with

the care of PwCF, a dedicated evaluation through referral to a gastroenterologist or hepatologist may be prudent.

S6. The CFF recommends that all persons with CF who have cholestatic liver test (Direct Bilirubin, GGT, and/or alkaline phosphatase) elevation, abdominal pain consistent with a biliary cause and inconclusive abdominal ultrasound should undergo magnetic resonance cholangiopancreatography (MRCP) to detect hepatolithiasis, choledocholithiasis, biliary strictures, and/or biliary obstruction.

PwCF are at risk for biliary complications, which include the development of symptomatic large-duct biliary strictures, gallbladder disease, and intra/extrahepatic biliary lithiasis leading to obstruction. This can manifest clinically with acute cholangitis in the setting of right upper quadrant pain, jaundice and/or fever and chills. Although abdominal US imaging has excellent diagnostic accuracy for gallbladder pathology, it is less accurate for detection of intra and extrahepatic biliary tree abnormalities. MRCP imaging is superior to US for assessment of the biliary tree and has been well-studied in chronic biliary diseases[46, 47, 48] and in small case series of PwCF.[49, 50, 51, 52, 53] Therefore, in PwCF who have findings that are concerning for biliary disease without an adequate explanation by US imaging, MRCP should be obtained to help guide therapeutic decisions.

MONITORING RECOMMENDATIONS

M1. The CFF recommends that in persons with CF and liver involvement, a liver specific physical examination be performed at least annually and at each in-person visit to monitor for the progression of disease.

The most common physical exam finding of aCFLD is an enlarged firm liver with or without splenomegaly.[1] Other findings of progressive liver disease, such as ascites, are typically absent until the late stages of aCFLD. A composite score including liver and spleen size on physical exam, in addition to ALT and GGT values had a greater sensitivity and specificity (85% and

82% respectively) for predicting microscopic liver injury compared to hepatomegaly alone.[24] As such, a more nuanced physical exam of the liver including size (enlarged vs. normal), texture (smooth vs. nodular) and firmness is recommended. Despite low specificity, a liver specific physical exam is non-invasive, easily repeatable, requires minimal additional time and no additional cost, thus yielding a favorable cost to benefit ratio. We recommend liver-specific physical exam for persons with CFHBI and aCFLD at each in-person visit, at a minimum of once per year.

M2. The CFF recommends that for persons with CF and hepatobiliary involvement at least one liver fibrosis index be calculated and followed at least annually.

Liver fibrosis indices used in the assessment of other liver diseases have been applied to the detection of CFHBI and progression to aCFLD. Elevations of these indices have been associated with nodular liver appearance on US, presence of portal hypertension and varices, and more advanced liver fibrosis in CF. Studies of APRI, FIB-4, Forns index, and GPR found that each of these indices had high sensitivity and low specificity for the detection of liver fibrosis.[54, 34, 20, 17] The current recommendation is to choose at least one liver fibrosis index and follow results annually to aid in both detection and progression of liver CFHBI and aCFLD. The components of APRI, FIB-4, Forns index, and GPR are captured in the recommended annual labs for all persons with CF. As application of these liver fibrosis indices is relatively new in CF, there is some variation in the literature of normal values. Table 1 summarizes the literature for APRI and GPR.

M3. The CFF recommends for persons with CF and hepatobiliary involvement an abdominal US be performed at least every 2 years to monitor for the progression of disease.

US is a non-invasive technique that is safe and low risk for all patients with CF. This technique is almost universally available in all CF centers worldwide and is useful in discriminating hepatobiliary involvement and grossly monitoring the progression of liver disease over time. No adverse effects on quality of life have been identified in using US to diagnose pre-symptomatic liver disease in children with CF.[55] While discrepancies in interpretations have

been reported between centers, sequential studies at a single center read by similarly experienced radiologists can provide important longitudinal information regarding hepatobiliary involvement in CF. For this reason, we recommend that individuals with CFHBI undergo an abdominal US (including liver and spleen) at least every 2 years to detect new onset or evolving heterogeneity of the liver parenchyma, nodularity, hepatomegaly, splenomegaly, reversal of flow in the portal venous system, or ascites. Reversal of portal venous blood flow can be detected by routine US color flow measurements. Separate Doppler measurements may not be necessary but can be considered on individual basis, based on local radiologist preferences for use of Doppler to detect portal venous flow. If centers use SWE for elastography, then US tests may be done on an annual basis.

M4. The CFF recommends that persons with CF and hepatobiliary involvement or advanced liver disease undergo evaluation of liver stiffness with elastography at least annually, if available, to monitor for the progression of disease.

Multiple studies have shown that TE and SWE can not only detect CFHBI, but also be used to follow progression of stiffness over time to monitor progression of disease in both children and adults.[9, 8, 56] For both modalities, highest accuracy is achieved when comparing an individual's elastography values over time using the same modality. Although MRE provides richer information about variation of stiffness in different regions of the liver, there is currently insufficient evidence to recommend MRE over the more accessible and economical TE or SWE for monitoring. Given the greater availability of TE and SWE for both children and adults, and evidence of reproducibility and detection of change over time, it is recommended that all persons with CFHBI have either TE or SWE performed annually. As much as possible, annual measurement should be performed using the same technology (i.e., either TE or SWE) to allow for year-over-year comparisons.

