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GASTROINTESTINAL MANIFESTATION OF CYSTIC FIBROSIS IN CHILDREN: AN OVER-VIEW

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ABSTRACT

In the past, cystic fibrosis was considered a lung disease, but gastrointestinal manifestations are becoming increasingly important with improved life survival. Inspissation of secretions into the hollow structures of the gastrointestinal tract due to a CFTR defect is the usual pathophysiology. In this review, we aim to provide an up-to-date overview of the most important aspects of GI and liver disease in CF.

KEYWORDS: Gastrointestinal manifestation, Cystic fibrosis, Children.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive multisystem disease caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located in chromosome 7 and essential for the regulation of chloride and sodium transport in epithelial cells.[1] It is highly expressed on the epithelial cells of the respiratory, gastrointestinal, and reproductive tracts. It is hypothesized that a lack of CFTR function results in altered mucus secretion in the luminal environment, causing inflammation, obstruction, and dysfunction of various organs.[2,3] To have cystic fibrosis, an individual must inherit a defective copy of the CF gene.

Respiratory disease remains the leading cause of morbidity and mortality in patients with CF but addressing the GI complications that often arise early in life, before pulmonary manifestations are evident. With the improvement in life expectancy, gastrointestinal comorbidities are of increasing clinical and scientific interest. Up to 85% of patients with CF experience GI symptoms, so addressing the GI aspects of this disease is of paramount importance. Timely detection and intervention are critical to optimize the overall health and well-being of patients. This article provides an overview of the GI manifestation of CF and the management of the disease.

Gastrointestinal consequence of cftr dysfunction

Gastroesophageal Reflux Disease (GERD):

GER was first described in 1975 by Feigelson et al. in patients with cystic fibrosis (CF).[4] GERD is common in CF patients; based on various studies, its prevalence has increased since childhood and is often implicated as playing a role in the pathogenesis of CF lung disease.

An increased frequency of transient inappropriate relaxation of the lower esophageal sphincter and delayed gastric emptying play important roles in the development of GER.[5] In addition, increased abdominal pressure due to chronic cough, higher gastroesophageal pressure gradient, low gastric PH, and supine position during chest physiotherapy are also risk factors for GERD in CF.

GERD due to microaspiration, reflux bronchospasm, or increased airway inflammation.[6] is thought to contribute to pulmonary disease in CF based on an association between GERD and pulmonary disease observed in multiple studies. Impact of GERD on lung function in CF patients not yet clearly established. In a study enrolling pediatric patients with CF, GER was correlated with decreased lung function and early infection with Pseudomonas aeruginosa and Staphylococcus aureus.[7]

The clinical manifestation and diagnostic method of GERD in CF patients are similar to those in non-CF individuals. Vomiting and posseting are the most common clinical manifestations of GERD in patients with CF, followed by parent-perceived irritability in the infant. GERD can be asymptomatic or present as chest pain, dysphasia, odynophagia, food impaction and/or cough.

Diagnosis is generally made based on clinical symptoms and response to PPIs (older children). Esophageal monitoring PH probe, multi-channel intraluminal

impedance measurement [MII]) may be useful to aid in diagnosis. Endoscopy and biopsy of the upper gastrointestinal tract are recommended when alarming symptoms are present, or complications are detected.

Management

The principle of management of GERD in CF is the same as that of GERD in non-CF patients.

- **Diet and Lifestyle adjustments:** Eating smaller, more frequent meals is recommended. Some patients may benefit from avoiding, restricting, and/or limiting foods associated with reflux, such as: E.g. acidic foods, spicy foods, caffeine and chocolate. A high-fat diet can cause GERD through delayed gastric emptying.Elevating the head of the bed can be beneficial. Chest physiotherapy should be done before meal.
- **Drug:** Acid suppression with PPI is an appropriate treatment strategy for patients with CF and GERD for 4-8 weeks. In clinical practice, patients requiring long-term PPI treatment; Careful selection of therapeutic management is required. The patient should be monitored for response and potential side effects including pulmonary exacerbations, vitamin B12 deficiency, hypomagnesemia, and bone health.
- **Surgery:** Surgical management of Nissen fundoplication in patients with GERD complications, including esophageal stricture, failure to thrive, resistance to medical treatment, or uncontrolled respiratory symptoms that appear to be related to GERD.

