Gastrointestinal and Hepatobiliary Disease in Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is a multiorgan disease, and gastrointestinal (GI) manifestations can contribute to significant morbidity and mortality for individuals with CF. Up to 85% of patients with CF experience GI symptoms, thus addressing the GI aspects of this disease is paramount. With the advent of highly effective CF transmembrane conductance regulator modulators that are increasingly available, many individuals with CF now have significantly improved life expectancy. With these advances, GI manifestations that can be a detriment to quality of life such as gastroesophageal reflux disease, dysbiosis, and chronic abdominal pain have become a priority for patients and caregivers. In addition, as individuals have increased longevity, it has become essential for care providers to be aware of topics such as hepatobiliary disease and colorectal cancer screening. An understanding of the wide scope of GI manifestations in CF can enable providers to optimize the overall health and well-being of their patients. In this review, we aim to provide an up-to-date overview of key aspects of GI and hepatic disease in CF.

Keywords

- meconium ileus
- gastroesophageal reflux disease
- distal intestinal obstruction syndrome
- dysbiosis
- hepatobiliary
- pancreatic function

General and Upper Gastrointestinal Disease

Gastroesophageal Reflux Disease

Gastroesophageal reflux (GER) is a physiological process, which is described as the effortless retrograde flow of gastric contents into the esophagus. This can become a pathological process, gastroesophageal reflux disease (GERD), when associated with negative consequences, which may include esophagitis, dysphagia, Barrett's esophagus, or failure to thrive. Individuals with cystic fibrosis (CF) have many predisposing clinical factors to developing GERD, including medications such as α-adrenergic agents, high-fat diet, increased intra-abdominal pressure, and need for postural drainage. It is well established that individuals with CF have a high prevalence of GER, between 35 and 81%, although the etiology of this is not clearly understood.[1–3] Increased frequency of transient lower esophageal sphincter relaxations (TLESRs) has been shown to be a predominant contributing factor, while other causes may include delayed gastric emptying and lower amplitude of primary peristalsis.[2,4] A study using high-resolution manometry impedance (HRM-MII) showed that the increased gastroesophageal pressure gradient due to pronounced inspiratory negative pressure drives reflux in patients with CF during TLESRs.[5] It is postulated that GER may negatively impact pulmonary function through aspiration of gastric contents, increased airway inflammation, and reflex bronchospasm.[6] Duodenogastroesophageal reflux (DGER), the reflux of bile acids (BAs) and other duodeno-pancreatic secretions, can be increased in patients with CF, with BAs present in saliva and sputum in some, signifying aspiration of duodenogastric contents. Aspiration of BA, in turn, has been associated with

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increased airway inflammation as measured by neutrophil elastase, and is negatively correlated with lung function in CF (forced expiratory volume in 1 second [FEV1] % predicted).[7]

Gastric dysmotility has been described in patients with CF and may manifest as anorexia, belching, bloating, early satiety, epigastric pain, postprandial fullness, nausea, and/or vomiting. It may also interfere with oral medication delivery and absorption.[8,9] A systematic review of the literature found that up to 38% of individuals with CF have gastroparesis.[8] Conversely, a subgroup of nondiabetic patients with pancreatic insufficient CF were identified to have rapid gastric emptying associated with postprandial hyperglycemia, a finding that normalized with pancreatic enzyme replacement therapy (PERT) administration.[10] While delayed gastric emptying is prevalent in patients with CF, studies have shown there to be a poor correlation between clinical manifestations and abnormal gastric emptying.[9] Other studies have shown mixed results regarding a relationship between delayed gastric emptying and GERD.[2,9] A challenge to the assessment of gastric emptying is that there is not a standardized protocol used in scintigraphy and breath testing relies on normal small bowel absorption and pulmonary function. Smartpill, a wireless motility capsule, may be helpful to better characterize gastric emptying, but is not widely available for clinical purposes nor is it approved for use in children. Thus, gastric motility is altered in many individuals with CF and should be considered in the appropriate clinical context; however, its etiology is likely multifactorial and no clear guidelines for its assessment and treatment currently exist.

There is a lack of established guidelines for the diagnosis and treatment of GERD in individuals with CF. Evaluation includes a history and physical exam, and oftentimes this is adequate to establish a probable diagnosis. Other tools for assessment are summarized in ►**Table 1** and may include an upper gastrointestinal (GI) series to evaluate anatomy and a gastric emptying study, although neither of these studies is sensitive nor specific for establishing the diagnosis of GERD. Upper endoscopy can be useful if symptoms persist despite initial medical management to rule out other diagnoses (e.g., candidiasis, eosinophilic esophagitis, celiac disease) and to screen for complications of GERD such as Barrett's esophagus. Finally, multichannel intraluminal impedance and pH testing (MII-pH) is the gold standard test for diagnosing acid and nonacid reflux, as well as characterizing the proximal extent of reflux and response to therapy.

Treatment options for GERD are summarized in ►**Table 2** and can include diet and lifestyle modifications, medications, as well as surgical interventions. Acid suppression is often the first-line pharmacologic approach and may be helpful in providing symptomatic relief as well as healing esophagitis and peptic ulcers. It is important to note that acid-suppressing medications do not reduce the number or extent of reflux episodes, but simply decrease the acidity of the refluxate. Promotility agents can be employed to address gastroparesis, but efficacy of these agents in reducing GERD has not been clearly proven. Macrolide antibiotics including erythromycin and azithromycin act by stimulating motilin receptors on GI smooth muscle, thereby improving gastric emptying. These medications have been shown to enhance esophageal motility; however, the long-term benefit of these medications in CF has not been demonstrated.[11–13] Finally, fundoplication may be considered for patients with severe GERD and worsening lung disease and has been shown to slow decline in lung function and improve weight gain.[14] In further support of its efficacy, several studies have found improved allograft survival when fundoplication was performed within 90 days of lung transplantation.[15,16]

Dysbiosis, Dysmotility, and Inflammation in the CF Intestine

CF transmembrane conductance regulator (CFTR), the gene responsible for CF, is expressed throughout the intestine. CFTR intestinal dysfunction occurs early in development and is present in all genotypes.[17] CFTR mRNA expression is highest in the duodenum and decreases along the small intestine, with moderate expression of CFTR found in the large intestine.[18] Expression of CFTR contributes to the dramatic shift from acidic to alkaline pH in the proximal duodenum, allowing for optimal nutrient digestion and absorption. CFTR-mediated bicarbonate secretion is also necessary for the expansion and solubility of the intestinal mucus,[19] with dysfunction resulting in deficient anion and fluid transport leading to

Table 1 Common evaluation modalities for GERD

Test	Indication	Advantages	Drawbacks
Upper GI series	Assessment of anatomy	Can rule out intestinal malrotation	Radiation exposure
Gastric emptying study	Evaluation for gastroparesis	Low radiation	Lack of standardization of test protocols and interpretation
Impedance probe	Quantification of acid/nonacid reflux	Can assess efficacy of treatment and symptom association	Invasive test
Upper endoscopy	Medication refractory symptoms	Direct visualization, can screen for malignant changes, can rule out other conditions such as eosinophilic esophagitis or candidiasis, allows for sampling of duodenal fluid for bacterial quantification	Invasive test, requires anesthesia, risks of bleeding, infection, perforation

Abbreviation: GERD, gastroesophageal reflux disease.

