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Gallbladder and bile duct disease in Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is a multi-organ, clinically diverse disorder caused by mutations in the cystic fibrosis transmembrane conductance receptor (CFTR). Awareness of extra-pulmonary manifestations, including gastrointestinal and hepatobiliary disturbances, is an increasingly important part of providing high-quality care to patients with CF. Furthermore, biliary disorders, including gallbladder and bile duct disease, are common complications of CF. Therefore, a thorough understanding and efficient clinical evaluation of the gallbladder and biliary tree is an important aspect of integrated care for the patient with CF in order to prevent progression of undetected pathology. This best practice article summarizes the basis for gallbladder and bile duct pathology, describes the context and clinical presentation of biliary disease, and provides recommended approaches to delivery of high-quality care for patients with CF.

Keywords: Cystic fibrosis; Gallbladder; Bile Duct; Biliary; Cholestasis

1. Background

The CFTR gene is highly expressed throughout the entire biliary tree, including both intrahepatic and extrahepatic biliary epithelia [1]. Furthermore, CFTR expression in the gallbladder epithelium is one of the highest of all human tissues, a key observation made by early studies searching for CFTR expression throughout the gastrointestinal tract [2]. Therefore, the biliary tree is an important site for CFTR activity and its absence can result in clinical disease as a result of several mechanisms including decreased biliary bicarbonate secretion, sensitivity to inflammatory toxins, and disruption of normal bile acid circulation.

The CFTR protein, which regulates chloride channel activity, plays a fundamental role in cells that regulate fluid and ion concentrations. In the biliary epithelium, the CFTR protein is localized in the apical membrane and drives fluid and bicarbonate secretion [1]. The importance of CFTR in maintaining homeostasis in the biliary tree through a bicarbonate balance has been highlighted in the "bicarbonate umbrella" hypothesis, in which a proper alkaline balance is critical to prevent cholangiocyte damage by hydrophobic bile acids [3,4]. Therefore, loss of CFTR function may contribute to pH dysregulation resulting in injury of the biliary tree. This protective mechanism is of particular importance in the gallbladder, where bile acids are the most concentrated.

Recent investigations have identified a second mechanism by which the loss of CFTR in the biliary epithelium may lead to biliary disease in CF. Investigators working with mouse models of CF found that CFTR deficiency results in increased vulnerability to bacterial endotoxin, which results in a pathologic innate immune response with secretion of inflammatory cytokines within biliary cells [5]. Therefore, loss of CFTR may make the biliary tree more sensitive to inflammation from bacterial products from the intestine, which can lead to chronic damage and eventual fibrosis of the biliary tree. Interestingly, studies have shown that inflammation of the colon can result in significant biliary injury when CFTR is not functional, highlighting the role of the CFTR protein in protecting the biliary tree against inflammatory toxins derived from distant sites within the body

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[6,7]. These and other important insights have allowed for emerging studies of candidate agents to reduce inflammatory damage in the biliary tree in CF, such as modulation of peroxisome proliferator activator receptor (PPAR) activity [8].

Finally, there is evidence of the importance of CFTR in bile acid homeostasis. Early studies in children with CF detected increased loss of bile acids in the feces, which was thought to reduce the bile pool and thus worsen malabsorption [9–11]. However, a study from Strandvik et al. suggested that well-nourished adult patients with CF had normal bile acid concentrations and bile acid pool compared to controls [12]. Interestingly, they also found low to normal cholesterol saturation levels in bile, a surprise given the known association of CF with biliary stones. While the exact nature of the defects in bile acid composition in patients with CF remains unclear, a recent study of CFTR deficient mice revealed down-regulation of primary bile acid synthesis and impaired emptying of the gallbladder, thus impairing the enterohepatic circulation of bile acids and decreasing the exposure of organs such as the liver to toxic bile acids [13].

