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REVIEW

Cystic fibrosis: An update for clinicians. Part 2: Hepatobiliary and pancreatic manifestations

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Abstract

This paper, the second in the series, will build on the first and explore the importance of liver and pancreatic manifestations of cystic fibrosis (CF) and the effect on morbidity and mortality of this multifaceted genetic condition. It will also further develop the critical role of the gastroenterologist as part of the multidisciplinary group of clinicians and allied health staff in the effective management of patients with CF.

Introduction

Liver disease is the third leading cause of death in cystic fibrosis (CF). Its importance in clinical practice has become apparent because of substantial gains in survival due to improved respiratory and nutritional management. However, the clinical significance and management of liver disease in the CF population is enigmatic and inadequately informed by reliable data. While 72% of autopsies on deceased adult patients with CF reveal significant liver damage (focal biliary fibrosis), the importance of inflammation and fibrosis during childhood and early life is harder to define.[1] Clinically significant hepatobiliary manifestations of CF are reported to occur in 15–30% of children, and liver failure said to account for approximately 2.5% overall mortality.[2,3] Cirrhosis is reported in 5–10% of pediatric populations, but in only 1.4% of the total United States CF population, with no new cases reported after 18 years of age.[4,5] This indicates a significant survival disadvantage for children diagnosed with cirrhosis. This has been suspected since earliest autopsy descriptions of children dying with CF with 10–40% demonstrating significant hepatic fibrosis, increasing with age, ranging from "focal biliary fibrosis" to established multilobular cirrhosis. Recent prospective studies by Rowland[6] and Lewindon[7] indicate coexisting significant disease, in the form of portal hypertension or fibrosis–cirrhosis, to be an additional risk factor for early mortality. Past and current mortality statistics likely underestimate the true burden of cystic fibrosis liver disease (CFLD) as it is often silent until an advanced stage and most diagnostic modalities lack sensitivity, specificity, or are too invasive. In particular, transient abnormalities of serum transaminases are common throughout the life of the patient with CF yet have a poor reliability for identifying significant fibrosing CFLD or predicting those who will later develop CFLD. In addition, therapy is limited to medications that may improve "numbers" but may not affect outcome. As advanced CFLD does not appear for the first time after early adulthood, there may be factors unique to childhood and adolescence that contribute to the natural history of fibrosis. There is a clear need to develop a better understanding of this manifestation of CF, its natural history, investigation, and management. Current approaches are discussed, and where necessary, the reader is referred to recent reviews on the subject.

Pathogenesis. In normal liver, cystic fibrosis transmembrane conductance regulator (CFTR) functions on the apical surface of cholangiocytes to provide the principal drive to hydration of bile. Impaired CFTR function leads to thickened, inspissated secretions, and biliary obstruction from plugging. Subsequent accumulation of bile salts can cause hepatocyte injury, and inflammation and fibrosis within the portal tracts.[2,8–10] In addition to the cytotoxic and fibrotic effects of accumulated bile salts, it has been postulated that altered bile components with a more hydrophobic bile acid pattern and increased detergency from augmented bile acid-to-phospholipid ratio may predispose the cholangiocytes to injury.[11,12] Taurocholate concentrations in bile and serum from children with CF also correlate with liver fibrosis implicating retained bile salts in the pathogenesis of CFLD.[13] Retained bile salts have been shown to activate bile duct epithelial cells and hepatocytes to release monocyte chemotaxis protein 1 (MCP-1) which stimulate the chemotaxis of hepatic stellate cells to the portal tracts and regions of fibrosis in the CF liver. Recent work

suggests mechanical effects of flow at the apical membrane of cholangiocytes stimulate ATP release and chloride (Cl) secretion further regulating biliary secretion. Thus, reduced bile flow from CFTR dysfunction could exacerbate abnormalities in bile formation,[14,15] accumulation of toxic bile concentrations, and canalicular damage.