M5. The CFF recommends that persons with CF hepatobiliary involvement or advanced liver disease receive consultation with a pharmacist with experience in CF and hepatobiliary disease to identify high risk medications, polypharmacy, therapy

modifications, and risk based on their hepatobiliary disease every 6 months, unless there have been no medication changes, to improve morbidity and mortality.

Polypharmacy is common in CF. Use of antibiotics ranges from short courses to complicated long-term regimens against non-tuberculous mycobacteria and multi-drug resistant organisms colonizing the respiratory tract. In addition, PwCF commonly have other medical problems that require additional medications. CFTR modulators, which are metabolized by the cytochrome P450 system have also entered the daily regimen of PwCF with further concerns for drug-drug interactions.[57] Other important considerations include consumption of supplements (e.g., herbals) and alcohol, which can impact liver metabolism and function. Multiple studies have shown that involvement of a pharmacist in in-patient and out-patient settings results in improved outcomes for treatment of infections, decreased length of hospitalizations, decrease in medication errors, and improved safety for PwCF.[58, 59, 60, 61] Given that many medications and supplements are metabolized through the liver, PwCF with elevated liver enzymes, CFHBI, aCFLD, and post-transplant are at risk for complicated drug-drug interactions. Preventative measures, such as avoiding herbal supplements, minimizing or abstaining from alcohol, and obtaining Hepatitis A and B vaccinations should be discussed.

M6. The CFF recommends that persons with CF and advanced liver disease undergo liver specific physical examination and measurement of AST, ALT, GGT, alkaline phosphatase, conjugated (or direct) bilirubin, albumin, platelets, and international normalized ratio (INR) at least every 6 months to detect progression of liver disease.

Elevations of AST and ALT are seen during hepatocellular inflammation and of GGT during cholestasis or biliary inflammation. GGT elevation has been associated with the presence of CFHBI or progression to aCFLD.[11, 16, 15, 3] Elevated conjugated bilirubin may occur in aCFLD with profound hepatocellular destruction. Albumin and INR are markers of liver synthetic function. Previous studies have not specifically evaluated the utility of monitoring albumin and INR to detect progression of hepatobiliary disease in CF. However, in the presence of aCFLD, understanding liver synthetic function is essential in evaluating progression of liver disease and risk for comorbidities such as ascites or variceal bleeding. Low or decreasing platelets over time

may indicate development/progression of portal hypertension, regardless of the absolute value.[62, 33] aCFLD is generally a slowly progressive disease for which twice-yearly evaluation of inflammation, cholestasis, liver function, and progression of portal hypertension will allow earlier recognition of changes in those PwCF who have already been identified to have aCFLD.

M7. The CFF recommends that persons with CF and advanced liver disease, receive a nutritional assessment for malnutrition and liver specific macro- and micronutrient deficiencies every 6 months by a dietitian experienced in CF. When abnormalities are identified a treatment plan and monitoring of nutritional rehabilitation should be developed.

There is increased nutritional burden for persons with aCFLD.[1] There is evidence of increased fat malabsorption due to decreased biliary function, increased catabolism due to inflammation within the biliary tree and liver, increased rates of CF-related diabetes (CFRD) and metabolic bone disease.[1] Decreased volume and flow of bile, as well as variable bile composition, affect the absorption of fats and fat-soluble vitamins. Essential fatty acid deficiency has been shown to persist in persons with aCFLD despite adequate nutrition therapy.[63, 64] Annual nutritional evaluation by a dietitian with CF-specific expertise is presently included in the CFF guidelines.[65, 66] It is recommended that nutritional evaluation be expanded to at least twice a year by a dietitian with expertise in both CF and advanced liver disease. If nutritional abnormalities are noted during the evaluation, a comprehensive nutritional rehabilitation plan should be developed and implemented. Follow-up should involve increased frequency of reassessments and proactive adjustments with the overall goal of improving nutritional status.

M8. The CFF recommends, for persons with CF and advanced liver disease, beginning CF related diabetes (CFRD) screening at the diagnosis of advanced liver disease, even if earlier than age 10 and then annually thereafter, to provide early diagnosis and treatment of CFRD (using methodologies described in the most current CFRD Guidelines).

The liver plays an integral role in glucose metabolism. There are limited studies specifically evaluating oral glucose tolerance testing (OGTT) in the setting of aCFLD, but existing data

indicate impaired glycemia, insulin secretion, insulin sensitivity and clearance.[67] An increased incidence of CFRD in patients with aCFLD as compared to those without liver disease has been described.[68, 1] An increased incidence of CFRD was found in a cohort of 88 CF children with baseline heterogeneity or cirrhosis on ultrasound.[69] A case-controlled cohort study from Australia found an odds ratio of 2.61 (95% confidence interval: 1.55-4.47) for CFRD in those with aCFLD compared to no CFHBI[70] A positive association between ALT elevation and insulin resistance was identified in a cross-sectional study of 273 CF adults screened for CFRD.[71] Development of CFRD requires additional monitoring for prevention of nutritional instability. Thus, it is important to screen children <10 years-old with aCFLD for insulin resistance and CFRD upon aCFLD diagnosis.