Despite the existence of multiple mechanisms by which CFTR dysfunction predisposes to biliary damage, not all patients with CF develop clinical manifestations nor is there homogeneity in the hepatobiliary injury itself. It is estimated that 5–10% of patients with CF will develop multilobular cirrhosis before adolescence, most frequently a complication of focal biliary cirrhosis involving small bile ducts [14,15]. Progression of focal biliary cirrhosis to multilobular cirrhosis and the management of end stage liver disease in CF are discussed in an accompanying Best Practice Guideline [16]. By contrast, the frequency of other biliary manifestations of CF, including large-duct sclerosing cholangitis, microgallbadder, gallbladder dyskinesia, and symptomatic cholelithiasis are not well understood with a subsequent wide range of reported prevalence [17,18]. The Cystic Fibrosis Foundation Patient Registry reported in 2014 that 0.6% of all Registry participants had gallstones, while 0.8% required cholecystectomy or other intervention [19]. In addition, there was a small increase in the burden of gallbladder disease in adults as compared to children and adolescents. There is much less specificity in the Registry regarding the frequency of biliary duct disorders such as sclerosing cholangitis in patients with CF.

2. Disorders of the gallbladder

2.1. Clinical presentation and differential diagnosis

It has long been recognized that patients with CF can develop gallbladder abnormalities. This may include small or absent gallbladder, gallbladder dysfunction, symptomatic cholelithiasis, and malignancy. Pioneering studies of gross anatomy in CF from the 1960s described a variety of pathologic findings including contracted gallbladders with web-like trabeculation, abnormally high concentrations of surface mucin, thick colorless bile, and a surprising lack of inflammatory infiltrates [20,21].

Early imaging studies of the gallbladder in patients with CF likewise revealed a high frequency of abnormalities, including microgallbladder in up to a third of all patients [22–24]. Furthermore, some authors have reported on the utility of gallbladder evaluation *in utero* as a prenatal screening tool during the second trimester for detection of CF [25]. While MR cholangiography is the best modality for the assessment of the biliary tree, ultrasound imaging is a much better imaging study for assessment of the gallbladder in patients with CF [26].

Abnormal gallbladder function has also been characterized in patients with CF. In a study of children with CF, there was significantly more hypokinesis compared to controls along with a greater frequency of gallstones [27]. Another study reported that 3.6% out of 670 patients with CF developed symptomatic gallbladder disease, the majority of whom were adults with obstructive cholelithiasis or cholecystitis [28].

Gallstones are quite frequently detected in patients with CF [29], and multiple studies have analyzed the characteristics of stones in this patient population. Given the frequent development of steatorrhea and malabsorption in CF, it was originally thought that cholesterol stones would be found in these patients since fecal loss of bile acids can result in compensatory lithogenic bile followed by cholesterol stones. However, while cholesterol stones are more frequent in the general population, black pigmented stones are more commonly found in patients with CF [30,31]. Furthermore, detailed studies have found that bile in patients with CF is not supersaturated with cholesterol, as initially thought [32]. Supporting this assessment is the observation that remarkable improvements in nutrition and pancreatic enzyme replacement in recent decades have not significantly reduced the incidence of gallstones in these patients [33]. Indeed, black specific pigmented stones are thought to result from abnormal acidification of the bile, a mechanistic defect created by the absence of CFTR in the biliary epithelium itself. In addition, bile stasis due to gallbladder hypokinesia and biliary strictures may serve as a nidus for further stone formation.

Symptomatic gallbladder disease requiring consideration for cholecystectomy may occur in up to 4% of patients [33]. Assessment may be complicated in the setting of CF by a broad differential diagnosis of multiple potential sources of pain, including acid reflux, gastroparesis, dysmotility from small intestine bacterial overgrowth, acute pancreatitis in pancreatic sufficient patients, constipation, and distal intestinal obstruction syndrome (DIOS) in pancreatic insufficient patients (Table 1).