While no clear genotype–phenotype correlation has been identified, CFLD seems to be confined to those CF patients who are pancreatic insufficient with severe (class I–III) mutations.[9] CFTR is only one of three Cl channel receptors expressed by cholangiocytes, possibly explaining the phenotypic variability in clinically relevant liver disease.[13] However, interest also remains in the role of modifier genes such as SERPINA-1, whereby the heterozygous Z-allele mutation of alpha-1-antitrypsin are overrepresented in children with CF and liver disease over those without.[16] Male gender is also a risk factor for CFLD.[16] Meconium ileus at birth has long been associated with the finding of multilobular cirrhosis in autopsies, and this link remained strong in a single clinical study.[17]

Hepatic manifestations of CF. The range of CFLD manifestation is outlined in Table 1. However, the major determinant of clinical outcome and the pathognomonic hepatic lesion in CF is focal biliary cirrhosis (FBC),[18] which can progress to multilobular biliary cirrhosis (MBC) and predispose to portal hypertension (PH). Characteristically, portal hypertension is the main clinical concern, often far in advance of synthetic dysfunction and without need for evolution of FBC to MBC as evidenced by reports of liver transplantation for PH in the absence of MBC.[19] The original descriptions of FBC in CF autopsies are of chronic inflammation in expanded portal tracts, ductular proliferation, and variable fibrosis in 2–3 foci of a histopathological section.[20,21]

The lack of a diffuse reaction has previously given cause for concern regarding the reliability of liver biopsy to diagnose severity of fibrosing disease in patients presenting for evaluation. Steatosis has been found in up to 70% of liver biopsies from children with suspected CFLD and represents the commonest identified histological abnormality.[22] This has been thought to be secondary to selective nutritional deficiencies and altered phospholipid metabolism.[6] The significance of steatosis in CF biopsies is unknown; however, it is known that nonalcoholic steatohepatitis can lead to cirrhosis.[23] It is likely that the spectrum of CFLD extends from uncorrected steatosis and nondiffuse biliary fibrosis eventually to PH and cirrhosis.

Table 1 Liver manifestations of cystic fibrosis

Type of hepatic manifestation	Approximate frequency seen
Hepatic steatosis	25–70%
Focal biliary cirrhosis	20–30%
Microgallbladder, sludge, other	15–30%
Neonatal cholestasis	< 10%
Multilobular biliary cirrhosis	5–10%
Common bile duct stenosis [distal]	Uncommon
Drug toxicity	Undefined
Cholangiocarcinoma	Rare

Diagnosis and follow-up. The diagnosis of CFLD in the context of the patient in the CF clinic is challenging. Biochemical abnormalities are very common in CF patients, vary over time, and are often absent even in those patients with advanced cirrhosis.[24] No noninvasive modality is able to discriminate the presence of liver fibrosis from nonspecific liver inflammation or steatosis. To address the issue of CFLD diagnosis, Colombo *et al*[18]established criteria based on positive liver histology or the presence of any two of the following clinical criteria present over a 1-year period: hepatomegaly, elevated liver biochemistry and ultrasound abnormalities other than hepatomegaly. Combined, the clinical criteria predict the development of PH in 42% of patients with CF.[7]

Exclusion of other causes of liver dysfunction in children such as viral infection, drugs, metabolic disorders, and other structural hepatobiliary conditions is part of all CF clinic[4,25] protocols.

Hepatobiliary ultrasound is often recommended as the first line noninvasive investigation[12] and commonly undertaken in most CF centers. However, it does not detect fibrosis until advanced when the presence of macronodular cirrhosis and splenomegaly indicating portal hypertension have already developed.[26] Nor does ultrasound reliably distinguish between the common occurrence of steatosis and the more significant presence of fibrosis. Abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) may be useful in discriminating between steatosis and fibrosis, but the former requires ionizing radiation. The latter is the modality of choice to assess intrahepatic and extrahepatic biliary tree abnormalities in most cholestatic disorders. However, in CF populations cholangitic lesions are detected in many patients both with and without confirmed CFLD and has little discriminatory value,[4,27] and has thus not been recommended for routine use.

Liver biopsy has not been widely employed to evaluate liver disease in CF populations, principally because of the perceived but poorly tested concern over sampling error in a condition characterized by a patchy distribution, and due to its invasive nature. However, this was recently addressed by a cohort study where biopsy was the only modality to reliably detect liver fibrosis and predict the development of later portal hypertension. Dual pass biopsy helped to address sampling concerns and improved the reliability of fibrosis assessment in 38% of patients.[8] These findings are interesting and may be helpful in studying the evolution of the fibrosis–cirrhosis pathways and the development of noninvasive markers.