Table 2 Treatment options for GERD; dosing references: Lexicomp, Maqbool and Pauwels (2017),[185] Demeyer et al[120]

Modality	Common medications/examples	Dosing	Potential adverse effects/drawbacks
Lifestyle modifications	Limiting acidic, spicy foods, caffeine, alcohol, tobacco, chocolate. Smaller, more frequent meals. Elevation of head of bed.	NA	None
Histamine blocker	Ranitidine, famotidine	Ranitidine: Pediatric: 5–10 mg/kg/d divided twice daily Adult: 75–150 mg twice daily Famotidine: Pediatric: 0.5–1.0 mg/kg/dose given twice daily Adult: 10–20 mg twice daily	Generally well tolerated, tachyphylaxis reported with chronic use, not as effective at acid reduction as PPI.
Proton pump inhibitor	Omeprazole, pantoprazole	1–3 mg/kg/d in 1–2 doses, adult maximum dose 80 mg/d	Concerns for bone health, renal dysfunction with long-term use
Prokinetic	Reglan	Pediatric: 0.1–0.2 mg/kg/dose 3–4 times daily Adult: 5–10 mg dose 3–4 times daily	Black box warning in pediatrics, tardive dyskinesia
	Erythromycin	Pediatric: 3–5 mg/kg/dose given 3–4 times daily Adult: 40–80 mg dose 3 times daily	Tachyphylaxis, QT prolongation
	Azithromycin	Pediatric: 5 mg/kg/d Adult: 400 mg/d	
Operative	Nissen fundoplication		Operative procedure, may result in dysphagia or chronic retching

Abbreviations: GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

thick, inspissated mucus, which in turn contributes to gut dysmotility and fosters microbial dysbiosis. This alteration in the gut microbiome can alter immune responses, drive chronic inflammation, and further induce mucus secretion and compound dysbiosis, perpetuating the process.[19]

Small intestinal bacterial overgrowth (SIBO) is defined as a disease state in which the ordinarily low bacterial burden in small intestine increases in excess of 10^5 to 10^6 colony-forming units/1 mL of sampled fluid. Individuals with CF have several risk factors for developing SIBO, summarized in ►**Table 3**, and consequently 30 to 50% of patients suffer from this condition.[20,21] Symptoms can include diarrhea, abdominal pain, and bloating, although some patients may be asymptomatic.[22] SIBO can result in weight loss due to bacterial competition for ingested nutrients, secretion of toxins and metabolites causing intestinal inflammation and injury, and deconjugation of bile salts with subsequent fat malabsorption.[19] Laboratory findings associated with SIBO are related to nutrient malabsorption and may include deficiencies of fat-soluble vitamins, vitamin B12, and/or iron.[22,23] The gold standard for diagnosis of SIBO is the direct aspiration and culture of duodenal fluid; however, this is an invasive approach, and may underestimate bacterial burden in patients with CF due to increased concentration of bacteria in the adherent mucus layer.[23,24] Breath testing is a noninvasive testing modality that measures exhaled hydrogen or methane produced by bacterial fermentation after ingestion of a lactulose or glucose load. The inclusion of the methane measurement is of particular importance as individuals with CF are more likely to not produce hydrogen from lactulose than non-CF patients.[25] Confounding factors with the use of breath testing in CF include frequent antibiotic exposure, delayed intestinal transit, and gas retention due to mucus plugged airways.[23]

Table 3 Risk factors for small intestinal bacterial overgrowth

Decreased bicarbonate secretion, lower luminal pH
Increased viscosity of intestinal mucus
Prolonged small intestinal transit time
History of bowel surgery
Frequent antibiotic use
Frequent antacid use

Dysmotility is an important contributing factor to the pathophysiology of the CF intestine. In health, the intestinal migrating motor complex clears the intestinal lumen of mucus and bacteria. Slowed small intestinal motility has been described as a frequent cause of SIBO.[26] CFTR dysfunction has been shown to lead to significantly delayed small bowel transit, both in CF mouse models as well as individuals with CF.[27–30] This delayed small bowel transit may be both a cause and effect of dysbiosis, as we know that animals that are germ-free or colonized only with *Escherichia coli* have slower intestinal transit than those with normal flora.[27] This is likely relevant to our CF population as the predominant species that overgrows in the CF mouse small intestine is *E. coli*, and treatment of CF mice with the osmotic laxative

polyethylene glycol (PEG) normalized intestinal transit time, reduced intestinal mucus accumulation, eradicated bacterial overgrowth, and led to better weight gain.[28]

Given that the CF intestine is commonly affected by dysbiosis and dysmotility, intestinal inflammation can often ensue. Increased fecal calprotectin, a stool biomarker of inflammation derived from neutrophils and eosinophils, is seen in up to 85% of pancreatic insufficient patients with CF.[17,31] Capsule endoscopy has shown mucosal ulceration, erythema, and mucosal breaks in 71% of patients with CF and pancreatic insufficiency (PI) and 46% of those with pancreatic sufficiency (PS).[31] Intestinal inflammation seen in the setting of CF is less likely associated with typical symptoms of inflammatory bowel disease (IBD) such as blood and mucus in the stool and more often presents as malabsorption and poor weight gain despite adequate PERT dosing. Previously, an increased prevalence of Crohn's disease has been reported in patients with CF.[32] More recent studies describing the intestinal inflammation that is seen in CF highlight that the diagnosis of Crohn's may be challenging to discern from CF enteropathy, and requires careful consideration. Furthermore, anti-*Saccharomyces cerevisiae* antibody (ASCA), a serum biomarker identified in 60 to 70% of patients with Crohn's disease, was also found in 20% of individuals with CF, none of whom clinically met diagnostic criteria for Crohn's disease.[33] It is hypothesized that this seropositivity may be due to exposure to fungal organisms via intestinal or pulmonary sources or due to nonspecific immune dysregulation.

Clinical symptoms of dysbiosis and intestinal inflammation are frequently nonspecific, including abdominal pain, diarrhea, and bloating. As mentioned above, testing for SIBO and intestinal inflammation may include endoscopy, breath testing, as well as stool calprotectin. Further investigation may be indicated to rule out other etiologies such as appendicitis, distal intestinal obstruction syndrome (DIOS), constipation, *Clostridioides difficile*, or IBD.

Oftentimes empiric treatment is employed without diagnostic testing with the goal of reducing symptoms and improving fat absorption. Treatment options for SIBO are summarized in ►**Table 4**. Antibiotics are commonly used and targeted at gram negative and anaerobic bacteria; they can be given as an isolated treatment course, or as part of a more continuous rotating cycle. Laxatives such as PEG can be utilized to improve intestinal motility and thereby decrease bacterial burden. There has been considerable interest in the role of probiotics in treating CF-related intestinal dysbiosis. One systematic review showed beneficial effects of probiotics on fecal calprotectin, pulmonary exacerbation risk, and quality-of-life indicators.[34] Another systematic review found limited low-quality evidence on the effects of probiotics.[35] While administration of probiotics has shown promise in reducing intestinal inflammation, there is no current recommendation on their use in CF. Finally, CFTR-modifying therapy has been shown to improve the proximal intestinal pH, promote a more favorable microbiota, decrease intestinal inflammation, and to improve weight gain.[36,37] It is hopeful that continued advances in therapies to improve CFTR function will result in amelioration in many of the GI manifestations of CF.

Abdominal Pain

Individuals with CF commonly experience abdominal pain, which can limit ability to participate in CF-related care and negatively impact quality of life. In a comparative study of patients with CF, 60% of children and 36% of adults reported chronic abdominal pain.[38] Lusman and Grand have provided an excellent review of the pathophysiology and evaluation of abdominal pain in CF.[39]

Given the prevalence of pain symptoms in CF, routine pain assessment should be part of standard care. Key to the evaluation of abdominal pain is a thorough history including the duration, location, and the character of the pain as well as associated features that either aggravate or alleviate the symptoms. History should also include pancreatic function status, as patients with PS may present with pancreatitis. Past surgical history is relevant as a history of meconium ileus (MI) or bowel resection may suggest increased risk of bowel obstruction. Physical exam is helpful to assess overall appearance of the patient, localize the pain, and detect peritoneal signs if present. ►**Table 5** outlines the differential diagnosis of abdominal pain based on location of pain, with many of these etiologies discussed in more depth elsewhere in this review. Laboratory work-up may include complete blood count, comprehensive metabolic panel, C-reactive protein, celiac screen, stool studies for infection, stool calprotectin, fecal elastase (if PS), and fecal occult blood. Abdominal imaging can be helpful in differentiating constipation (left-sided stool burden) from DIOS