2.2. Diagnostic workup

In the acute setting, evaluation should be performed with ultrasound to rule out gallbladder wall edema and stranding. Biliary scintigraphy should also be considered to evaluate the emptying of the cystic duct. Additionally, for patients with biliary colic, biliary scintigraphy with CCK may reveal significant hypokinesia. One study evaluated hepatobiliary scintigraphy in children with CF and reported a wide spectrum of findings in this population, especially in the presence of advanced parenchymal liver disease [34]. Therefore, while quantitative scintigraphy measurement to document visualization of the gallbladder is helpful, it is important to be aware of variability of hepatic findings in patients with known liver disease. Lastly, several

Table 1
Differential diagnosis of gallbladder disease in patients with cystic fibrosis.

Etiology	Characteristics	Potential evaluation
Symptomatic cholelithiasis	• Gradual onset of squeezing right upper quadrant pain following meals • Presence of gallstones on ultrasound	• Biliary scintigraphy
Gallbladder dyskinesia	• Pain similar to Symptomatic Cholelithiasis but without gallstones	• Biliary scintigraphy with CCK
Acute cholecystitis	• Sudden, constant right upper quadrant pain, fever and chills	• Ultrasound, biliary scintigraphy, surgical evaluation
Acid reflux	• Epigastric discomfort and reflux following meals	• Trial of acid suppression • Diagnostic upper endoscopy
Gastroparesis	• Pain hours after meals • Uncontrolled diabetes	• Gastric emptying scan • Trial of motility agent
Small intestine bacterial overgrowth	• Bloating, generalized discomfort, and loose stool	• Empiric trial of antibiotic
Pancreatitis	• Mid-abdominal pain that is sudden (acute pancreatitis) or constant (chronic pancreatitis) following meals	• Serum amylase and lipase • Pancreatic imaging
Distal intestinal obstruction syndrome	• Acute abdominal pain, emesis, lack of bowel movements	• Urgent abdominal imaging to rule out obstruction

studies have reported on the long latency between initial development of symptoms and appropriate intervention in patients with CF, highlighting the challenge of assessing abdominal pain in these patients who often have multi-system dysfunction [35,36].

2.3. Routine management

One of the first articles to describe management of symptomatic gallbladder disease in patients with CF over a 25-year observation period suggested that patients in need of cholecystectomy could safely undergo surgery unless pulmonary function was severely compromised [28]. Indeed, two of eleven patients who had surgery for symptomatic gallbladder disease experienced improvement in lung function that was attributed to decrease in pain leading to improvement in coughing mechanisms and lung expansion. Another study by the same group has similarly recommended cholecystectomy for patients with CF and symptomatic gallbladder disease and suggests early surgical intervention, when needed, to avoid further deterioration of lung function over time and associated increased morbidity [35]. In this study of 20 patients with CF who had their gallbladders removed, 85% had gallstones, while 30% had microgallbladder and interestingly 20% had narrowing of the cystic or common bile duct, which may have contributed to the symptoms. Finally, a small retrospective study of patients with CF and symptomatic gallbladder disease demonstrated a significant improvement in quality of life in these patients after laparoscopic cholecystectomy [37].

2.4. Complications and their management

Although cholecystectomy is a routinely performed surgery around the world, patients with CF may be at increased risk of complications. These may include worsening pulmonary function post anesthesia, perioperative infections or exacerbations of colonized organisms, delayed resumption of nutrition post-operatively, and acute DIOS due to bowel inactivity and use of pain medications. Indeed, earlier studies reported postoperative morbidity of up to 10% and mortality of 5% [35], resulting in concerns about the appropriateness of surgical intervention [38]. However, the use of laparoscopic techniques [39] and even epidural anesthesia [40] may be associated with reduced morbidity in high-risk patients. It is important to highlight that increased awareness of the unique challenges of CF care, and improved anesthesiology and perioperative techniques in these situations, can significantly improve care delivery and outcomes for these patients [41].

For patients in whom lung function is severely compromised, non-surgical interventions such as lithotripsy or use of ursodeoxycholic acid (UDCA) have been attempted, though neither has been associated with significant relief. A report by Colombo et al. showed that UDCA did not result in dissolution of gallstones in any of the 10 patients studied, likely due to the black pigment composition of stones in CF, rather than cholesterol stones [42]. Therefore, adequate options are lacking for CF patients with symptomatic gallbladder disease who also have advanced lung disease, for whom conservative management with symptom control may be best.