More recently, noninvasive assessments of liver fibrosis such as transient elastography (TE) (Fibroscan Echosens, Paris) and Acoustic Imaging has stimulated interest with respect to assessing the natural history of fibrosis–cirrhosis in CFLD. A recent preliminary study on the use of TE in children and adults showed the ability to discriminate between patients with and without established portal hypertension.[28] However, both TE and Acoustic Imaging require validation against other objective measures of fibrosis such as histology and against long-term hard outcomes such as evolution of PH, bleeding risk, cirrhosis, synthetic failure, and transplantation. This will require large cross-sectional and longitudinal studies before it finds a place in routine management. Despite the potential availability of better proxy markers of hepatic fibrosis, it is important to recognize that clinically significant non-cirrhotic portal hypertension can occur, which may be underestimated by biopsy

Table 2 Investigation of cystic fibrosis-associated liver disease

Clinical exam Hepatomegaly ± splenomegaly	Poor sensitivity for early significant fibrosis
Serum liver biochemistry	Often normal, rarely more than 2 × ULN even in advanced fibrosis
Ultrasound	Poor sensitivity for early, significant fibrosis, increased echogenicity usually from steatosis
Cholescintigraphy scan	Unclear role
CT scan	Poor discriminator for fibrosis
Magnetic resonance imaging	Clarifies steatosis
MRCP/ERCP	Bile duct abnormalities not discriminatory for development of fibrosis cirrhosis
Liver biopsy	Invasive but is a validated test for fibrosis and possible predictor of PHT with sampling concerns (dual pass improves accuracy)
Elastography	Role in early fibrosis detection not determined

ULN, Upper limit of normal; PHT, portal hypertension.

and noninvasive methods like TE,[29,30] hence a high clinical suspicion should be maintained in the face of normal investigations.

Despite the limitations of commonly employed noninvasive assessments (physical examination, liver function tests, and ultrasound) of liver disease in the CF population, these remain the cornerstones for diagnosis. There is consensus among gastroenterologists that annual review of CF patients should include a clinical assessment of hepatosplenomegaly as well as a full blood count, liver enzymes, and fat soluble vitamin levels,[25] and that hepatobiliary ultrasound should be considered as often as every 2 years. This is in an attempt to identify "early" disease and flag those children that require closer scrutiny and more frequent assessment from a liver viewpoint. The follow-up of patients either with significant fibrosis/cirrhosis with and without portal hypertension is covered in an extensive review by Debray and colleagues and will not be covered in detail by this review[6] (See Table 2 for summary of different investigation modalities).

Clinical course. The clinical course of CFLD is highly variable and not all those with hepatomegaly, altered liver enzymes or architecture based on ultrasound findings will develop MBC.[7] However, clinically apparent CFLD, particularly those with fibrosis–cirrhosis and/or portal hypertension, usually develops around puberty and subsequently displays a slowly progressive course.[28] In the biggest study to date, no new case of liver disease was first detected after 20 years of age.[5] Hence, the development of significant liver fibrosis occurs during childhood. An Irish study showed that children with significant CFLD (fibrosis–cirrhosis on liver biopsy and or portal hypertension) were shorter and lighter, had altered body composition and worse pulmonary function compared to age and sex-matched children with CF and no clinically significant liver disease.[31]

Over a 7-year follow-up period, seven of 36 (19.4%) CFLD patients had died or underwent liver transplantation compared with three of 36 (8.3%) of CF controls.[7] While this represents a non-significant trend ($P = 0.3$), it correlated with a difference of 3 years in potential years of life lost. Approximately 10% of patients with CFLD died from liver complications or needed liver transplantation, and 30% developed varices over the 7 year follow-up.[7] In this study, 40.7% CFLD had CF related-diabetes, compared to 15.2% CF controls ($P = 0.02$).