Table 4 Treatment of small intestinal bacterial overgrowth

Medication	Dosing	Duration
Metronidazole	Pediatric: 20 mg/kg/d divided in 2–3 doses Adult: 500 mg three times daily	10–14 d
Rifaximin	Pediatric: >3 y: 200 mg three times daily Adult: 550 mg three times daily	10–14 d
Sulfamethoxazole/trimethoprim	TMP 12 mg/kg/d divided in 3 doses	10–14 d
Amoxicillin/clavulanate	Pediatric: 40 mg/kg/d divided in 3 doses Adult: 500 mg three times daily	10–14 d
Probiotics	Per package; no clear recommendation for a specific product	Continuous
Polyethylene glycol (PEG)	No specific dosing recommendation—goal of 2–3 soft bowel movements daily	Continuous

Table 5 Differential diagnosis of abdominal pain based on location[39]

Epigastric	GERD, gastritis, peptic ulcer disease, pancreatitis
Left upper quadrant	Gastritis, splenic infarct, pneumonia, pancreatitis
Right upper quadrant	Hepatobiliary, pancreatitis, pneumonia
Periumbilical	Functional abdominal pain, DIOS, early appendicitis, SIBO, bowel obstruction
Left lower quadrant	Constipation, ovarian, urinary tract infection
Right lower quadrant	DIOS, appendicitis, ovarian, urinary tract infection
Poorly localized	Functional abdominal pain, SIBO, celiac disease, gastroenteritis, intestinal inflammation, lactose intolerance

Abbreviations: DIOS, distal intestinal obstruction syndrome; SIBO, small intestinal bacterial overgrowth.

(right-sided partial/complete obstruction). Abdominal ultrasound is the modality of choice to evaluate for hepatobiliary pathology, intussusception, as well as renal or gynecologic disorders. Computed tomography (CT) scan may be considered for evaluation of acute abdomen. Endoscopic evaluation can be indicated for further evaluation of chronic pain unresponsive to initial management, and can aid in the diagnosis of GERD, eosinophilic esophagitis, peptic ulcer disease, *Helicobacter pylori* infection, celiac disease, SIBO, and bowel inflammation.

Treatment of pain in CF can be specific to the underlying diagnosis, or more focused on achieving symptomatic relief in the case of functional abdominal pain.

Celiac Disease

Celiac disease is a chronic autoimmune condition characterized by mucosal injury to the proximal small bowel resulting in malabsorption of nutrients. Prevalence rates in the general population range from 1:300 to 1:200. The disease is strongly associated with HLA-DQ genes DQ2 (90–95% of cases) and to a lesser extent DQ8. Multiple studies have now shown that celiac disease is more common in the CF population, despite fairly representative HLA-DQ genotypes. One study reported a prevalence of 1:83 in Scandinavian patients with CF.[40] This increased prevalence is hypothesized to be due to increased intestinal permeability resulting from intestinal inflammation. Symptoms include abdominal pain, distention, poor growth, and diarrhea, all of which can be difficult to identify as related to celiac disease in the setting of pancreatic insufficient patients with CF. Diagnosis can be made by screening with serologic testing: tissue transglutaminase-IgA (tTG-IgA) and endomysial-IgA (EMA). The gold standard for diagnosis is upper endoscopy with duodenal biopsies showing villous atrophy, crypt hyperplasia, and an increase in intra-epithelial lymphocytes. Treatment is life-long adherence to gluten-free diet.

Ileocolonic Disease

Meconium Ileus

MI is an intestinal obstruction by thick, adhesive meconium that typically involves the terminal ileum and occurs in 12.5 to 25.9% of the CF population.[41] It develops in utero, and is thus often the earliest manifestation of CF. Both CFTR and non-CFTR genetic factors are thought to contribute to its pathophysiology. MI is more common in those with more severe CFTR mutations.[41] Abnormal CFTR protein in the small intestine results in diminished $HCO3^-$ and Cl^- excretion, needed to promote water secretion.[42] Ca^{2+} ions typically associate with mucins in a tight matrix, and $HCO3^-$ chelates calcium within the bowel lumen, allowing for normal mucin expansion. With loss of CFTR function, an acidic, dehydrated luminal environment ensues where this matrix is not effectively disrupted, and the resultant compacted, dehydrated mucus and other factors combine to form abnormally sticky and tenacious meconium that occludes the intestinal lumen.[43–46] Meanwhile, non-CFTR genes appear to influence MI pathogenesis, with studies demonstrating increased concordance in monozygotic twins and increased risk of MI with a family history of the same,[47–49] while genome-wide linkage analyses have identified candidate genes that may promote or protect against this condition.[48,50]

MI may be identified prenatally. Antenatal ultrasound may identify hyperechoic masses, corresponding to inspissated meconium.[43] Most with this finding do not have MI, with the differential diagnosis being broad.[51,52] Because the finding often subsequently resolves, antenatal ultrasounds should be repeated at least every 6 weeks, with referral to perinatologist recommended for coordination of multidisciplinary care should findings persist.[43,52,53] Other sonographic findings include peritoneal calcifications, dilated bowel proximal to the obstruction, and polyhydramnios.[51,53,54]

Clinical presentation is often within 48 hours of life. In simple, or uncomplicated MI, luminal obstruction by inspissated meconium concretions anywhere from the distal ileum to proximal colon leads to proximal bowel distension, while the distal "microcolon" is small in caliber. Nonspecific signs and symptoms of lower GI tract obstruction in the neonate result, such as bilious vomiting, abdominal distension, or failure to pass meconium.[55,56] Approximately 50% of cases are complicated by segmental volvulus, atresia, ischemic necrosis, or perforation and extrusion of meconium, leading to meconium peritonitis or giant meconium pseudocyst formation.

Management should begin by prescribing nothing per os and intravenous (IV) fluids as needed, with passage of oral or nasogastric (NG) tube often done to decompress the GI tract and minimize risk for emesis and aspiration. A partial septic work-up followed by antibiotic therapy should be considered; suggested investigations include electrolytes, complete blood count, lactate, and abdominal X-rays.[53,56] Nonspecific X-ray findings may include dilated bowel loops, air-fluid levels, and an absence of air in the rectum. Abdominal calcifications may be present if a prior perforation is contained or has closed, and a "soap-bubble" appearance may be noted in the right lower quadrant due to mixing of meconium and swallowed air in the

distal ileum, also referred to as Neuhauser's sign.[56,57] If stable, a contrast enema can help differentiate MI from other etiologies of bowel obstruction, and assess for complications such as segmental volvulus or atresia. In MI, it demonstrates microcolon, and filling defects corresponding to inspissated meconium pellets in the distal intestine.[56]

Treatment of simple MI should start with an enema using a radio-opaque hyperosmolar solution under fluoroscopic guidance, for safety and to confirm that contrast has refluxed into the terminal ileum. The hyperosmolar solutions promote intraluminal fluid movement to soften and hydrate the tenacious meconium, while their administration by continuous positive pressure may also aid in disimpaction.[43,58] Following hyperosmolar enema, rapid passage of semiliquid meconium is expected, with continued passage of meconium over the following 24 to 48 hours. In addition to clinical assessment, serial abdominal radiographs may be considered at 12- to 24-hour intervals to assess for retained meconium and exclude late perforation.[43] Warm saline enemas (~10 mL/kg) with or without 4% N-acetylcysteine, or repeat hyperosmolar enemas can be considered every 12 to 24 hours during this time to aid in evacuation of residual meconium.[43,53] Contemporary studies suggest that hyperosmolar enemas are successful at disimpaction of simple MI approximately 35 to 55% of the time.[55,56,59,60]

Potential complications from nonoperative management must be considered in advance. It is important to ensure IV access and adequate hydration prior to and following the enema, as transient osmotic diarrhea and diuresis are expected thereafter, placing the newborn at risk for hypovolemic shock.[43,58] Rectal or colonic perforation rates have varied from 2.7 to 23%,[61–63] and may result from distension by infusion of contrast or subsequent osmotic fluid shifts into the intestine, or from direct mucosal injury by the contrast medium. Intestinal hypoperfusion secondary to hypovolemia and overdistension of microcolon from the enema can contribute to bowel ischemia and necrotizing enterocolitis. Strategies that may lower the risk for such complications include low-pressure infusion under fluoroscopic guidance, use of less hyperosmolar contrast agents, and avoidance of inflating balloon-tipped catheters.[43]

Surgical management is required for persistent and complicated MI, and the varied strategies employed aim for meconium disimpaction and establishment of intestinal continuity with preservation of intestinal length where possible.[43] Intraoperative disimpaction is achieved via irrigation through tube enterostomy, which may be done through an appendiceal stump after appendectomy, followed by resection of compromised bowel and a primary anastomosis or enterostomy.[64–67] Resection with anastomosis may increase risk for anastomotic leakage and morbidity compared with primary anastomosis, but results are inconclusive.[60,67,68] This needs to be weighed against the fluid, electrolyte, and nutrient losses from an enterostomy, which should be reversed as soon as possible.