There is an increased risk of cancers of the gallbladder and of the bile ducts in patients with CF, including both those who have and have not received lung transplantation, as recently reported from registry data [43]. This finding is part of a wider observation in CF, namely an increased malignancy risk throughout the digestive track, for reasons that are not fully clear. It is possible that absence of CFTR throughout the digestive track contributes to a chronic inflammatory state that increases the risk of epithelial dysplasia. This is an area of intense research and studies to improve the assessment of gastrointestinal cancer risk for patients with CF are urgently needed. At this time, there is a lack of evidence-based data to recommend imaging of the gallbladder specifically for cancer screening purposes, although it should certainly be obtained for any patient who develops symptoms concerning for gallbladder disease. Furthermore, detection of anatomic abnormalities such as polypoid lesions of the gallbladder, even in asymptomatic patients, should be further assessed and surgical intervention pursued if appropriate.

2.5. Potential clinical trials endpoints

There is a need for larger multi-center, high-quality clinical studies to characterize the burden of symptomatic gallbladder disease in patients with CF. Furthermore, it is unknown whether current and next-generation CFTR correctors can influence the formation of gallstones in patients with CF or

their progression to clinical presentation. Therefore, clinical trials evaluating new pharmacotherapies in CF should consider incorporating a baseline assessment of gallstone burden and subsequent re-assessment of stone burden following treatment. In addition, specific trials focused on cholelithiasis in CF should consider additional measures including serial serum bile acid measurements to determine changes in primary and secondary bile acids with pharmacotherapy. Finally, there is a need for additional studies to determine optimal cutoffs for surgical suitability in patients with CF who have significant compromise in lung function.

2.6. Future directions

Given the frequency and burden of cholelithiasis in patients with CF, future management goals should include earlier identification of patients with abdominal pain with appropriate imaging modalities, and new clinical trials with bile acid modulators and CFTR correctors to evaluate methods to prevent gallstone formation.

2.7. Clinical practice points

- Maintain a high degree of suspicion for gallbladder disease in patients with right upper quadrant pain. Pursue early ultrasound imaging and also consider scintigraphy, where available, to assess for gallbladder dyskinesia.
- For patients with gallbladder disease who need surgical resection, multi-disciplinary evaluation by the pulmonologist and anesthesiologist should be pursued to assess surgical risk.
- Perioperative care for a patient undergoing cholecystectomy should preempt potential morbidity through early feeding, close attention to respiratory status and vigilance for respiratory infections, and promoting bowel movements to prevent DIOS.

3. Disorders of the biliary tree

3.1. Clinical presentation and differential diagnosis

Children and adults with CF may develop intra- or extrahepatic biliary strictures and segmental dilation visible by ultrasound, MR cholangiography (Fig. 1) or by fluoroscopy taken during an endoscopic retrograde cholangiopancreatography (ERCP). The pattern and appearance of these strictures is often similar to that found in patients with Primary Sclerosing Cholangitis (PSC). Indeed, this complication of CF may be referred to as a sclerosing cholangitis variant. The strictures reflect ongoing inflammation and fibrosis in the biliary tree, and may be further complicated in CF by the accumulation of thick, inspissated mucus or intra-biliary cholelithiasis. While the incidence is not accurately known, one study reported a frequency of 3.9% in a well-defined CF cohort [44]. In addition to large bile duct strictures, detected by imaging or by ERCP [45], intrahepatic biliary ductule involvement is quite common on histologic analysis of the liver and the latter is the basis for development of focal biliary cirrhosis.