Therapy. There is yet to be a therapy proven to change the disease course and long-term prognosis of CFLD. More generalized management such as optimizing nutritional state and fat soluble vitamins as well as monitoring for complications of portal hypertension are the mainstay of treatment.[4,32]

Ursodeoxycholic acid is widely used, and it has been shown to improve serum liver biochemistry and histological changes.[30,33,34] It is safe and addresses many of the putative causes of CFLD by stimulating calcium-dependent chloride channels and bile-dependent bile flow, reducing the hydophobicity and hence toxicity of retained bile acid.[14] However, there have been no long-term studies performed, and current data demonstrate no effect on survival.[30] A Cochrane Review concluded there was no good evidence to support its use.[35]

Several novel approaches have been examined. Recent data suggest that children with CF have lower than expected insulin-like growth factor-I relative to their growth hormone (GH) production. Furthermore, the response to endogenous GH is further reduced in children with CFLD. In a very small trial, Stalvey *et al*. demonstrated improved growth and improved liver function following administration of recombinant human GH.[36] Until further data become available as to the safety and efficacy of this intervention, it cannot be recommended in routine management of CFLD.

Cirrhosis and PH can negatively impact respiratory function due to organomegaly, ascites, and intrapulmonary shunting.[12]

Prior to consideration for liver transplantation, several alternative "bridging" interventions have been considered by clinicians in the field including splenectomy (complete or partial) and transjugular intrahepatic portosystemic shunt (TIPS). Both of these approaches lack sufficient data in the CF population, which may pose various specific concerns. A retrospective review by Linnane *et al*. reviewed nine CF patients who underwent splenectomy predominantly for hypersplenism, thrombocytopenia and portal hypertension, and demonstrated both short and long-term benefit. Despite fears of post-splenectomy overwhelming sepsis, the patients in this series had no evidence of such, and actually demonstrated improved pulmonary function.[37] Partial splenectomy for management of PH in CF patients with preserved liver function has also been demonstrated a reliable and well-tolerated technique which may prevent or significantly delay the need for liver transplantation.[38] More recently, interest has spread to the use of partial splenic embolization for the management of PH. Several case reports exist,[39–41] however, there is currently insufficient experience on its use in CFLD to suggest its use in routine management of these challenging patients.

A major concern with TIPS in these patients with severe CFLD with PH is the high risk of ensuing encephalopathy. Despite reported acceptable outcomes in some patients with acceptable hepatic function,[42] the authors recommend this procedure primarily as a bridge to liver transplant in severe CFLD.

Liver transplantation is a rare occurrence in patients with CF, and as such there is limited data on the benefits. The experience of a transplant unit in Australia demonstrated 1 and 4-year post-transplant survival of 75% in eight isolated liver transplants performed in CF patients over a 22-year period. Most were colonized with pseudomonas and fungus at the time of transplant, however, the cohort all had relatively preserved lung function (FEV1 59–116%), which did not appear to deteriorate post-transplant.[43] Available data would suggest a significant survival benefit compared to those who remained on the waiting list.[44,45] In those patients with known severe CFLD, deterioration in pulmonary function could be an important indication to proceed with transplant.[43] There is a concern about more rapid deterioration of patients post-lung transplant in those with CFLD compared to those without CFLD, as such, patients with CFLD are often excluded from lung transplantation. This makes the early diagnosis of advancing liver disease and consideration for liver transplantation prior to pulmonary failure more important. A recent retrospective review of perioperative and post-transplant outcomes suggested that CF patients with cirrhosis caused by CFLD can safely be considered for sole lung transplantation provided there is no evidence of significant hepatocellular dysfunction with decompensated cirrhosis or hepatic synthetic failure.[46]

There is developing interest in the role of simultaneous liver–pancreas transplantation for CFLD in patients who also have CF-related diabetes (CFRD). While there is only limited worldwide experience, a recent survey of pediatric transplantation centers worldwide revealed eight cases, all of whom had restoration of exocrine and endocrine pancreatic function. While en-bloc transplant of liver, pancreas, and C-loop of the duodenum is technically comparable to isolated whole liver transplants, the benefit of requiring no bile duct anastomosis may be advantageous; however, there remains inadequate experience to support this. More provocatively, 24% of transplant centers surveyed would consider simultaneous liver–pancreas transplantation in cases of demonstrated exocrine pancreatic insufficiency, even in the absence of overt CFRD.[47]

It is clear that liver disease in CF is an important contributor to morbidity and mortality, yet management has been confounded by the lack of readily available, noninvasive tools for the reliable early detection and subsequent monitoring of evolving fibrotic liver disease. This has also confounded assessment of interventions to change the natural history of CFLD. Both are fertile areas for future research.