Following interventions for MI, the focus shifts to optimizing nutrition, with enteral feeds established as soon as possible and attention to sodium losses. Given that the vast majority of such patients have PI, PERT should be initiated as soon as a minimal amount of oral/enteral feeds is tolerated, as diagnosis cannot be confirmed until an accurate stool sample for fecal elastase measurement can be taken when the bowel is in continuity and stools have improved consistency.[53] In addition to short-term nutritional and surgical complications, neonatal cholestasis is common.[69] In the long term, CF patients with prior MI have not been shown to differ in pulmonary function, nutritional status, or survival; however, they have higher rates of DIOS in addition to possible postsurgical complications.[70–72]

Distal Intestinal Obstruction Syndrome

DIOS is a CF-specific obstructive process beginning in the ileocecum secondary to an adherent, viscid fecal mass associated with dehydrated intestinal contents and densely packed mucus.[73] While DIOS is often considered more common in adulthood with reported prevalence of 15.8% and incidence as high as 35.5/1000 patient-years,[74,75] recent studies using consensus definitions have shown incidences of 6.2 to 7.7 per/1,000 patient-years in pediatrics, comparable to 7.8/1,000 patient-years in adults.[72,76]

The pathophysiology of DIOS is considered related to the consequences of CFTR dysfunction on intestinal fluid and electrolyte transport, fat absorption, and motility. CFTR genotypes associated with severe phenotype have been associated with DIOS,[48,74] likely via dehydration of luminal contents because of defective intestinal chloride and water secretion, defective BA secretion through CFTR-dependent mechanisms, and concurrent fluid sodium absorption through upregulation of the epithelial sodium channel.[73] DIOS has also been associated with PI, which itself is predicted by severe CFTR genotype. Poorly absorbed fat entering the ileum can activate the ileal brake, leading to a reduction in gastric emptying and intestinal transit, a plausible mechanism supported by an association between DIOS and PERT nonadherence.[76] Significantly delayed small intestinal transit has been demonstrated in CF,[77] impairing clearance of mucus plugging and viscid stool. While this was thought to be related to intestinal inflammation, CFTR deficiency in murine models leads to functional and structural changes in ileal smooth muscle that support the importance of modifier genes.[78] Perhaps unsurprisingly, a prior history of MI is considered a strong risk factor, while constipation has also been associated with DIOS, as they are all thought to share similar pathophysiology.[72,76] Likely the most significant risk factor for DIOS is having had a prior episode, with up to 20% of patients experiencing recurrence in follow-up.[72]

Concordance analysis, on the other hand, has suggested that the risk for development of DIOS is mainly due to nongenetic factors,[48] with literature supporting other factors that may contribute to secretory or motility dysfunction, including secondary effects of CF-related diseases and their management. For instance, both DIOS and constipation have been associated with hotter peak temperatures preceding presentation, suggesting that higher ambient temperatures or other causes of insensible fluid losses may promote more intestinal intraluminal dehydration in the presence of CFTR dysfunction.[79] Increased incidence of DIOS following lung transplantation may be related to perioperative fever, dehydration, pulmonary infection, narcotic analgesia, or immobilization,

or related to prior adhesions or postoperative ileus.[80,81] Still other associations with DIOS include prior laparotomy, CF-related diabetes mellitus, CF-related liver disease (CFLD), and *Pseudomonas aeruginosa* colonization.[76,81]

The diagnosis of DIOS has been aided by definitions established by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) CF Working Group, which requires the presence of abdominal pain and/or distension, as well as a fecal mass in the ileo-cecum.[72] Pain is generally periumbilical or in the right lower quadrant. The fecal mass can be palpable in the right lower quadrant, and diagnosis is often aided by abdominal X-ray or CT, which demonstrates a bubbly mass corresponding to fecalization in the distal ileum, sometimes extending proximally and/or into the right colon.[73,82] This presentation with partial obstruction defines incomplete DIOS, whereas the preceding features as well as complete intestinal obstruction, as evidenced by bilious vomiting and/or small intestinal air fluid levels on abdominal radiography, define complete DIOS.[72]

Chiefly on the differential diagnosis, constipation may similarly present with abdominal pain or distension, but is more gradual in onset, associated with weeks to months of altered bowel frequency or consistency and its symptoms are generally alleviated by conservative-dose laxatives; furthermore, abdominal imaging, if performed, shows stool accumulation in the rectum and/or colon.[72,73] One must also consider other etiologies for acute right lower quadrant pain. CF patients are at risk for intussusception, adhesions, volvulus, and fibrosing colonopathy, or less commonly, GI malignancy or Crohn's disease, each of which may generate acute obstructive symptoms.[73] Further, DIOS must be distinguished from other common sources of acute, focused abdominal pain in the general population, including infectious gastroenteritis, appendicitis and its associated complications, diverticulitis, nephrolithiasis, adnexal or testicular torsion, and ectopic pregnancy.

Goals of management are luminal rehydration and mobilization of the fecal mass from above and/or below. Medical treatment strategies remain largely empirical and vary between centers, but are reportedly effective, with surgical treatment rarely required.[72] Treatment decisions depend on factors at presentation, such as hydration status, willingness or ability to tolerate large volumes orally or enterally, and severity of obstruction. For incomplete DIOS, hydration and osmotic laxative preparations containing PEG are often effective. PEG dosing varies based on weight and tolerance; it can be given at 2 g/kg/day, with higher doses tolerable as guided by best practices cleanout regimens in preparation for colonoscopy. Alternatively, iso-osmotic PEG solutions with electrolytes can be given at 20 to 40 mL/kg/h, to a maximum of 1 L/h over 8 hours.[73,83] In complete DIOS, PEG and other laxative preparations may not be tolerated or fail. In such cases, patients are often given IV fluids, NG tube decompression, and hospitalized. Radio-opaque hypertonic contrast media (e.g., sodium meglumine diatrizoate, Gastrografin) should be considered next, orally, enterally, or by enema. The therapeutic enema administration technique is described, with similar considerations and precautions as per its use in MI.[73,84] N-acetyl cysteine may be used as an adjunct therapy in DIOS for its mucolytic effect, but it is often unnecessary, and releases hydrogen sulfide, creating a bad odor and taste that can induce nausea.[82,85] Treatment success is supported by alleviation of symptoms, clear fecal effluent, with objective improvement by abdominal imaging.[82]

Given the high rate of recurrence of DIOS, some posit that it reflects an acute presentation of a permanent condition, with intermittent exacerbations when there is excessive accumulation of intestinal contents.[73] By extension, proactive initiation of scheduled laxative regimens in affected patients should be considered to prevent further episodes, often with routine use of osmotic laxatives. However, there is no validated prophylactic strategy, and while there may be a role for N-acetyl cysteine or intestinal secretagogues such as linaclotide and lubiprostone, neither have been studied in this setting.[82] Further, prucalopride, a selective serotonin receptor agonist with prokinetic effects, was well tolerated in a small case series of pancreatic-insufficient females with a history of refractory constipation or DIOS.[86] Evaluation for modifiable contributors, including nonadherence to or under-dosing of pancreatic enzymes, or insufficient fluid and electrolyte intake, is also recommended.