Meconium ileus (MI)

Meconium ileus is an intestinal obstruction due to thick adherent meconium that typically affects the terminal ileum and occurs in 12.5% to 25.9% of newborns with CF.[9]

Abnormal CFTR protein in the small intestine causes decreased HCO3- and Cl- excretion, which is required to promote water secretion.[10] Hence, dehydration and an acidic luminal environment ensue; thick, viscous mucus and other factors combine to form sticky and viscous meconium, which occludes the intestinal lumen.[2,3,11]

Patients with MI generally present with abdominal distension and failure to pass meconium with or without vomiting within the first three days of life. MI is two types:

- Complex / Complicated MI: Complicated MI with intestinal pathology including intestinal perforation, meconium peritonitis, atresia or volvulus. Prenatal perforation can cause meconium peritonitis and intra-abdominal calcification. Up to 40% of MI in neonates with CF is complex.[12]
- Simple MI: If there is no associated gastrointestinal pathology, it is simple MI.

Diagnosis

An abdominal x-ray should be taken to see-

- Dilated bowel loops with or without air fluid levels.
- A ground glass appearance in the right lower quadrant due to inspissated meconium in the ileocecal area.
- May show the classic soap bubble sign in the distal small intestine.

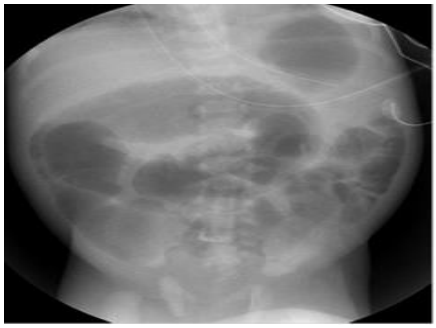


Figure 1: Plain X ray shows dilated loops of bowel, indicating intestinal obstruction. The 9hour –old male infant had a known prenatal diagnosis of intestinal obstruction. (Courtesy of Michael Callahan, MD).

Contrast X-ray: is performed when there is no evidence of a perforation, and the diagnosis is confirmed. Typically, small microcolon and meconium pellets are seen in the terminal ileum, and the ileum proximal to the obstruction is dilated.

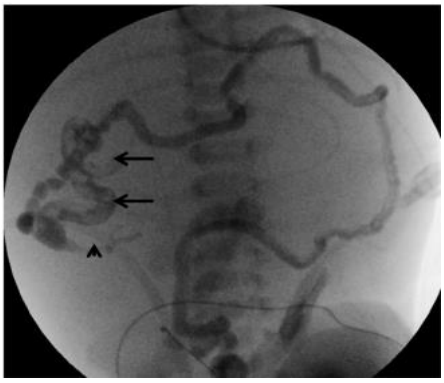


Figure 2: Barium enema in a 2-year-old boy diagnosed as having cystic fibrosis showing filling defects of the terminal ileum (arrows) distal to the appendix (arrowhead) with prominent microcolon diagnostic of meconium ileus.

All infants with MI should be evaluated for CF.