M9. The CFF recommends that persons with CF and advanced liver disease receive multidisciplinary care from pulmonology, gastroenterology/hepatology, endocrinology and when appropriate, a transplant center, to optimize liver outcomes.

While there is limited CF specific literature, there is ample literature in other liver and lung diseases emphasizing the importance of multidisciplinary care in improving outcomes, especially when transplant is being considered.[72, 73] This can be especially important when considering liver alone or combined multi-organ transplants.[74] The CFF guidelines for lung transplant developed in 2019 emphasize that communication between the primary CF center and the lung transplant team is crucial in providing optimal care for persons with advanced lung disease necessitating transplantation. As noted in recommendations M7 and M8, aCFLD is often complicated by nutritional challenges and derangements in glucose metabolism, which will impact both pre- and post-transplant considerations. A multidisciplinary approach is critical to assuring a patient is stable for transplant and thrives after receiving a transplant. This should include not only medical providers, but social workers, psychologists, physical therapists, and dietitians who are instrumental in addressing the psychosocial and nutritional challenges associated with chronic disease and the added burden of transplant.

M10a. The CFF recommends that adults with CF and advanced liver disease with esophageal varices be managed according to the relevant most current published

guidelines, such as those from the American Association for the Study of Liver Diseases or the Baveno group.

M10b. The CFF cannot provide a recommendation for or against endoscopic variceal surveillance in children with advanced liver disease, due to insufficient evidence.

A large retrospective review of the CFF registry data from 2003-2012, with a mean age of 18.1 years, found 3.6% were documented to have cirrhosis.[75] Of those, the 10-year cumulative risk for variceal bleed was 6.6% with the mean age of first variceal bleed being 18.8 years (range 0.89 – 45.14).[75] In a different study, CF patients with variceal bleeding were five times more likely to undergo liver transplantation, but all-cause mortality was not impacted by variceal bleeding.[75] Screening for varices is performed by esophagogastroduodenoscopy (EGD), which allows for the identification and characterization of varices and therapeutic intervention.[76] Based on current Baveno consensus recommendations, in adults with compensated cirrhosis, the initial screening endoscopy may be deferred if platelet count is ≥ 150,000 and the liver stiffness, as measured by TE, is ≤ 20 kPa.[76, 77, 78, 79] Although these criteria have not been studied in aCFLD, it is reasonable to follow the most current consensus guidelines for EGD surveillance in adults; initiating EGD surveillance when platelet and/or liver stiffness thresholds are crossed and performing surveillance every 1-2 years thereafter.[77] Endoscopic screening and prophylaxis of variceal bleeding have not been adequately studied in children with aCFLD or other pediatric liver diseases, and therefore evidenced-based recommendation cannot be made for or against endoscopic surveillance in children with aCFLD at this time. As liver guidelines for children continue to evolve, recommendations for surveillance endoscopy in children with aCFLD should be aligned with recommendations made for all children with advanced liver disease and hypersplenism.

M11a. The CFF recommends that all CF children with cirrhosis or suspected cirrhosis, are screened annually for hepatocellular carcinoma with abdominal US and serum alpha-fetoprotein.

M11b. The CFF recommends that all CF adults with cirrhosis or suspected cirrhosis are screened for hepatocellular carcinoma using the most current screening guidelines as per

American Association for the Study of Liver Diseases or European Association for the Study of Liver Disease.

While the incidence of hepatocellular carcinoma (HCC) in CF cirrhosis is unknown, multiple case reports demonstrate that HCC is a complication of CF and cirrhosis.[80, 81, 82] It can be speculated that with increased survival of PwCF, the duration of cirrhosis in patients with aCFLD will increase resulting in a rise in HCC in CF. Based on this consideration and current guidelines, we recommend patients with CF and cirrhosis, or suspected cirrhosis, undergo liver US twice a year for adults and annually for children with yearly serum concentration measurements of serum alpha-fetoprotein (AFP) for all.[83, 84] AFP is considered a biomarker for HCC and has been utilized in multiple liver diseases to detect HCC once the presence of cirrhosis has been established. However, HCC can occur even in the presence of normal AFP so HCC monitoring should also include abdominal US.

TREATMENT

T1. The CFF recommends against the routine use of ursodeoxycholic acid to prevent advanced liver disease in all persons with CF.

Several small randomized controlled trials (RCT)[85, 86, 87, 88, 89] and multiple cohort studies[90, 91, 92, 93] in persons with CF liver disease (based on prior definitions) have shown improvements in liver enzymes (AST, ALT, GGT) with ursodeoxycholic acid (UDCA) treatment duration between 6 months to 2 years. However, no studies have shown that UDCA prevents the development of aCFLD or liver transplant. In 2017, a Cochrane Review concluded that there was insufficient evidence to justify its routine use in CF.[94] Since then, one longitudinal cohort study (n=3,417), with up to 6 years follow-up, showed an association of UDCA on survival in persons without cirrhosis, but UDCA was also associated with increased odds ratio of having cirrhosis (2.87, CI: 1.55-5.32, P=0.001).[95] Two recent large cohort studies (n=1,591 and 3,328) found no difference in the incidence of aCFLD for those treated with UDCA compared to those not treated.[96, 97] Because the data do not support that UDCA prevents aCFLD, we do not recommend

its routine use to prevent aCFLD. There are currently no data on liver outcomes in PwCF that discontinue UDCA. As such, CF care providers should utilize discretion regarding indications for continuation or discontinuation of UDCA treatment for those presently on UDCA.