Encouragingly, patients with CF suffering from recurrent DIOS have been shown to have similar pulmonary and nutritional status and survival rates compared with other CF patients in long-term follow-up.[87]

Constipation

Constipation is a significant medical issue in CF, with reported pediatric prevalence of 47% and point prevalence of 20% at routine outpatient clinic visits.[88] Constipation and DIOS in CF likely share similar underlying mechanisms, such as dysmotility and altered intestinal fluid handling; however, constipation has not been shown to be more frequent in CF than in the general population, where functional constipation predominates.[89] Supporting that DIOS and constipation in CF are interrelated obstructive phenomena, both have been independently associated with prior MI. Constipation has not been associated with CFTR genotype or PI, though it has been associated with lower fat absorption.[88] The latter contradicts previous misconceptions that increasing PERT may cause severe constipation,[90] and suggests that fat malabsorption may slow intestinal transit and contribute to constipation, as has been purported for DIOS. Finally, CFTR dysfunction is suspected to reduce intestinal fluid secretion in affected CF patients with constipation, with average fluid and fiber intake not differing from CF controls.[88]

The ESPGHAN CF Working Group Diagnostic criteria for constipation in CF require (1) abdominal pain and/or distension, or either (2a) reduced frequency or (2b) firmer consistency of bowel movements over the last few weeks or months, and (3) for symptoms to be relieved by the use of laxatives. This definition, in contrast to DIOS, highlights the more gradual onset of symptoms in constipation, and the absence of an ileocecal mass.[72] The criteria also emphasize a change in bowel movements; of note, many patients with CF with chronic constipation may report daily bowel movements.[91] While abdominal radiography has a role in differentiating DIOS and constipation in those with acute abdominal pain, it has

poor sensitivity and specificity for diagnosing constipation in children with CF, even with the application of scoring systems.[88]

In the absence of evidence-based guidelines, therapeutic principles and options for constipation in CF are similar to that for DIOS, as well as that for constipation in the general population. Initially, PEG-based laxatives are often preferred, given their established effectiveness in functional constipation and favorable safety profile. Other laxatives with osmotic and/or stimulant properties (e.g., lactulose, milk of magnesia, bisacodyl, senna) as well as enemas may be used as additional or second-line treatments.[88,92] Mineral oil should be used with caution in CF; while it does not deplete fat-soluble vitamin stores despite theoretical interference with absorption,[93] it can cause lipoid pneumonia and tissue damage if aspirated.[94] The prokinetic prucalopride, initially approved for the treatment of chronic constipation refractory to laxatives in women, has demonstrated efficacy and safety in both men and women.[95] In a case series of women with CF and a history of refractory constipation or DIOS, prucalopride provided symptomatic benefits and reduced need for additional treatments.[86]

Of the intestinal secretagogues, the chloride channel activator lubiprostone has been formally studied in a small number of adults with CF as additional therapy and decreased overall symptoms of constipation.[96] Linaclotide, a guanylate cyclase-C agonist, has yet to be studied in CF patients, perhaps because its primary effect requires downstream activation of CFTR, but was recently shown to increase intestinal fluidity and motility in CF murine models through inhibition of sodium absorption through sodium/hydrogen exchanger 3 (NHE-3).[97] Nevertheless, the reliance of both linaclotide and lubiprostone on retained CFTR function to activate intestinal chloride secretion may limit their overall efficacy in CF, and neither have been approved for pediatric use.[82]

Intussusception

While intussusception is relatively common in infancy, it is rare in older children and adults. After the first year of life symptomatic intussusception is more commonly due to a pathologic lead point. Intussusception requiring medical treatment occurs in approximately 1% of CF patients, an incidence that is 10 times more than in the general population.[98] This may be an underestimate of the true incidence, as it was established in an era when more advanced treatments for CF were limited and life expectancy was dramatically more limited. In patients with CF there is a bimodal age distribution of intussusception, with peaks in infancy and at 10 years of age. There is a male predominance of 2:1, which is similar to that of the general population.[99] There are several proposed lead points of intussusception in CF. First, the fecal concretions associated with DIOS can serve as a lead point for colo-colonic intussusceptions.[100,101] Second, patients with CF often have distended appendices, due to inspissated mucofeculant contents, which can lead to ileo-colonic intussusceptions. Finally, enteric polyps can serve as lead points.

Clinical features of intussusception include abdominal pain, vomiting, and bloody stools, although only approximately 20% of patients present with this classic triad.[99] Individuals with CF may have abdominal pain for a multitude of reasons, which can make the diagnosis challenging. The sudden onset of severe right lower quadrant pain with intussusception can mimic the presentation of DIOS. In children the onset of symptoms is often sudden and severe, while in adults the presentation is more insidious, which can lead to delayed diagnosis.[102] On physical exam there can be a palpable abdominal mass. Diagnosis is typically made via ultrasound or CT, with the classic "doughnut" or "target" sign.[103] The first-line treatment is contrast enema, which can be both diagnostic and therapeutic. Exploratory laparotomy may be necessary if enema fails or intussusception is persistent, but when associated with CF, surgical intervention is often not necessary.[104] Given that intussusceptions in patients with CF are often related to inspissated secretions, management approaches may include an aggressive bowel regimen after the intussusception has been reduced. Adherence to PERT may help to prevent reoccurrence. Intussusception is a relatively rare but important cause of abdominal pain in individuals with CF.

Appendicitis and Appendiceal Changes

Appendiceal disease in CF represents a spectrum, from simple mucoid distension to acute appendicitis, with or without complications. Mucoid distension of the appendix with thick, inspissated luminal contents is well described in CF.[105] This finding is often incidental, with CT and ultrasound studies in asymptomatic CF pediatric and adult patients demonstrating appendiceal enlargement, with mean diameters of 10.6 and 8.3 mm, respectively, significantly greater than those of the general population.[106,107] In some cases, however, mucoid distension has been associated with intermittent right lower quadrant pain or intussusception that has resolved following appendectomy, with the enlarged appendix presumably acting as a lead point.[105]

Interestingly, the incidence of acute appendicitis in CF is reportedly lower than that of the general population. Possible explanations for this include recurrent or chronic antibiotic use or higher rate of incidental appendectomies in CF, and a protective effect of retained mucus, maintaining luminal distension and thereby limiting luminal occlusion and acute inflammation.[108,109] Historically, those who develop acute appendicitis have a high rate of complications like appendiceal perforation and abscess formation, which has been attributed to delayed diagnosis. In some cases, delayed presentation was noted, speculated due to underlying chronic abdominal pain or less impressive symptoms possibly related to concurrent long-term antibiotics. In other cases, consideration of other diagnoses at presentation, particularly DIOS, was a factor.[105,109] Clinical diagnosis can be supported with laboratory testing and imaging, with the caveat that appendiceal enlargement is not a valid criterion for acute appendicitis in CF, especially with associated hyperattenuating appendiceal content. Periappendiceal fluid and fat stranding, though, are uncommon in asymptomatic CF patients and would support appendicitis.[107] Medical and surgical management of appendicitis should proceed as per general recommendations.

Clostridium difficile Infection

Clostridium difficile is a gram-positive organism that is responsible for potentially life-threatening colitis. Risk factors for development of *C. difficile* infection include antibiotic use, hospitalization, and use of proton pump inhibitors, all of which are common components of CF care. Despite this, *C. difficile* associated colitis is uncommon in individuals with CF. It is important to note that asymptomatic *C. difficile* carriage rates of up to 47% have been described in CF patients; however, 77% of the strains identified were nontoxigenic.[110] When patients with CF do develop *C .difficile* associated colitis, they often do not present with the classic symptom of diarrhea. Patients more commonly present with abdominal pain and distention, rapidly progressing to toxic megacolon.[111,112] *C. difficile* colitis in CF can mimic a myriad of other conditions including DIOS, appendicitis, pancreatitis, constipation, intussusception, and IBD, among others. Timely diagnosis requires abdominal CT scan which reveals colonic distention, colonic wall thickening, fat stranding, and ascites.[112] Blood work may show marked leukocytosis and hypoalbuminemia, and stool testing is positive for *C. difficile* toxin. Therapy follows the standard clinical practice guidelines for *C. difficile* infection and includes oral or IV metronidazole for mild to moderate cases and oral vancomycin for severe cases.[113] In short, despite the increased carriage rate, and relatively low incidence of *C. difficile* associated disease in the CF population, a high index of clinical suspicion for this condition must be maintained given the high rate of morbidity.