Pancreatic manifestations of cystic fibrosis

Virtually, 100% of patients with CF will have pancreatic disease. Pancreatic damage generally arises from ductal/glandular obstruction due to an inability to hydrate macromolecules within ductal lumens.[48,49] Pancreatic damage begins in utero, with lesions found in neonates and fetuses as young as 17 weeks gestation, and this process continues into infancy and early childhood.[50,51] Typical lesions consist of luminal dilation of acini by zymogen material with progressive thinning of lining epithelium.[52] The interstitial pools of zymogen elicit an inflammatory response, with eventual loss of exocrine tissue and replacement by connective tissue.[53] The destruction of the pancreas can be so extensive, that in one study, 72% of patients imaged with magnetic resonance imaging did not have a pancreas detected as an anatomical entity.[54]

There are three clinical pancreatic manifestations of CF: exocrine PI, pancreatitis, and diabetes mellitus.

Exocrine pancreatic insufficiency

Among all affected organs in CF, the exocrine pancreas is the most reliable phenotypic marker of CFTR function.[55,56] Eighty-five percent of CF patients are PI, the remainder retain sufficient residual function to be classified as pancreatic sufficient (PS).[57] The loss of pancreatic function usually develops early in life. Waters *et al*. demonstrated that 63% of infants with CF are PI at newborn screening with nearly 30% of those who are PS at screening becoming PI over the next 36 months.[58] Recent work has demonstrated that those who lose pancreatic function over the first decade are either homozygotes or compound heterozygotes for class I–III mutations.[59,60]

The exocrine pancreas has remarkable reserve capacity as fat maldigestion with resultant steatorrhea only occurs when pancreatic colipase/lipase secretion falls below 1–2% of normal levels.[61] Fat is the most sensitive macronutrient to malabsorption with gastric lipase production insufficient to compensate for loss of pancreatic function.[62] Pancreatic protease (trypsin, chymotrypsin, etc.) secretion has not been assessed in relation to fecal nitrogen excretion but is likely at similarly low levels. Carbohydrate digestion remains intact despite near absence of pancreatic amylase secretion, reflecting both brush border enzyme activity and the ability of colonic bacteria to hydrolyse unabsorbed carbohydrate from the small intestine.[63]

Macronutrient malabsorption, if uncorrected, leads to acute and chronic malnutrition with weight loss and linear growth failure.[64] Persistent protein loss is associated with development of hypoproteinemia and edema and accounts for the Kwashiorkor-like presentations of CF infants in non-screened populations.

In addition to macronutrient malnutrition, micronutrient malnutrition can also occur, most particularly with fat soluble vitamins. Mild–moderate steatorrhea may not alter stool appearance and growth may also be normal, as patients compensate by increasing food intake.[65]

Prolonged untreated PI is associated with a worse long-term outcome. This was first demonstrated by Corey *et al*. who compared outcomes of over 1000 patients from the CF clinics in Boston and Toronto. Boston patients followed the traditional low fat, high-energy diet *versus* the Toronto patients who employed more liberal fat intake and pancreatic exocrine replacement therapy (PERT). Patients from Toronto were taller, heavier, and had a higher median age survival.[66]

Diagnosis of PI. Pancreatic exocrine function is assessed by direct and indirect methods. The direct method is by nasoduodenal tube aspiration and measurement of the stimulated output of enzymes and bicarbonate released into the duodenum. This is the most sensitive and specific measure, however, it is rarely performed in the clinical setting due to its invasive nature, cost, and time burden.

Indirect measures of PE are predominantly based on assessing clinical outcome of PI with fecal fat measures, or measuring enzyme levels in stool. Of the indirect methods, 72-h fecal fat excretion, expressed as coefficient of fat absorption (CFA) is considered the gold standard. Steatorrhea is defined by excretion of more than 7% of ingested fat. In infants below 6 months, test results are considered abnormal if CFA is > 15% as pancreatic and biliary secretion is yet to mature. In children consuming an Medium chain triglyceride (MCT)-rich formula, the fecal fat measure will be inaccurate if the Van de Kamer method of analysis is utilized, hence the Jeejeebhoy modification should be utilized by the laboratory.[67]

Despite the well-validated data, justifying the 3-day fecal fat measurement, this test is often not standardized with a weighed fat intake between ingested dye markers, and in addition the test is poorly tolerated by patients, parents, and laboratory staff alike. Hence, other markers have been employed.