T2a. Efficacy: The CFLD Guidelines Committee cannot recommend for or against the use of CFTR modulator treatment to improve liver outcomes in persons with CF and hepatobiliary involvement or advanced liver disease when age-appropriate, genotype-specific modulator therapy is available due to insufficient evidence.

T2b. Safety: The CFLD Guidelines Committee recommends, based upon expert opinion, the use of CFTR modulator treatment in persons with CF and CF hepatobiliary involvement in the setting of close monitoring by a CF gastroenterologist and/or hepatologist and pharmacist because the benefits to CF lung disease outweigh the liver related risk.

T2c. Safety: The CFLD Guidelines Committee cannot recommend for or against the use of CFTR modulators in persons with CF with advanced liver disease and portal hypertension without decompensation due to insufficient evidence.

T2d. Safety: The CFLD Guidelines Committee recommends against CFTR modulator use in persons with CF and decompensated advanced CF liver disease, as determined by a consultant Hepatologist based on thresholds such as sustained INR>1.5, abnormal direct bilirubin, low albumin, refractory ascites or encephalopathy.

T2e. Transplant: The CFLD Guidelines Committee recommends, based upon expert opinion, for CFTR modulator treatment in persons with CF who have received a liver transplant because the benefits to CF lung disease outweigh the liver related risk. There should be close monitoring and collaboration with the transplant team/pharmacist in these individuals as drug-drug interactions need to be noted and monitored.

There is a lack of controlled prospective data on liver-associated outcomes of CFTR modulator treatment in persons with CFHBI, aCFLD, or those who have undergone liver transplantation. Most clinical trials excluded PwCF with a history of liver disease, such as cirrhosis with portal hypertension, or solid organ transplantation. These recommendations were made by the committee based on currently available data and expert opinion with respect to safety and efficacy in line with recommendations from drug manufacturers and government regulatory bodies.

Currently, nearly all studies examining the effects of CFTR modulators on liver health are relatively small, single center retrospective studies (lumacaftor/ivacaftor: 3 studies, cumulative n=124; elexacaftor/tezacaftor/ivacaftor: 4 studies, cumulative n=57).[98, 99, 100, 101, 102, 103] Collectively, the data suggests that lumacaftor/ivacaftor may improve liver enzymes, APRI, and GPR.[100, 101, 102] One large retrospective review of a U.S. private insurance claims database examined 955 CF patients on CFTR modulators between 2012-2017 and found decreased cirrhosis in those on modulators.[104] Potential effects of elexacaftor/tezacaftor/ivacaftor are less clear, with one study showing decreased liver stiffness, but another showing no change, or even increased liver stiffness in PwCF on elexacaftor/tezacaftor/ivacaftor.[98, 99] Some evidence suggests improvements in hepatic steatosis.[105, 103] Improvements in cholesterol biosynthesis and bile acid homeostasis have also been reported.[106, 102] While data on CFTR modulators and liver health is increasing, to date there is insufficient evidence to make a recommendation on its use to improve liver outcomes in persons with CF and hepatobiliary involvement.

There have been isolated reports of severe toxicity.[107, 108] Clinical trials of CFTR modulators reported transaminase elevations >3x ULN in about 5% of CF subjects; however very few required treatment discontinuation.[109, 110, 111, 112] Treatment interruption with re-challenge is sufficient in most cases.

Additional studies showed marked improvements in forced expiratory volume in one second (FEV_1), disease specific quality of life questionnaires (e.g., CFQ-R), pulmonary exacerbations, rate of lung function decline, hospitalizations, and nutritional status that were demonstrated in multiple clinical trials.[113, 114] Based on expert opinion, in persons with CFHBI or aCFLD, the benefits of CFTR modulator treatment may outweigh potential liver related risk and close monitoring should be implemented. Specifically, for those with liver transplant, drug-drug interactions need to be noted and carefully monitored to prevent rejection and maintain the health

of the transplanted liver. Small case series note improvements in quality of life, body mass index, and lung function, similar to PwCF without a liver transplant.[115, 116]

T3. The CFF recommends cholecystectomy for all CF persons with symptomatic gallbladder disease and other interventions (such as ERCP) for all CF persons with symptomatic biliary tract disease.

Biliary tract abnormalities can be present at birth, at diagnosis, or subsequently develop in infants and adults.[117, 118, 119, 120] Biliary colic may occur in a small number of PwCF upon initiation of CFTR modulator therapies.[121] Cholecystectomy is generally safe, with conservative pre- and postoperative pulmonary management.[122, 123] Laparoscopic cholecystectomy is preferred over the open approach.[124, 2, 125] Following the standard of care in non-CF persons, therapeutic ERCP, percutaneous transhepatic cholangiography or intraoperative cholangiogram should be performed with cholecystectomy in the setting of documented or suspected choledocholithiasis.[2, 53]

T4. The CFF cannot recommend for or against the use of non-selective beta-blocker treatment for the prevention or treatment of variceal bleeding in persons with CF and advanced liver disease with portal hypertension due to insufficient evidence.