Fibrosing Colonopathy

Fibrosing colonopathy was first described by Smyth et al in 1994 in five children who had developed submucosal fibrosis and stricturing of the ascending colon, all of whom had received high-dose pancreatic enzymes.[114] Additional cases were then reported in the literature, primarily in children age 2 to 7 years old and were often associated with very high PERT dosing, over 50,000 lipase units per kilogram per day.[115–117] Other reported risk factors for fibrosing colonopathy include the use of histamine H_2-receptor blockers, corticosteroids, or recombinant human DNase. These case reports led to the recommendation that PERT dosing be limited to 2,500 units of lipase per kilogram/meal or 10,000 units/kg/day and high-strength formulations were promptly removed from the market.[118] Definitive causation for fibrosing colonopathy has not been established however, and rare cases have been reported in patients without any enzyme exposure.[119] Furthermore, it is possible that some patients with milder symptoms are not diagnosed, as abdominal pain is common in patients with CF, and screening with ultrasound and colonoscopy are not routine practice.[115] With this in mind, fibrosing colonopathy remains a relevant consideration in patients presenting with symptoms of intestinal obstruction.

Clinical symptoms of fibrosing colonopathy can include abdominal pain, intestinal obstruction, constipation, diarrhea, and hematochezia.[120] Ultrasound may show reduced peristalsis, colonic wall thickening >2 mm, and ascites. Magnetic resonance imaging (MRI) has also been shown to be a useful imaging modality in the evaluation of CF patients with fibrosing colonoopathy.[121] Diagnosis is made via colonoscopy which shows edematous, stiff, or ulcerated mucosa affecting primarily the proximal colon with relative rectal sparing.[114] Strictures are often seen, along with colonic shortening and loss of haustrations. Histopathologic features include a thick band of submucosal fibrosis, eosinophilia, cryptitis, and disruption of the muscularis mucosa. Management of strictures can be challenging, requiring balloon dilatation and surgical intervention, although noninvasive treatment of an adult patient with corticosteroids and antibiotic therapy has been described.[122]

Colorectal Cancer

Despite similar overall cancer risk in CF compared with the general population, there is a 3.5 to 6.5-fold increased risk of digestive tract cancers in CF.[123,124] While increased incidence has also been demonstrated for esophagogastric, small intestinal, hepatobiliary, and gallbladder malignancies in CF, such patients are at increased risk for colorectal cancer (CRC), the predominant digestive tract cancer in both CF and the general population.[123] Furthermore, patients with CF have an increased incidence of bowel cancer throughout the lifespan, with $>70\%$ of cases diagnosed before 50 years of age, and a reported mean age of diagnosis of CRC of 40 years.[123] Thus, the concern for CRC, in particular, has become significant in the CF population, more so given that the median age of survival continues to increase in many countries.[125]

There are several reasons to explain the increased risk of CRC in CF. There are several known associations with CRC in the general population that disproportionately affect the CF population, such as a high-fat diet, low amounts of vigorous physical activity, and diabetes mellitus.[126,127] Impaired CFTR function and repeated courses of antibiotics are associated with intestinal stasis, chronic gut inflammation, and malabsorption of nutrients, some of which may be protective against colonic carcinogenesis.[128] Meanwhile, a growing body of literature indicates that intestinal microbial dysbiosis may play a role in tumorigenesis, by damaging DNA, activating oncogenic signaling pathways, producing mutagenic metabolites, suppressing antitumor immunity, and promoting inflammation, which may in turn induce the expression of microorganisms with genotoxic capabilities.[129,130] In support of this, bowel cancer risk is particularly high among patients classified as having severe genotype or a history of DIOS.[123] Further, patients with CF are at significantly increased risk for CRC after lung transplantation relative to nontransplanted CF patients and non-CF recipients, suggesting that some of these processes may be exacerbated by immunosuppressants.[123,128]

However, chronic intestinal inflammation alone does not account for the increased risk for intestinal cancer, with a recent study suggesting the role of *Cftr* as a tumor suppressor gene in intestinal carcinogenesis. More specifically, the loss of *Cftr* gene alone was found to induce colonic and small intestinal tumor formation in intestinal-specific *Cftr* knockout mice with $>60\%$ penetrance and altered gene expression in tumors, while low CFTR expression in non-CF patients with early stage CRC was independently associated with decreased disease-free survival.[131] Unsurprisingly, CF colorectal screening and

surveillance programs have demonstrated an accelerated rate of polyp development and growth, with high detection of adenomas, including advanced polyps, on surveillance and re-screening colonoscopies at relatively short intervals.[132] Subsequently, CF has been recognized as a colon cancer syndrome, in which a posited model of tumorigenesis involves CFTR dysfunction, chronic inflammation, dysregulation of the immune response and intestinal stem cells, with ultimate activation of β-catenin.[131,133]

CF-specific CRC screening recommendations were recently developed in response to these concerns.[133] These proposals emphasize collaboration between patients, CF care providers, and endoscopists in decision making and execution of screening and surveillance, with careful consideration of risks and benefits for each patient given their underlying comorbidities and quality of life, and acknowledgment that an adequate bowel preparation is difficult to achieve in patients with CF who require intensive regimens for optimal examination. Supported by modeling estimates, the CF Foundation recommends CRC screening beginning at age 40 in CF and at 30 years of age and older within 2 years of transplantation in solid organ recipients, with re-screening every 5 years.[133] Surveillance for patients with previously identified adenomatous polyps should be within 3 years or less depending on most recent endoscopic findings, given the high rates of recurrent adenomas and advanced polyps.[132,133] Colonoscopy is currently the preferred screening tool, given that it allows for simultaneous detection and removal of polyps, the lack of evidence for other screening modalities in the high-risk CF population, and the relatively higher reported incidence of right-sided colon polyps in CF that would not be detected by sigmoidoscopy.[123,133] Further research will be required to re-evaluate these recommendations.

Hepatobiliary Disease

CF-Related Liver Disease

In the liver, CFTR is not found in hepatocytes, rather it is localized to the apical surface of the bile duct epithelium.[134] While the pathophysiology of CFLD is not clearly elucidated, it has been thought that the abnormal biliary chloride transport leads to inspissated bile in the small bile ducts which results in obstruction, inflammation, and ultimately fibrosis.[135,136] Additionally, it is proposed that the alterations of the intestinal microbiome seen in CF lead to cytokine activation of the hepatic stellate cells, further contributing to liver injury.[136] Recent studies have identified obliterative portal venopathy and noncirrhotic portal hypertension as the underlying pathophysiology for some individuals with CFLD.[137–139] A retrospective analysis of explants from children with CF and portal hypertension identified nodular regenerative hyperplasia in 94%, as well as decreased portal vein diameters.[139] Biliary obstruction with inspissated luminal contents was not seen. These observations suggest that portal vascular compromise may contribute to the complex and likely multifactorial pathogenesis liver disease seen in CF.