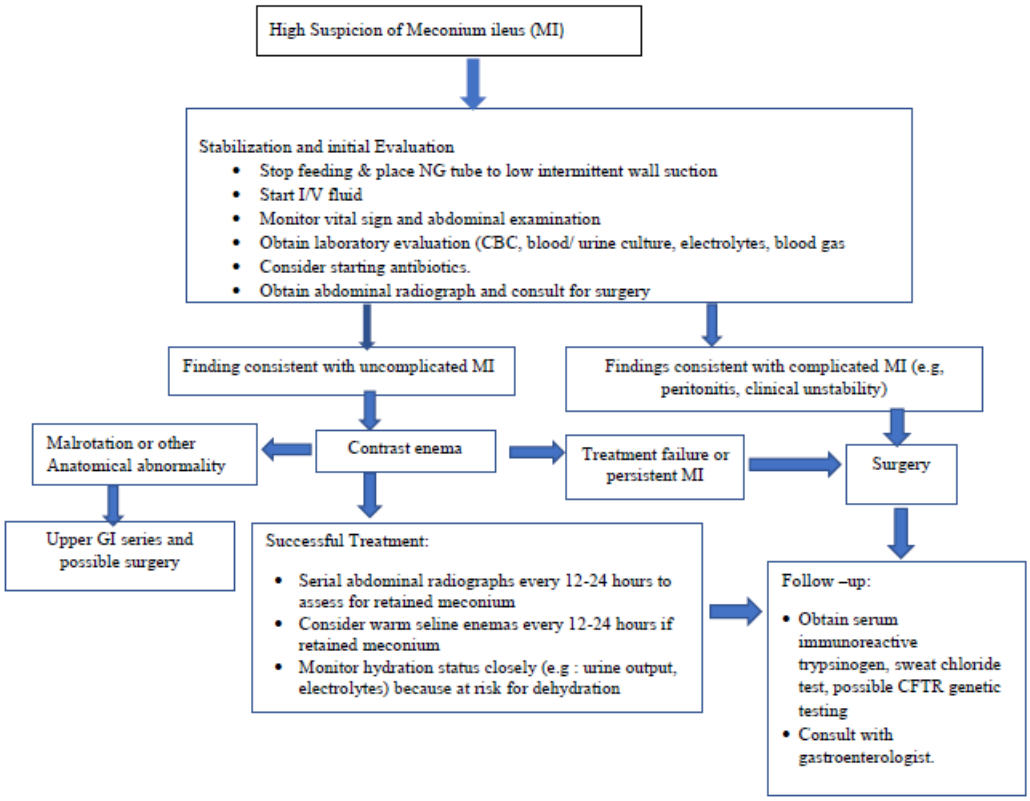
Management

Initial treatment include- nil per os status, adequate hydration, evaluation of infection and placement of nasogastric tube.

Contrast enema: The stable infant is provided with a hypertonic enema to lavage the meconium plug. This procedure can be repeated several times to avoid surgery.

Surgery: required for complicated MI.

The treatment algorithm for MI is shown in Figure 3



Distal intestinal obstruction syndrome

DIOS is unique in cystic fibrosis, formerly known as meconium ileus equivalent. DIOS is a chronic, recurrent form of partial intestinal obstruction that often occurs in older adolescence with a prevalence of 10% to 15%.[13]

DIOS results from the accumulation of viscid fecal material in the intestinal lumen in combination with sticky, mucous intestinal contents adhering to the intestinal wall of the terminal ileum and cecum, which is strongly connected to the crypts and villi and difficult to remove. Intestinal inflammation may be another etiological factor that has been clearly demonstrated in the mouse model.[14] The exact cause of DIOS is unknown, but several precipitating factors of DIOS have been identified, including - abnormal properties of the intestinal mucus, dehydration of the intraluminal contents, slow intestinal transit, poor compliance with pancreatic enzyme therapy and a prior h/o of MI.[15]

The ESPGHAN CF and Pancreatic Disease Working Group has defined Complete DIOS as the combination of

- Complete intestinal obstruction; as evidence by bilious vomiting and fluid levels in the X-ray of the abdomen
- A fecal mass in the ileocecum & abdominal pain on distension

Incomplete or impending DIOS is defined as-

- Short H/O of abdominal pain and/or distension
- A fecal mass in ileocecum but without sign of complete obstruction.[16]

Patients with DIOS typically have intermittent episodes of pain that may or may not be localized in the lower Rt quadrant. A nontender or mildly tender, palpable mass is felt in the lower Rt quadrant. Patients with incomplete bowel obstruction due to DIOS usually pass stool of normal consistency and frequency. Some patients suffer from intractable chronic pain that is difficult to manage. In rare cases, complete intestinal obstruction can occur.

DIOS should not be confused with simple constipation, which is also common in CF patients with pancreatic insufficiency. In constipation, the mass in the lower Rt quadrant is usually not palpable and the stool pattern and consistency is abnormal and physical examination shows the rectum is full of stool.

DIOS can be diagnosed in CF patients with the classic triad:

- Abdominal pain and distension,
- An RLQ mass
- A plain abdominal x-ray shows accumulation of stool in the distal small bowel and right colon, with little or no stool distal to this obstruction. The stool is described as bubbly or granular in appearance, air fluid levels and small bowel dilatation may be present. Other imaging methods also support the diagnosis. CT is commonly used to differentiate DIOS from surgical causes of abdominal pain, including appendicitis. DIOS is characterized on CT scan by proximal small bowel dilatation and inspissated fecal matter in the distal ileum.