In adults with portal hypertension and gastroesophageal varices, non-selective beta-blocker (NSBB) treatment is recommended for both primary and secondary prophylaxis of variceal bleeding.[76,126] Randomized clinical trials assessing the benefits or harms of NSBB versus placebo or no intervention for primary prophylaxis of esophageal variceal bleeding are lacking for children with chronic liver disease and in children or adults with aCFLD.[127] Although NSBB may have potential adverse effects on pulmonary disease, no studies assessing worsening of CF lung disease were identified.

T5a. The CFF cannot recommend for or against primary variceal prophylaxis for children with CF and advanced liver disease with portal hypertension and varices due to insufficient evidence.

T5b. The CFF recommends that for children with CF and advanced liver disease with portal hypertension, varices, and prior variceal hemorrhage, current guidelines for secondary prophylaxis be followed in consultation with a pulmonologist and anesthesiologist with expertise in CF.

T5c. The CFF recommends that adults with CF and advanced liver disease and portal hypertension (with or without prior variceal hemorrhage), should undergo primary or secondary prophylaxis according to current guidelines in consultation with a pulmonologist and anesthesiologist with expertise in CF.

Existing literature in non-CF liver disease supports the use of endoscopic variceal ligation (EVL), sclerotherapy, and non-selective beta blockers as primary prophylaxis in adults with portal hypertension at high risk for variceal bleeding and for management of variceal hemorrhage.[76, 126] However, in the pediatric population, there are few studies[128] and no guidelines to inform management. Nevertheless, EVL and sclerotherapy are preferred methods for the treatment of variceal hemorrhage and the prevention of rebleeding. Anatomic and size limitations may favor sclerotherapy for small children in whom the EVL equipment cannot be used. There is insufficient evidence regarding safety and efficacy for the use of nonselective beta blockers in children as noted.

There is a notable lack of data in both adults and children with aCFLD regarding primary or secondary variceal prophylaxis. The preferred intervention is EGD with EVL or injection sclerotherapy if limitations require it. Procedure related risks include bleeding and complications of general anesthesia, particularly in the setting of advanced lung disease.

T6a. The CFF recommends that for persons with CF and cirrhotic or non-cirrhotic portal hypertension with INR ≤1.5, normal direct bilirubin and albumin, no encephalopathy and no refractory ascites, portosystemic shunt or liver transplantation be considered as long-term treatment.

T6b. The CFF recommends that for persons with CF and cirrhotic or non-cirrhotic portal hypertension with INR>1.5, abnormal direct bilirubin, low albumin, refractory ascites or

encephalopathy, liver transplantation be considered as the appropriate long-term treatment. Portosystemic shunt placement may be a bridge to transplantation for management of intractable variceal bleeding.

Overall, there is a lack of evidence in CF persons comparing portosystemic shunt to liver transplant outcomes. There is no data to inform on which type of shunts should be performed. CFF registry data show evidence of hepatic decompensation in some with aCFLD and portal hypertension.[129, 75] Liver transplantation data for children and adults with CF show lower adjusted survival rates than other chronic liver diseases but are still acceptable.[130, 131] There are limited long-term portosystemic shunt data. Short-term data suggest reduced GI bleeding with a low incidence of hepatic encephalopathy in aCFLD without decompensation and that portosystemic shunt serves appropriately either as a stand-alone long-term treatment or a bridge to liver transplantation in individuals experiencing complications of portal hypertension.[132, 27, 133]

Liver transplantation in selected individuals has not been shown to be a detriment to underlying lung function.[134] Improvements in nutritional status and quality of life were noted in liver transplant recipients when compared to non-transplanted PwCF.[135, 136] There were lower 5-year survival rates in liver transplant recipients that were significantly higher in non-transplanted PwCF.[74, 136] The need for liver transplantation in the era of CFTR modulator treatment needs further study. Highly effective CFTR modulator treatment has the potential to delay liver transplantation and warrants further study.

T7. The CFF recommends that for persons with CF and advanced liver disease and advanced lung disease that may be considered for lung or liver transplant, combined lung-liver transplantation be considered to optimize long-term treatments.

Lung-only and liver-only transplantations are proven interventions for PwCF with lung or liver decompensation.[129, 137] As the CF population ages, there may be a higher frequency of PwCF presenting with both advanced lung and liver disease. Persons with aCFLD requiring liver transplantation with advanced lung disease (FEV_1<40%) would not currently be listed for liver-only transplantation at most centers because of the risk of advanced lung disease complications during and after transplantation.[138] There have been reported declines in lung function following liver-only transplantation.[134] Likewise, PwCF and advanced lung disease requiring lung

transplantation with aCFLD would not currently be listed for lung-only transplantation at most centers because of the risks associated with aCFLD post-lung transplant.

There are insufficient data on opportunistic infection, lung function, glycemic control, or quality of life following combined lung-liver transplantation. Mortality and morbidity are similar with combined lung-liver transplantation and lung-only or liver-only transplantation.[139, 140, 141] There is higher post-transplant morbidity associated with higher lung allocation scores (LAS >50).[142] Lung allograft rejection appears to be lower in combined lung-liver transplantation compared to lung transplantation alone.[143, 144] More studies are needed to determine when combined lung-liver transplantation should be considered over liver transplantation alone.