CFLD is a relatively nonspecific term and includes a wide range of hepatobiliary involvement. A proposed classification of CFLD is outlined in ►**Table 6**.[140] Most individuals with CF will have some hepatic involvement, but progression to clinically significant disease such as cirrhosis is rare. Liver disease is most commonly diagnosed in the pediatric population, with the highest incidence in the first decade of life, and 90% is diagnosed prior to 18 years of age.[141,142] While historically CFLD has been thought of as a disease process primarily affecting the pediatric population, newer data suggest that adult-onset liver disease may be more prevalent

Table 6 Proposed phenotypic classification of CFLD[140]

1. Multilobular cirrhosis established by imaging, biopsy, direct visualization, or elastography a. Without portal hypertension b. With portal hypertension c. With synthetic liver failure
2. Liver involvement without cirrhosis evidenced by one or more of the following: a. Abnormal ALT (1.5 × upper limit of normal) i. Persistent (2–3 abnormal values over more than 6 months) ii. Intermittent b. Abnormal GGT i. Persistent (2–3 abnormal values over more than 6 months) ii. Intermittent c. Ultrasound imaging abnormalities i. Heterogeneous increased echogenicity pattern ii. Homogeneous increased echogenicity pattern d. Hepatic steatosis (on biopsy) e. Hepatic fibrosis (on biopsy) f. Hepatomegaly g. Portal hypertension i. Hypersplenism ii. Esophageal or gastric varices
3. No evidence of liver involvement (normal examination, imaging, ALT, GGT)

Abbreviations: ALT, alanine aminotransferase; CFLD, cystic fibrosis-related liver disease; GGT, gamma-glutamyltransferase.

Table 7 Risk factors for development of severe CFLD[141]

Young age (median age: 10 y)
Pancreatic insufficiency (99%)
Patient who had 2 severe, loss-of-function CFTR mutations (92%)
Male gender (63% of patients are male, 37% female)
Normal or mildly elevated liver enzyme levels with an APRi >0.264 and FIB-4 >0.358
More severe abnormalities in blood work markers of disease severity in patients with varices and those requiring transplantation (i.e., platelets, albumin, INR, and total bilirubin)

Abbreviations: CFLD, cystic fibrosis-related liver disease; CFTR, cystic fibrosis transmembrane conductance regulator; INR, international normalized ratio.
Note: APRi (aspartate aminotransferase-to-platelet ratio index): (AST [IU/L]/ULN AST $\times$ 100/platelet count [10^9/L]).
FIB-4 (Fibrosis-4): (Age [y] $\times$ AST [IU/L]/platelet count [10^9/L] $\times$ square root ALT [IU/l]).

than previously described, with a second peak occurring in the mid-30s.[143] Risk factors for developing severe CFLD were identified in a worldwide multicenter study and are summarized in ►**Table 7**.[141]

Elevation of liver function tests can be seen in up to 50% of young children with CF and often normalizes by age 2 to 3.[144,145] Additionally, up to 41% of children will have had abnormalities in liver function tests at some point by the age of 12, and 30% of adults will have persistently elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by 20 years of age.[146] Despite this, longitudinal studies have found that only 20 to 30% of individuals with CF develop focal biliary cirrhosis, and 5 to 10% develop multinodular cirrhosis.[146,147] No specific CFTR genotypes have currently been identified to be at increased risk for the development of liver disease; however, individuals who also have α-1 antitrypsin deficiency have a sevenfold increased risk for the development of CF-associated cirrhosis.[148] Cirrhosis in individuals with CF is generally not associated with synthetic liver dysfunction, however, can lead to significant morbidity, mainly related to variceal bleeding. Liver disease is the third leading cause of death for individuals with CF, accounting for 2.5% of overall mortality.[147,149]

Paramount in the surveillance for CFLD is a careful physical examination for hepatomegaly and/or splenomegaly, as serum biomarkers for liver disease can remain normal despite advanced disease. It is recommended that AST, ALT, gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and platelet count be assessed annually. If serum biochemistries are abnormal ($\geq 2 \times$ ULN) and physical exam does not reveal hepatosplenomegaly, it is suggested to repeat blood work in 6 months. If abnormalities persist, or hepatosplenomegaly is detected on exam, further investigation with complete abdominal ultrasound with Doppler flow study is recommended. Ultrasound may show heterogeneous echogenicity, irregular margins, or nodularity as well as evidence of portal hypertension or biliary abnormalities. It is important to rule out non-CF causes of liver disease such as α-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, celiac disease, viral hepatitis, hemochromatosis, as well as drug-induced liver injury (DILI).[144] Other useful imaging modalities include transient elastography (TE, FibroScan), a test which measures the velocity of sound waves passing through the liver and then coverts this measurement into a liver stiffness measurement. TE has been shown to be a noninvasive, reliable tool that, when used in combination with indices such as the AST-to-platelet ratio index (APRi), has good diagnostic accuracy in differentiating mild–moderate fibrosis from advanced fibrosis in CF.[150] Liver biopsy is considered to be the gold standard for diagnosis of cirrhosis, but it is an invasive test, and given the patchy nature of multilobular disease in CF, it can result in inadequate staging of disease. Given the risks and limitations of liver biopsy in patients with CF, it is not routinely recommended as findings rarely affect clinical management.[136] Biopsy is reserved for cases in which there is diagnostic uncertainty, and if liver biopsy is performed, dual pass sampling is recommended. Patients that have findings concerning for CFLD should be referred for further evaluation and management by a gastroenterologist or hepatologist.

Management of CFLD is currently quite limited. Ursodeoxycholic acid (UDCA) is the only pharmacologic agent available, improves biliary secretion, and should thereby delay progression of disease. It has been shown to improve biochemical parameters; however, there is no clear evidence that it prevents disease progression. A recent retrospective analysis of 3,328 CF patients with PI found that use of UDCA early in the disease process did not change the incidence of severe CFLD.[151] Whenever possible hepatotoxic prescription drugs should be avoided and patients should be advised to avoid alcohol as well as nonsteroidal anti-inflammatory drugs due to increased risk of bleeding. Careful attention to nutrition and fat-soluble vitamin supplementation is necessary due to increased incidence of malnutrition. Nutritional needs are further increased in CF cirrhosis due to decreased BA pool, which compounds fat malabsorption, in addition to increased catabolic state, and frequent anorexia. Patients with cirrhosis and signs of portal hypertension should be counseled on the signs of variceal bleeding, and primary prophylaxis with endoscopic banding may be considered. Patients with recurrent bleeding can benefit from transjugular intrahepatic portosystemic shunt (TIPS) procedure or surgical portal systemic shunting. While synthetic liver dysfunction is rare, patients with CFLD may require liver transplantation. With this in mind individuals with CFLD should be fully immunized. Indications for liver transplantation include evidence of cirrhosis that is complicated by ascites, encephalopathy, coagulopathy unresponsive to vitamin K, hypoalbuminemia, hepatopulmonary, and portopulmonary syndromes, severe quality-of-life issues, and deteriorating lung function.[144,152] There remains a need for further research in this area with regards to identifying early markers of liver disease as well as potential therapies.

Neonatal Cholestasis

Cholestasis is the earliest and most common neonatal manifestation of liver involvement in CF, often recognized by

elevated serum conjugated/direct bilirubin level > 1.0 mg/dL. Its incidence among infants diagnosed with CF within a statewide newborn screening program is considered low at 5.7%, but is approximately 140-fold greater than that in the general population of term infants.[69,153] MI and complicated MI are significant risk factors for the development of cholestasis, with incidence greater than 25% in infants with MI.[69]

In addition to jaundice, other features of CF-associated neonatal cholestasis are often nonspecific. Affected neonates may have acholic stools, hepatomegaly, splenomegaly, hypoalbuminemia and/or elevated serum transaminases, ALP, and/or GGT.[154,155]

Pathogenesis of neonatal cholestasis in CF is not well defined, but the predominant mechanism supported is related to intraluminal bile stasis. CFTR is expressed in cholangiocytes, which contribute up to 40% of bile. Defective cholangiocyte Cl^- and $HCO3^-$ transport results in decreased bile flow and abnormally thickened secretions, leading to bile duct plugging focally to multifocally anywhere within the portal system.[46] Autopsy and biopsy specimens may demonstrate excess, inspissated mucus in the biliary tract with plugging, or a pattern of focal biliary cirrhosis.[154,156] In most cases, portal tract expansion and ductular proliferation are noted, in keeping with extrahepatic biliary obstruction and at times indistinguishable from biliary atresia.[155–158]