It is important to recognize that bile duct strictures and associated complications frequently occur even in patients with

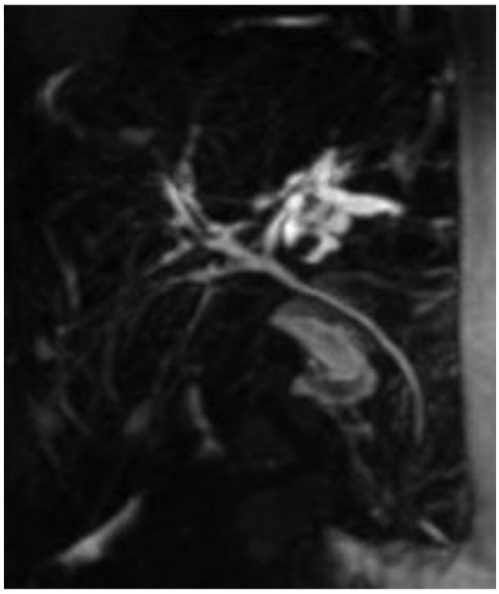

Fig. 1. A 3 year-old child, homozygous F508del detected by neonatal CF screening, had normal liver tests and no hepatomegaly. However, screening ultrasound and this subsequent MR cholangiogram revealed significant left intrahepatic bile ductal dilation.

pancreatic sufficiency and a mild overall manifestation of CF [46]. Furthermore, there is a common lack of association between liver test abnormalities and the presence of biliary strictures [45]. Indeed, a study of adults with CF who had MR cholangiography revealed PSC-like strictures or biliary lesions in 50% of patients who had no other evidence of liver disease [47]. However, 100% of patients with clinical liver disease displayed large-duct biliary lesions. Therefore, it is speculated that patients with abnormal liver function and hepatomegaly may be at a much higher risk of stricture development. In one controversial study, 96% of patients with liver disease had evidence of biliary tract obstruction on hepatobiliary scans, related to a stricture of the distal common bile duct [48]. Furthermore, there was an association between the presence of a distal common bile duct stricture and abdominal pain. It should be noted that at least one subsequent study, using ERCP evaluation for stricture assessment, did not reveal distal common bile duct strictures in patients with CF, though intrahepatic strictures were found in 12 of 14 patients [49]. Therefore, while uncertainty remains as to the development of distal common bile duct strictures in patients with CF, it is clear from the existing literature that patients with clinically apparent liver disease have a very high likelihood of developing large duct strictures, and even those with no known liver disease may have similar findings.

Given the burden of bile duct strictures, it is somewhat surprising that patients with CF do not more frequently develop clinical complications of large duct biliary strictures common to disorders such as PSC including bacterial cholangitis and cholangiocarcinoma. Nonetheless, these have been well documented in the literature and in clinical practice. One recent study described a small cohort of adults with CF and large duct strictures who developed recurrent pyogenic cholangitis, several of whom ultimately required hepatobiliary surgery for refractory

biliary disease [50]. Additionally, there are multiple case reports of adult patients with CF and biliary disease who developed cholangiocarcinoma, including at least one in the setting of immunosuppression after lung transplantation [51–54]. Finally, biliary tree abnormalities due to intrahepatic lithiasis or choledocholithiasis can present in a similar fashion as strictures and this may require careful evaluation by experienced providers (Fig. 2).

3.2. Diagnostic workup

Patients with CF who exhibit symptoms suggestive of hepatobiliary disease, or who have unexplained elevations in liver enzymes including serum alkaline phosphatase (ALP) in adults and gammaglutamyl transferase (GGT) in children, should receive a liver ultrasound for further evaluation [18]. Additional imaging with MR cholangiography is usually not necessary unless there are symptoms suggestive of biliary colic, cholangitis, or if there are findings on ultrasound of large bile duct dilatation.

3.3. Routine management

For patients who develop symptomatic biliary strictures, intervention of advanced endoscopists with ERCP for balloon dilation and or stenting should be considered. As with gallbladder disease, it is not known whether cancer screening by monitoring of strictures with imaging by ultrasound or MR cholangiography is beneficial for patients with CF.