NO CONSENSUS

There was not sufficient consensus (<80% agreement) to recommend a diagnostic liver biopsy in PwCF who are found to have evidence of portal hypertension. Since the 1999 guidelines, liver biopsies in CF have generally fallen out of favor given their low specificity in detecting patchy disease.[17] However, recent studies, including analysis of liver explants following liver transplantation, highlight the growing recognition that a significant proportion of portal hypertension in CF may be due to non-cirrhotic nodular regenerative hyperplasia.[145, 146, 147,148, 149] The cause of this finding in the context of CF is unclear but histological analysis suggests a vascular abnormality including obliterative portal venopathy. Despite the risk of ascites and variceal hemorrhage, the clinical course of non-cirrhotic portal hypertension usually differs from cirrhotic portal hypertension given the preserved liver function which might obviate the need for liver transplantation. For this reason, differentiation between cirrhosis and nodular regenerative hyperplasia can provide valuable clinical information. However, liver biopsy with or without portal pressure measurement is invasive and can be associated with morbidity, and rarely mortality, carrying additional risk in PwCF with compromised lung function. Furthermore, the threshold for determining findings of portal hypertension by examination, calculated liver indices, non-invasive imaging and standard US imaging is unclear, raising the possibility of unnecessary liver biopsies in some PwCF. Therefore, further study of the frequency of non-cirrhotic portal hypertension, clinical thresholds for obtaining histologic assessment, and the impact of this testing on clinical care in CF is needed before routine recommendation for biopsy

can be made. Multidisciplinary consultation (including gastroenterologists/hepatologists) on this matter is encouraged.

CONCLUSION

The current, updated CFF recommendations for hepatobiliary complications in PwCF build on the foundation that the 1999 guidelines set, but compiles data generated over the last 20+ years to add more granularity and clarity in how we diagnose, monitor, and treat patients with CFHBI and aCFLD. As can easily be appreciated, there remain topics of great interest to our committee and the greater CF community that we cannot yet answer. These areas are ripe for additional research, and we urge researchers and funding agencies to consider these as areas of priority. The medical burden experienced by PwCF is tremendous. We readily recognize that our recommendations may add additional medical appointments and tests to what may be currently done at individual centers and this subject was discussed during the evaluation of every recommendation. A strength of our committee is its multidisciplinary composition, with pulmonologists, gastroenterologists/hepatologists, endocrinologists, a pharmacist, an individual with CF, and a family member of PwCF. The recommendations integrated inputs from all these individuals and the final recommendations are an attempt to balance medical burden with improving hepatobiliary outcomes and overall morbidity and mortality of PwCF. As we continue to gather more data in these areas (and in some yet to be defined), we are eager to re-visit the recommendations we currently set forth. As examples, we anticipate that the increase in CFTR modulator use and the development and implementation of anti-fibrotics and other medical interventions for persons with CFHBI and aCFLD may alter the course of liver disease in CF. Yet, we are confident the guidelines presented here will direct providers in ways that will positively transform the hepatobiliary care of persons with CF now.

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Table 1. Non-Invasive Determinants of Liver Fibrosis in CF.

LIVER FIBROSIS INDICES			
Index	**Formula**	**Thresholds for aCFLD (F3-4 fibrosis)**	**Hepatitis B Threshold for F3-F4 fibrosis[1]**
APRI	[(AST/ULN AST)/PLT] x 100	≥ 0.433[2]	< 0.5 normal,> 1.5 fibrosis[3]
GPR	[(GGT/ULN GGT)/PLT] x 100	≥ 0.198[2]	≥ 0.32[3]
FIB-4	(Age in Years x AST)/(PLT x √ALT)	Insufficient Data	Insufficient Data
Forns Index	[(7.811-3.131 x ln(PLT)] + [(0.781 x ln(GGT)] + [(3.467 x ln(Age)) – (0.014 x cholesterol)]	Insufficient Data	Insufficient Data
LIVER STIFFNESS MEASUREMENT			
	Thresholds for CFHBI	**Thresholds for aCFLD (F3-F4 Fibrosis)**	**Hepatitis B Threshold for F3-F4 fibrosis**
Transient Elastography[4]	> 5.95 kPa[5]	> 8.7 kPa[6]	> 8.8 kPa[7]
2-D Shear Wave Elastography	> 1.45 m/s[8] > 6.85 kPa[11]	> 1.84 m/s[8] > 9.05 kPa[11]	> 8.9 kPa[9,10]

[1] Values for Hepatitis B are included for comparison.