In infants with CF and cholestasis, a targeted evaluation with consideration of other etiologies is still recommended, often in concert with pediatric gastroenterologist/hepatologist. Biliary atresia, in particular, must be considered in the presence of acholic stools. Conversely, term neonates with unexplained cholestasis should be evaluated for CF.[153,157]

In a retrospective cohort study, cholestasis in CF was diagnosed within the first 2 months, with total serum bilirubin level peaking within the first 3 months of life in all cases, with diagnosis and peak bilirubin occurring significantly earlier in those with a history of MI.[69] While cholestasis should generally resolve within the first year of life with no sequelae, in some cases it may persist up to 5 years, and reported cases of liver failure and death are noted.[69,154,155]

Management of cholestasis is considered mostly supportive, with close monitoring of growth and fat-soluble vitamin status warranted. UDCA treatment has been described and may benefit patients with neonatal cholestasis, but there is insufficient evidence to justify its routine use in CF.[69,154,155]

Hepatic Steatosis

Hepatic steatosis is a common hepatic finding in CF at any age, with reported prevalence of 23 to 70%, although no specific neonatal data are available.[149,159] It is often associated with malnutrition or deficiency of a trace element or mineral (choline, carnitine, essential fatty acids); however, this is not always the case, so could also be secondary to CFTR dysfunction.[149,160,161] It typically presents as hepatomegaly with soft and smooth liver edge to palpation, without signs of chronic liver disease or portal hypertension, possibly in association with elevated transaminases.[162,163] On ultrasound, it is characterized by homogenous hyperechogenicity of the hepatic parenchyma, but steatosis and fibrosis are best distinguished by histology. The differential diagnosis for hepatic steatosis in the neonate includes infections, genetic/metabolic disorders, parenteral nutrition, and medications. In CF, hepatic steatosis is generally considered to be benign with no proven association with cirrhosis; however, it is not known whether such progression is possible, as has been noted in nonalcoholic fatty liver disease. Management centers on nutritional rehabilitation where appropriate, which may lead to resolution of steatosis.

Gallbladder and Biliary Tract Involvement

Gallbladder abnormalities have been observed in 25 to 50% of CF patients, most of which are incidentally found on imaging.[162] Of particular importance in the neonate is the finding of a microgallbladder. While it is benign and does not require treatment, it can mimic a similar finding in biliary atresia, which raises diagnostic uncertainty if there is concurrent cholestasis.

Gallstones are more frequent in pediatric CF populations, with reported pediatric incidence of 3 to 25%.[162] It is unclear why those with CF are predisposed to gallstone formation, but gallstones are more likely to be pigmented and are unlikely to dissolve after UDCA treatment.[164,165] Pathogenesis is likely multifactorial, possibly related to cholestasis, gallbladder hypokinesia, increased calcium–mucin binding, lower biliary pH, and/or increased enterohepatic circulation leading to hyperbilirubinbilia.[166,167] Recommended treatment of symptomatic cholelithiasis in CF is generally similar to that of the general population.

Cholangiopathy has been increasingly recognized in CF, with associated changes considered to be a form of liver involvement in CFLD.[162] Large duct abnormalities reportedly include biliary strictures and segmental dilation, similar to those in sclerosing cholangitis, diffuse narrowing or focal strictures of the common bile duct, and calculi within the intra- and extrahepatic bile ducts.[168] Large-duct cholangiopathy in CF is thought to share similar pathophysiology with the histologic changes within intrahepatic bile ductules that are the basis for the development of focal biliary cirrhosis.[169] Several theories exist as to the role of CFTR dysfunction in cholangiopathy, including reduced bicarbonate secretion that may otherwise protect cholangiocytes from BA injury and increased vulnerability of the biliary epithelium to intestinal and other bacterial endotoxins.[170,171] As is the case with sclerosing cholangitis, biliary strictures likely result from ongoing inflammation and fibrosis, which can be complicated by calculi and accumulation of thick, inspissated mucus and associated local infection.[169]

The true prevalence and clinical significance of CF cholangiopathy is unknown, given that in adults it may be present in up to 50% of asymptomatic patients without other evidence of liver disease. However, there is a high likelihood of large duct disease in patients with clinically apparent liver disease, with speculation that this subset may be at increased risk for strictures.[172] Complications are rare but include obstructive jaundice with cholestasis and its associated consequences, bacterial cholangitis, and cholangiocarcinoma.[169,173,174] Management is only warranted for symptomatic biliary disease.

Supportive care may involve medical management of pruritus and supplementation of micronutrients, particularly fat-soluble vitamins, as needed.[169] UDCA may have a theoretical choleretic effect and is safe and well tolerated, but is not clearly supported by available evidence.[175] Symptomatic strictures, refractory intrahepatic lithiasis, and infections may require antibiotics, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic drainage, or surgical treatment.[173,174,176]

Pancreatic Disease

Pancreatic Insufficiency

PI has been one of the hallmark features of CF since the disease was first described. In the CF pancreas, initially proteins are secreted in normal amounts, but the volume and alkalinity of the ductal fluid are diminished due to impaired chloride secretion. These concentrated pancreatic proteins can precipitate, thereby obstructing the small ducts and leading to destruction and atrophy of the acini and ducts.[177]

More than 85% of the CF population rely on supplemental PERT to achieve adequate absorption of nutrients.[177] There is a strong correlation between CF genotype and phenotype with regard to the exocrine pancreas; individuals with two severe CFTR mutations (class I–IV) tend to be PI at birth, while those with two mild mutations (IV–V) or one severe and one mild mutation may be PS. Individuals with CF and milder mutations may become PI as time goes on and require monitoring for signs of malabsorption. CFTR2.org is a resource for patients and providers that provides information about known about specific genetic variants including the likelihood of developing PI. PS individuals may develop pancreatitis, and this should be considered in the differential diagnosis for abdominal pain.

Clinical symptoms of PI are related to malabsorption and include weight loss, gas, bloating, dyspepsia, and loose foul-smelling and greasy stools (steatorrhea).[178] The CF Foundation recommends that all individuals with CF have pancreatic status confirmed with laboratory testing upon diagnosis.[179] Fecal elastase-1 (FE-1) is the most commonly used testing modality with a sensitivity of 98 to 100% and a specificity of 93 to 100%.[180] This test can be performed on a randomly formed stool sample, does not require special handling, and is not affected by taking pancreatic enzyme supplementation. It can be falsely positive if performed on a watery stool sample, or in individuals with severe malnutrition. Individuals with clinical evidence of PI, or known to have two severe disease-causing CFTR mutations, can be started on PERT ahead of results.[178]

PI patients require lifelong pancreatic enzyme supplementation with every meal and snack to prevent malnutrition and the associated complications of stunting of stature, vitamin deficiency, and more rapid decline in pulmonary function. Pancreatic enzymes are rapidly degraded in an acidic environment, therefore most of the commercially available products are acid-resistant microencapsulated beads that dissolve at pH of 5 to 5.5.[181] Individuals with CF have decreased bicarbonate secretion in the duodenum which can lead to a delay in reaching this pH, and thus as a result PERT may not become active until reaching the more distal small bowel.[77] Patients with malabsorption despite adequate PERT dosing may benefit from a trial of a proton pump inhibitor to maximize absorption.[182] PERT dosing is typically based on body weight or fat content of meals. The CF Foundation recommends 500 to 2,500 units of lipase/kg/meal and half of that dose with snacks for weight-based dosing and dosing by fat content of meals is 500 to 4,000 units of lipase/g of fat.[179] Fibrosing colonopathy, mentioned elsewhere in this article, has been reported in individuals who were exposed to large doses of PERT, consequently, the total daily dosing of PERT is recommended to be less than 10,000 lipase units/kg/day.[115] Fat soluble vitamin supplementation (A, D, E, and K) is also necessary for PI individuals and should start upon diagnosis and be given with PERT. Serum levels of vitamins A, E, D, and PT/INR should be performed annually and reassessed 3 to 6 months after a change in dosing.[183] CFTR modulator therapy shows promise in ameliorating pancreatic function, especially if initiated in younger patients.[184]

Conflicts of Interest
None to declare.

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