Measurement of fecal elastase-1 is a noninvasive, simple test, and shown to be a reliable measure of pancreatic function.[68] Elastase-1 is highly specific for the pancreas and not present in PERT, hence there is no requirement to discontinue PERT for the test. Since fecal elastase is measured as a concentration per gram stool, results may be falsely low in the presence of diarrhea. Fecal elastase-1 has not yet been validated as a reliable screening test in breast-fed infants with watery, diluted stools. Although fecal elastase is highly sensitive for severe pancreatic insufficiency,[69] sensitivity is limited for detection of mild pancreatic insufficiency.[70] In those CF patients with PS, who deteriorate to PI, fecal elastase may not be sufficiently accurate to predict this. However, specificity and negative predictive value is high, so it is possible to exclude PI with 80% certainty.[71] Fecal elastase-1 has been suggested as a useful screening tool for longitudinal follow-up of PS patients.[72]

Another alternative pancreatic measure under investigation is sparse stool sampling for percentage fat (PF) analysis, in which multiple sample PF values < 30% were shown to be highly predictive for a CFA > 80%. This screening technique may have a role in identifying both suboptimal dosing in patients receiving PERT and fat malabsorption in those not yet receiving PERT.[73]

In older children with CF, radiolabeled carbon mixed triglyceride breath tests[13] are highly sensitive and specific in comparison with CFA for defining PI and PS.[74] There are less data supporting test validity in infants.

Various newer markers are being assessed as alternative and more sensitive markers of PI. One approach under investigation involves ingestion of a meal with a known fat content of lauric acid from coconut oil and of sucrose polybehenate (SPB) at a set ratio. SPB is a component of fat used in commercial production of fried snack foods and serves as a nonabsorbable lipid marker. The stool lauric acid: behenic acid ratio provides an assessment of fat absorption which correlates with CFA, but it is not sufficiently robust to replace CFA.[75]

Treatment of PI. The objectives of pancreatic enzyme replacement therapy (PERT) are to correct macro- and micronutrient maldigestion, alleviate abdominal symptoms attributable to maldigestion, help establish normal stools and bowel habits, and sustain normal growth and nutritional status.[76]

Table 3 Pancreatic enzyme replacement therapy guidelines

Dosing per dietary fat intake	
Age	Dose
Infants	500–1000 U/gram fat
	2000–4000 per breast feed/120 mL formula feed
Children	500–4000 U/gram fat
Dosing per bodyweight	
Age	Dose
< 4 years	1000 U/kg/meal
	Snack: half dose
> 4 years	500 U/kg/meal
Dose titration	
Commence on minimal dose; increase dose based on weight gain, steatorrhea, and coefficient of fat absorption testing	
Administration	
• Swallow whole or sprinkle capsule on applesauce (or other non-alkali soft food)	
• Rinse infant's mouth after administration	
• Co-administer proton pump inhibitor therapy to maximize efficacy of therapy	
• Assess fat-soluble vitamin (A, D, E and coagulation screen) and replace as necessary	

PERT dosing should be individualized, and the two primary approaches to dosing are based on body weight and on fat intake[76,77] (Table 3). Patients should be commenced on a minimum dose, and uptitrated based on weight gain and obvious steatorrhea and possibly CFA testing. Infants require 500–1000 units of lipase per gram of dietary fat, or 2000–4000 units lipase per breast feed or 120 mL bottle. Children require 500–4000 units lipase per gram of dietary fat.[76]

When dosing based on bodyweight, under 4-year-old patients may be given 1000 units lipase/kg each meal, and those over 4 years old may be given 500 units lipase/kg per meal.[76] For a snack, these doses may be halved.

PERT tablets or capsules should not be crushed or chewed. Patients unable to swallow tablets can be given delayed release capsules which contain enteric coated microspheres resistant to acid dissolution. These can be sprinkled onto soft food such as apple sauce and swallowed, but they should not be sprinkled onto foods with pH > 6 (e.g. milk, custard, or ice cream) as this may dissolve the enteric coating.[71] Gastric acid suppressant therapy, such as proton pump inhibitors, may improve the effectiveness of PERT[78] by assisting duodenal pH to rise above 6, facilitating dissolution of microsphere enteric coating, with release and activation of enzymes.