[2] AST ULN 30 U/L, GGT ULN 20 U/L[20]

[3] AST and ALT U/L 40, GGT ULN 60 U/L[150,151]

[4] *Note: While both transient elastography and MR elastography values are in kPa, they have different thresholds for fibrosis.*

[5] *AUROC of 0.76 with sensitivity of 55% and specificity of 87%.*[18]

[6] *AUROC of 0.87 with sensitivity of 75% and specificity of 100%.*[17]

[7] *AUROC of 0.887 with sensitivity of 74.0% and specificity of 63.8%.*[152]

[8] *AUROC for normal vs abnormal MRI elastography (MRE) of 0.94. AUROC for mild-moderate vs. severe fibrosis on MRE of 0.79.*[31]

[9] *AUROC of 0.92.*[153]

[10] *Threshold for chronic liver diseases, not specifically Hepatitis B.*

[11] *AUROC 0.79 for CFHBI vs. no-CFHBI with sensitivity of 75% and specificity of 71%. AUROC of 0.95 for advanced liver fibrosis with sensitivity of 88% and specificity of 87%.*[154]

Table 2: Recommendation statements.

#	Screening	Vote % (n)
S1	The CFF recommends that annual labs (total bilirubin, AST, ALT, alkaline phosphatase, GGT, Platelet Count) should be performed, at a time of clinica stability, for identification of hepatobiliary involvement in all persons with CF starting at CF diagnosis.	100 (22/22)
S2	The CFF recommends annual physical abdominal examination for hepatosplenomegaly for identification of advanced liver disease in all persons with CF starting at CF diagnosis.	100 (22/22)
S3a	The CFF recommends abdominal ultrasound to assess the liver and spleen a least every two years in persons with CF from childhood until late adolescence, starting at age 3 or at diagnosis, if diagnosed after age 3.	95% (21/22)
S3b	In adults with CF, there is value in baseline screening for CFHBI, but the optimal frequency of subsequent imaging for those with normal baseline findings is unknown and a specific recommendation cannot currently be made.	95% (21/22)
S4	The CFF recommends that persons with CF who are found to have hepatobiliary involvement (abnormal physical exam, persistently elevated liver enzymes, or abnormal abdominal ultrasound findings), should undergo baseline liver elastography, when available, for the identification of advanced liver disease.	100 (22/22)
S5	The CFF recommends that persons with CF and hepatobiliary involvement should receive a standardized evaluation for other causes of liver disease.	100 (22/22)
S6	The CFF recommends that all persons with CF who have cholestatic liver test Direct Bilirubin, GGT, and/or alkaline phosphatase) elevation, abdominal pain consistent with biliary cause and inconclusive abdominal ultrasound should undergo magnetic resonance cholangiopancreatography (MRCP) to detect hepatolithiasis, choledocholithiasis, biliary strictures, and/or biliary obstruction.	100 (22/22)

#	Monitoring	Vote % (n)
M1	The CFF recommends that in persons with CF and liver involvement, a liver specific physical examination be performed at least annually and at each in-person visit to monitor for the progression of disease.	100 (22/22)
M2	The CFF recommends that for persons with CF and hepatobiliary involvement at least one liver fibrosis index be calculated and followed at least annually.	95 (21/22)
M3	The CFF recommends for persons with CF and hepatobiliary involvement an abdominal US be performed at least every 2 years to monitor for the progression of disease.	100 (22/22)
M4	The CFF recommends that persons with CF and hepatobiliary involvement or advanced liver disease undergo evaluation of liver stiffness with elastography at least annually, if available, to monitor for the progression of disease.	100 (22/22)
M5	The CFF recommends that persons with CF hepatobiliary involvement or advanced liver disease receive consultation with a pharmacist with experience in CF and hepatobiliary disease to identify high risk medications polypharmacy, therapy modifications, and risk based on their hepatobiliary disease every 6 months, unless there have been no medication changes, to improve morbidity and mortality.	100 (22/22)
M6	The CFF recommends that persons with CF and advanced liver disease undergo liver specific physical examination and measurement of AST, ALT GGT, alkaline phosphatase, conjugated (or direct) bilirubin, albumin, platelets, and international normalized ratio (INR) at least every 6 months to detect progression of liver disease.	100 (22/22)
M7	The CFF recommends that persons with CF and advanced liver disease, receive a nutritional assessment for malnutrition and liver specific macro- and micronutrient deficiencies every 6 months by a dietitian experienced in CF. When abnormalities are identified a treatment plan and monitoring of nutritional rehabilitation should be developed.	100 (22/22)

M8	The CFF recommends for persons with CF and advanced liver disease beginning CF related diabetes (CFRD) screening at the diagnosis of advanced liver disease, even if earlier than age 10 and then annually thereafter, to provide early diagnosis and treatment of CFRD (using methodologies described in the most current CFRD Guidelines).	100 (22/22)
M9	The CFF recommends that persons with CF and advanced liver disease receive multidisciplinary care from pulmonology, gastroenterology/hepatology, endocrinology and when appropriate, a transplant center, to optimize liver outcomes.	100 (22/22)
M10a	The CFF recommends that adults with CF and advanced liver disease with esophageal varices be managed according to the relevant most current published guidelines, such as those from the American Association for the Study of Liver Diseases or the Baveno group.	100 (22/22)
M10b	The CFF cannot provide a recommendation for or against endoscopic variceal surveillance in children with advanced liver disease, due to insufficient evidence.	100 (22/22)
M11a	The CFF recommends that all CF children with cirrhosis or suspected cirrhosis, are screened annually for hepatocellular carcinoma with abdominal US and serum alpha-fetoprotein.	95 (21/22)
M11b	The CFF recommends that all CF adults with cirrhosis or suspected cirrhosi are screened for hepatocellular carcinoma using the most current screening guidelines as per American Association for the Study of Liver Diseases or European Association for the Study of Liver Disease.	100 (22/22)
#	**Treatment**	**Vote % (n)**
T1	The CFF recommends against the routine use of ursodeoxycholic acid to prevent advanced liver disease in all persons with CF.	100* (21/21)
T2a	Efficacy: The CFLD Guidelines Committee cannot recommend for or against the use of CFTR modulator treatment to improve liver outcomes in persons with CF and hepatobiliary involvement or advanced liver disease when age-appropriate, genotype-specific modulator therapy is available due	100* (16/16)