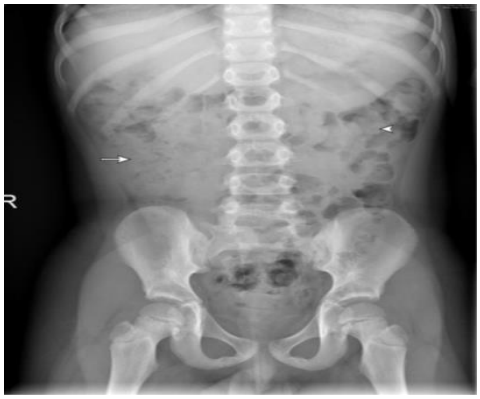


Figure3: Arrow indicates 'bubbly-granular 'mass in right lower quadrant, suggestive of distal intestinal obstruction syndrome. Arrowhead indicates hardened fecal mass. (Courtesy of Drucy Borowitz, MD.)

The treatment of DIOS is still largely empirical, since only a few RCTs are used to guide therapy. Initial treatment should aim to correct any fluid and electrolyte abnormalities and relieve the acute complete or incomplete fecal obstruction. Patients with incomplete DIOS are usually treated with oral rehydration combined with a stool softener (osmotic laxative containing PEG). PEG can be administered at 2 g/kg/day, maximum 80-100 g/day. Alternatively, sodium meglumide diatrizoate (Gastrografin) can be given orally or as a NG tube; 50-100 mL of water or juice for children <6 years and 100 mL diluted in 400 mL for elderly patients on day 1 and half the dose on the following days should be required.[17]

A stepwise approach is required in patients with complete DIOS. With moderate obstruction, PEG can be used. If DIOS is present with severe intestinal obstruction characterized by bilious vomiting, IV rehydration and nasogastric aspiration are started. The Gastrographin enema should be used by an experienced radiologist.

Surgery is rarely required with aggressive medical management. Before considering resection of the ileocecum laparotomy, with washout via an enterostomy should be attempted.[18]
Prophylaxis:

- All patients who experience DIOS; adherence to pancreatic enzyme replacement therapy (PERT) should be reviewed.
- To minimize recurrence; routine osmotic laxative should be emphasized.

Appendiceal disease
Appendicitis is a challenging problem in CF patients and is difficult to diagnose, especially in young children. In CF, appendicitis mimics DIOS because of its atypical presentation, in which classic symptoms are often absent. Interestingly, appendicitis is less common in children with CF than in the non-CF population, likely reflecting the frequent use of antibiotics in CF. The patient may present with an appendiceal abscess. Possible factors include luminal obstruction of the appendix with thick mucus, masking of acute symptoms by chronic antibiotic use, or delayed intervention due to confusion with DIOS. The physician should be more aware of this entity to avoid confusion or delay in diagnosis.

Intussusception
Thickened intestinal secretions predispose children with CF to intussusception, with 1% of patients most commonly being ileocolic.[19] In CF children, intussusception occurs later—the majority between 2 and 12 years of age, while in healthy infants and children intussusception is most common before the age of 1 year (60% of cases) or in early to later childhood (40% of cases) occurs.[20,21]

The patient usually suffers from intermittent colicky abdominal pain. Rectal bleeding is a late sign, and an abdominal mass is often not palpable.

The diagnosis can be made with ultrasound or a barium study, which can also be therapeutic. The ultrasound finding includes the 'doughnut sign' in the transverse scan and the 'pseudokidney' in the longitudinal scan. The barium study shows a lobulated soft-tissue mass and a coiled spring sign, usually located in the Rt iliac fossa.

It is noteworthy that intussusception is often intermittent and resolves spontaneously. surgical intervention is required when less invasive treatment is unsuccessful, and signs of peritonitis have developed.

Fibrosing Colonopathy (FC):
Fibrosing colonopathy, first reported in 1994, is an iatrogenic complication associated with shortening and fibrosis of the colon and is found exclusively in CF patients.

Fibrosing colonopathy (FC) characterized by severe submucosal thickening in the proximal colon with variable degrees of inflammation with eosinophils and mixed inflammatory cells. The exact pathogenic mechanism remains unclear. However, previous studies suggested that FC is associated with high-dose pancreatic enzyme > 5000 IU lipase/kg body weight. Other predisposing factors are still debated, including young age (2-3 years), H/O of GI complications (DIOS, MI), previous bowel surgery, corticosteroids or recombinant human deoxyribonuclease (dNase), H2-receptor blockers.[22] Symptoms include worsening abdominal pain, intermittent bowel obstruction, and passage of blood and mucus.