Similar to the clinical experience with large duct PSC [55], there is no clear evidence of benefit for the use UDCA in patients with CF who have strictures. Indeed, a recent Cochrane Review of published studies of UDCA for patients with CF, which analyzed all variants of CF liver disease, highlighted the significant heterogeneity of available studies and also concluded that there was insufficient evidence to make a recommendation [56]. However, UDCA is well tolerated by most patients, has been clinically used for several decades for treatment of other cholestatic disorders, and its use has been previously recommended for patients with CF liver disease at a dose of 15–20 mg/kg/day [18]. The rationale for the recommendation has been to promote bile flow due to the known choleretic property of UDCA. Finally, previous literature from patients with PSC taking high-dose UDCA raised the concern for an increased concentration of the toxic secondary bile acid lithocholic acid and associated disease progression [57]. However, a recent study demonstrated that patients with CF taking UDCA did not exhibit an increased serum concentration of toxic bile acids, which suggests that UDCA in these patients is safe [58].

3.4. Complications and their management

Patients with CF who have large bile duct strictures and significant or progressive stenosis may develop pruritus or jaundice as a result of impeded bile flow. Labs and MR cholangiography should be performed to look for dominant strictures that could benefit from endoscopic intervention. In addition, pruritus should be treated with appropriate pharmacotherapy. Medical management of pruritus in CF is similar to other cholestatic disorders and includes rifampicin and the bile acid resin cholestyramine, which is taken 20 min before a meal [59]. It is also important to recognize that patients with chronic cholestasis are at increased risk of fat-soluble vitamin deficiency and mineral bone deficiency, in addition to the risks conferred by pancreatic insufficiency. Therefore, assessment of fat-soluble vitamin levels (A, D, E, K) and bone density scans should be performed in all patients with CF who have biliary disease.

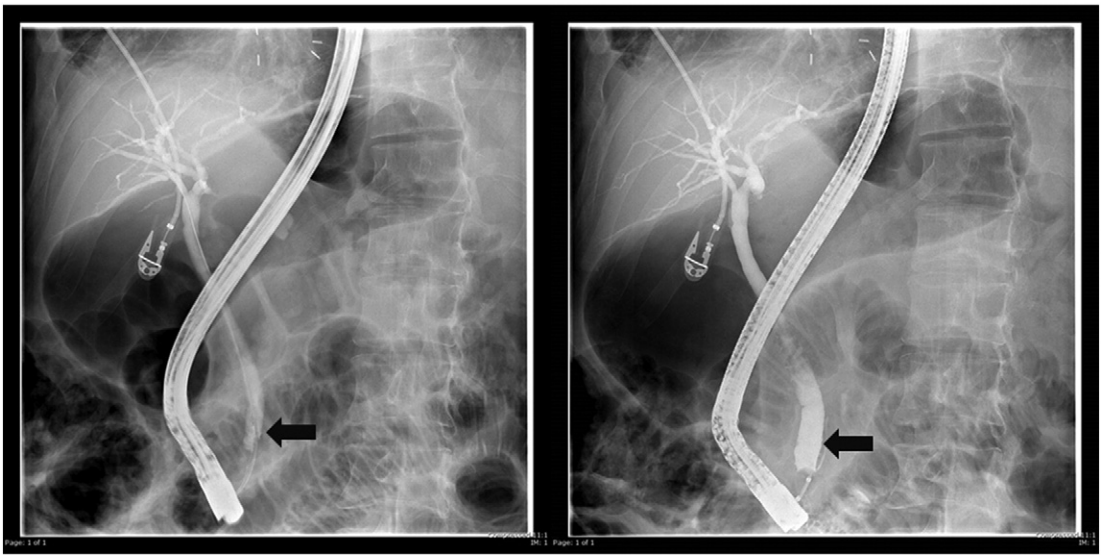

Fig. 2. A 49 year-old man with CF and bilateral lung transplantation developed new liver enzyme abnormalities. He had known cholelithiasis and also a significant decline in lung function from chronic rejection that precluded cholecystectomy. MRI imaging suggested new CBD dilation and fluoroscopy images taken during ERCP revealed a filling defect in the distal CBD (left panel, arrow) due to choledocholithiasis. Following balloon sweep and extraction of the retained stone the filling defect fully resolved (right panel, arrow).