	to insufficient evidence.	
T2b	Safety: The CFLD Guidelines Committee recommends, based upon expert opinion, the use of CFTR modulator treatment in persons with CF and CF hepatobiliary involvement in the setting of close monitoring by a CF gastroenterologist and/or hepatologist and pharmacist because the benefits to CF lung disease outweigh the liver related risk.	100* (16/16)
T2c	Safety: The CFLD Guidelines Committee cannot recommend for or against the use of CFTR modulators in persons with CF with advanced liver disease and portal hypertension without decompensation due to insufficient evidence.	100* (16/16)
T2d	Safety: The CFLD Guidelines Committee recommends against CFTR modulator use in persons with CF and decompensated advanced CF liver disease, as determined by a consultant Hepatologist based on thresholds such as sustained INR>1.5, abnormal direct bilirubin, low albumin, refractory ascites or encephalopathy.	100* (16/16)
T2e	Transplant: The CFLD Guidelines Committee recommends, based upon expert opinion, for CFTR modulator treatment in persons with CF who have received a liver transplant because the benefits to CF lung disease outweigh the liver related risk. There should be close monitoring and collaboration with the transplant team/pharmacist in these individuals as drug-drug interactions need to be noted and monitored.	100* (16/16)
T3	The CFF recommends cholecystectomy for all CF persons with symptomatic gallbladder disease and other interventions (such as ERCP) for all CF persons with symptomatic biliary tract disease.	100 (22/22)
T4	The CFF cannot recommend for or against the use of non-selective beta-blocker treatment for the prevention or treatment of variceal bleeding in persons with CF and advanced liver disease with portal hypertension due to insufficient evidence.	100 (22/22)
T5a	The CFF cannot recommend for or against primary variceal prophylaxis for children with CF and advanced liver disease with portal hypertension and	100 (22/22)

	varices due to insufficient evidence.	
T5b	The CFF recommends that for children with CF and advanced liver disease with portal hypertension, varices, and prior variceal hemorrhage, current guidelines for secondary prophylaxis be followed in consultation with a pulmonologist and anesthesiologist with expertise in CF.	100 (22/22)
T5c	The CFF recommends that adults with CF and advanced liver disease and portal hypertension (with or without prior variceal hemorrhage), should undergo primary or secondary prophylaxis according to current guidelines in consultation with a pulmonologist and anesthesiologist with expertise in CF.	100 (22/22)
T6a	The CFF recommends that for persons with CF and cirrhotic or non-cirrhotic portal hypertension with INR ≤1.5, normal direct bilirubin and albumin, no encephalopathy and no refractory ascites, portosystemic shunt or liver transplantation be considered as long-term treatment.	100 (22/22)
T6b	The CFF recommends that for persons with CF and cirrhotic or non-cirrhotic portal hypertension with INR>1.5, abnormal direct bilirubin, low albumin, refractory ascites or encephalopathy, liver transplantation be considered as the appropriate long-term treatment. Portosystemic shunt placement may be a bridge to transplantation for management of intractable variceal bleeding.	100 (22/22)
T7	The CFF recommends that for persons with CF and advanced liver disease and advanced lung disease that may be considered for lung or liver transplant, combined lung-liver transplantation be considered to optimize long-term treatments.	100 (22/22)

**Reduced numbers due to potential conflicts of interest.*

Table 3: Statement with No Consensus

PICO Question	Statement Considered by the committee	Percent Consensus (Did not achieve threshold)
In all persons with CF who are found to have portal hypertension (splenomegaly, thrombocytopenia, varices), is a diagnostic liver biopsy better than no liver biopsy at differentiating cirrhosis vs. non-cirrhotic portal hypertension?	The committee recommends consideration of a diagnostic liver biopsy to differentiate cirrhosis from non-cirrhotic portal hypertension in persons with CF who are found to have portal hypertension.	77.2

Figure 1. Pathway Summarizing Screening and Monitoring Recommendations. Flow diagram summarizing hepatobiliary disease screening and monitoring recommendations, as outlined within the manuscript. Blue color indicates screening and yellow color indicates monitoring. Footnote: [1]Should be performed at time of clinical stability.[SEP][2]CFHBI includes: elevation in liver enzymes above age-appropriate values for >3-6 months, abnormal liver/spleen exam, and/or abnormal US findings

[3]Advanced CF Liver Disease (aCFLD) refers to having one (or more) of the following: nodular liver, advanced fibrosis (F4), multilobular cirrhosis with or without portal hypertension or non-cirrhotic portal hypertension.