Newer formulations of PERT for infants and small children incorporating mini-microspheres improve fat absorption, improve stool frequency and characteristics, and improve patient growth parameters in comparison to regular PERT.[79] Other new formulations, such as liprotamase, a non-porcine PERT containing highly purified biotechnology-derived lipase, protease, and amylase, are showing promising results in clinical trials.[80]

PERT is a safe therapy; however, certain precautions need be taken. For infants, it is recommended that the mouth be swept after administration of PERT to prevent ulceration in the alkaline

salivary environment. Two large epidemiology studies in UK and United States showed an association between high-dose lipase therapy (> 20 000 U/kg/day) and the occurrence of fibrosing colonopathy (FC).[77,81] As a result of the subsequent reduction of dosing recommendations to a maximum 10 000 U/kg/day, reports of FC have become rare.[82] In clinical practice, compliance to therapy is the most important factor, however, on occasion the CF gastroenterologist may need to cast a wider net.[83]

Despite adequate PERT, follow-up of patients with CF demonstrates persistent essential fatty acid deficiency, particularly in linoleic and docosahexaenoic acids. One theory is that fat malabsorption is not the only cause of dyslipidemia, and other endogenous factors may contribute to its development.[84] Alterations to intestinal pH, mucosal abnormalities, and small bowel bacterial overgrowth have also been implicated as contributing to persistent fat malabsorption.[85] Acid suppressive drugs and broad spectrum antibiotics have been proposed and empirically employed to optimize fat absorption.[85] Despite insufficient evidence to draw firm conclusions, regular administration of omega 3 long-chain fatty acids[86] has also been proposed as beneficial in patients with CF. An approach to inadequate clinical response to PERT is suggested to the reader in Figure 1.

In addition to PERT therapy, prophylactic supplementation of fat-soluble vitamin A, D, E, and K is recommended along with a possible benefit of various antioxidants.[87] Monitoring of levels is part of standard management[88] as patients with CF have a full medication burden and have been shown to be less compliant with vitamin supplementation.

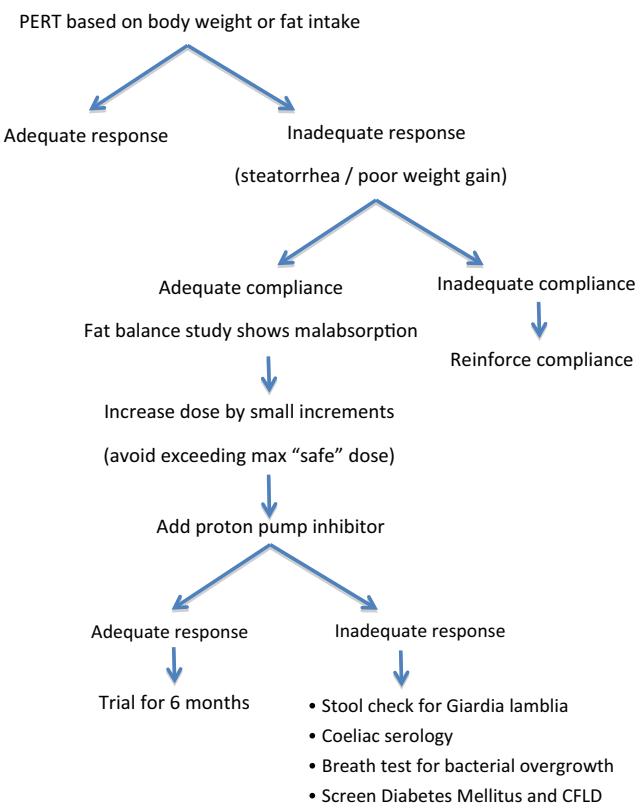

Figure 1 An approach to an inadequate clinical response to Pancreatic Exocrine Replacement Therapy (PERT). CFLD, cystic fibrosis liver disease.