Calcium and vitamin D supplementation should be provided (1500 mg/day calcium, 1000 units/day vitamin D).

A more serious complication of biliary tree disease in patients with CF is the development of refractory intrahepatic lithiasis, which can be associated with significant elevation of liver tests, biliary dilation, recurrent cholangitis and eventual atrophy of the affected hepatic lobe. Management options include antibiotic administration for acute cholangitis, ERCP for stone removal if the location is in mid-sized intrahepatic bile ducts, percutaneous drainage of the biliary tree, and even hepaticojejunostomy surgery which has been reported in patients with CF [60]. There is no current consensus on the best approach to this complication, and multi-disciplinary discussion regarding individualized management strategies should occur at experienced centers.

3.5. Potential clinical trials endpoints

It is clear that studies focused on the ability of pharmacologic approaches to improve outcomes for patients with CF and large bile duct strictures are needed. In addition to evaluation of UDCA, it would be of significant benefit to study new agents which are emerging for the pharmacotherapy of other cholestatic disorders, including modulators of FXR, RXR, PPAR, and new potent choleretics such as norUrsodeoxycholic acid in this patient population. Relevant endpoints for clinical trials should include measures of biliary lithiasis and stricture burden by high-quality imaging (MRCP), changes in serum markers such as alkaline phosphatase and GGT, and improvement in non-invasive surrogate measures of fibrosis in cholestatic disorders such as the Enhanced Liver Fibrosis (ELF) score [61,62].

3.6. Future directions

There is incomplete understanding of the pathophysiologic mechanisms and prediction strategies for patients with large-duct biliary strictures, including patients with CF. As such, advances in the field of cholestatic disorders such as PSC will be highly applicable to the CF community as well. Specifically, clinical studies of emerging potent bile acid modulators and anti-fibrotic agents directed at the epithelial-mesenchymal pathways which lead to biliary fibrosis are key future advances that will benefit patients with CF.

3.7. Clinical practice points

- Yearly liver tests including assessment of liver function (albumin, coagulation, bilirubin), inflammation (AST, ALT) and markers of cholestasis (ALP, GGT).
- If liver tests suggest cholestasis, or if there is abdominal pain, ultrasound liver imaging to screen for large bile duct strictures should be performed. Also consider detailed MR cholangiography to assess stricture burden and distribution in patients with known or suspected strictures.
- Perform liver tests and MR cholangiography in patients with new right upper quadrant pain and/or suspicion for acute cholangitis including pain, fever, chills or jaundice.
- Consider ERCP with management of choledocholithiasis or symptomatic dominant strictures or biliary obstruction, including balloon dilation and stenting.
- Manage pruritus with pharmacotherapy including rifampicin and cholestyramine.
- Monitor for mineral bone loss with bone density imaging, measure fat-soluble vitamin levels, and provide calcium and vitamin D supplementation.
- Uncertain:
  - Consider repeated MR imaging for patients with large bile duct strictures and worsening of cholestasis for cholangiocarcinoma screening.
  - Consider use of moderate dose UDCA (15–20 mg/kg/day) for patients with biliary disease.

4. Summary

While the exact burden of gallbladder and bile duct disease in patients with CF is unknown, it requires that care providers become familiar with the wide range of clinical presentations and their management. CF patients with symptomatic gallbladder disease should receive a multidisciplinary approach to management in order to avoid potential complications, especially in the peri-operative period. Similarly, patients with CF and bile duct disease require in-depth evaluation from key providers including advanced endoscopists in order to avoid unnecessary biliary manipulation and to treat symptomatic strictures. CFTR plays a critical role in the biliary tract, and as such is clearly deserving of relevant attention in the prioritization in CF research. This unmet need should be appropriately addressed through future pharmacologic and care-delivery clinical studies.

Conflict of interest

Authors declare no conflict of interest.

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