Pancreatitis

Pancreatitis is a less common manifestation of CF since the presence of acinar tissue is necessary for pancreatitis to occur. Hence pancreatitis does not occur in patients who are PI (85–90%), only in those who are PS.[49,55] Among PS-CF patients, only 10–20% develop pancreatitis,[89] implicating the contribution of CFTR genotype and non-CFTR genetic and environmental factors.[49] Complex genotypes such as a combination of CFTR and SPINK1 mutations, a specific trypsin inhibitor, increase the likelihood of developing recurrent acute pancreatitis or chronic pancreatitis.[90]

Studies of patients with idiopathic recurrent or chronic pancreatitis, revealed 40–43% carry CFTR mutations on one or both alleles, however only 10–20% fulfilled diagnostic criteria for CF.[91,92] The risk of pancreatitis may be related to the balance between degree of pancreatic acinar preservation and extent of acinar/ductal plugging due to inspissated secretions, both of which are factors of the phenotypic manifestation of CFTR mutations.[49]

Increasing data corroborates the higher susceptibility of CF carriers to chronic pancreatitis, despite having a normal gene sequence of the other allele.[93]

Because the prevalence of pancreatitis in patients with PS-CF is high, a strong index of suspicion must be maintained in any CF patient presenting with abdominal pain.

The occurrence of pancreatitis is a risk factor for progressive decline in exocrine and endocrine pancreatic function in PS-CF patients, hence exocrine pancreatic function should be repeatedly assessed in patients with PS-CF, particularly those who present with pancreatitis.[49]

Cystic fibrosis related diabetes mellitus (CFRD)

CFRD is primarily caused by insulin insufficiency as a result of pancreatic fibrosis and islet destruction. There is also a variable component of insulin resistance related to underlying chronic inflammation with bouts of superimposed acute infection.[94]

Epidemiological data from New South Wales and the Australian Capital Territory, Australia shows CFRD is increasingly recognized and affects approximately 20% of CF patients below 18 years of age. There is a rising incidence of CFRD since 2000 resulting from greater awareness and changes in screening practices.[95]

Various studies demonstrate worse survival in CF patients with diabetes, with chronic inflammatory lung disease seemingly exacerbated by CFRD. This may be due to the catabolic state of insulin deficiency contributing to reduced body mass and lean body weight, both significant factors in CF lung function. In addition, the hyperglycemic state causes a raised glucose content of pulmonary surface secretions creating a more favorable environment for bacteria.[96]

Aggressive insulin replacement therapy improves weight, pulmonary function, and survival in CFRD.[97]

Accelerated decline in lung function and body weight begins 2–6 years before the onset of overt diabetes in CF,[94] and patients

with impaired glucose tolerance have a greater rate of decline in lung function than those with normal glucose tolerance.[98]

Due to the more complicated disease course with CFRD, and its insidious, mostly asymptomatic development, routine annual screening is recommended in all CF patients aged 10 years and older. The screening tool of choice should be the oral glucose tolerance test (OGTT), since haemoglobin A1c, urine glucose or random glucose levels have been shown to have poor sensitivity in the CF population.[99] The major impediment to early diagnosis of CFRD is poor compliance with screening programs,[100,101] hence regular OGTT screening should be an established requirement in all CF services, with appropriate mechanisms in place to maximize compliance.

Current diagnostic criteria for CFRD were originally designed to forecast microvascular disease in type-2 diabetes, rather than CF-specific outcomes such as declining weight or lung function. It is plausible that insulin may be of greater benefit to respiratory function when given prior to the diagnosis of CFRD, after which structural lung disease may be irreversible.[102] In support of this hypothesis, a recent study by Kolouskova *et al*. demonstrated that early intervention of low-dose insulin therapy in those patients with abnormal glucose tolerance, but normal fasting glycemia, improved nutritional status, and stabilized pulmonary function.[103] Further studies are required to determine how current clinical practice should be altered toward earlier commencement of insulin in CF patients.

Conclusion and summary

There is no doubt that respiratory issues are paramount in CF and is the major cause of both morbidity and mortality. However, there are significant and clinically relevant gastrointestinal, liver, pancreatic, and nutritional manifestations of cystic fibrosis which must be detected and managed in a timely and structured manner. In order to address this, it is now "best practice" in all pediatric and adult CF centers that a gastroenterologist with a broad base of skills is involved in the care of these patients. These centers should also be closely aligned with medical education of this restricted but important field. This review should serve as a reminder that the gastroenterologist still has a significant role to play, and should feature as a critical member of the CF team.

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