Treatment includes reducing pancreatic enzyme supplementation (no more than 2500 lipase U/kg per meal) and surgical resection if progression leads to complete obstruction.

Rectal prolapse

CF has been commonly associated with rectal prolapse, with an estimated incidence of 3% in children with the disease.[23] Majority case related to constipation. Rectal prolapse usually occurs in toddler years but can present as early as 1st week of life as the initial presentation of CF. Children with denovo should have a sweat chloride test to rule out CF. Prolapse often cease with PERT after diagnosis of CF. Surgery is rarely necessary.

Constipation

Constipation is one of the most common gastrointestinal manifestations in CF patients, affecting nearly half of pediatric[24] and adult patients, and the most common cause of bloating and abdominal pain. Similar to DIOS, constipation is associated with pancreatic insufficiency (PI).

Patients present with prolonged H/O with increased stool consistency and/or decreased frequency, hypogastric abdominal pain, or bloating. Fecal mass will be palpable predominantly in the lower Lt quadrant. An abdominal radiograph may be required to distinguish constipation from DIOS, in which stool is distributed throughout the colon and not just the ileocecal region.[25]

Treatment is by oral laxatives with or without electrolytes. Fiber and fluid intake do not correlate with constipation in CF.[24] The appropriate dose of PERT should be evaluated.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is defined as bacterial colonization of the small intestine with colonic-type gram-negative bacteria. The prevalence in CF patients is considered high at up to 50%.[26] Bacteria can convert normal nutrients into non-absorbable and toxic substances, leading to enterocyte damage, malabsorption and malnutrition. SIBBO in CF overlaps with symptoms resulting from PI. Fat malabsorption and malnutrition can result from bacterial deconjugation of bile salts and impairment of their ability to emulsify fat in the intestinal lumen. Clinical symptoms of SIBO include bloating, flatulence,abdominal pain, diarrhea, weight loss, or failure to thrive. SIBO should be considered for persistent abdominal symptoms and persistent fat malabsorption unresponsive to an increase in PERT[27] Factors contributing to the development of SIBO in patients with CF include decreased gut motility, altered gut flora due to prolonged use of antibiotics, use of PPIs, gastrointestinal and respiratory malnutrition dysbiosis.[28]

The management of SIBO at CF is primarily empirical. Antibiotics covering gram-negative and anaerobic bacteria are preferred. The available data suggested both absorbable (e.g. amoxicillin clavulanate, metronidazole, fluoroquinolones) and non-absorbable antibiotics (e.g. aminoglycosides such as neomycin, rifamycin, gentamicin).[29] Due to high recurrence rates after successful treatment, rotating antibiotic treatment regimen with different oral agents have been suggested.[30]

Intestinal infection

The GI microbiota is altered in diversity, localization, and cell density in CF patients due to delayed intestinal transit, luminal hyperacidity, and frequent use of broad-spectrum antibacterial therapy with disruption of colonization resistance, use of PPIs, and mucus accumulation. CF newborns are associated with a significantly higher rate of Clostridiodes difficile carriers, resulting in a potentially fatal cause of pseudomembranous colitis. Patient present with atypical presentation such as acute toxic megacolon without diarrhea. However, progression to a symptomatic infection is observed less frequently due to inactivation of CFTR-induced Cl-secretion and may present atypically with symptoms of constipation or distal intestinal obstruction syndrome (DIOS).[31] Giardia lamblia is a common intestinal parasite in patients with PI of any cause, including CF. Patients present with increased diarrhea, abdominal distension, and anorexia.

Association with other gastrointestinal disease

Celiac disease and inflammatory bowel disease are more common in CF patients than in the general population. The pathophysiology of these 2 conditions shows similarities regarding intestinal inflammation, such as disruption of the microbiome and the barrier function of the intestinal epithelium.[32] Diagnosis of celiac disease can be difficult given the variable and non-specific presentation of celiac disease; tTG-IgA is often falsely elevated in patients with CF due to non-specific intestinal inflammation. A duodenal biopsy is required for definitive diagnosis.

The possibility of IBD should be considered in patients with growth failure, blood in the stool and persistent abdominal complaints despite adequate PERT treatment. A colon biopsy showing the definitive feature consistent with Crohn's disease or ulcerative colitis confirms the diagnosis.

Pancreatic manifestation

The pancreas is one of the earliest and most affected organs in CF. Exocrine Pancreas is most frequently affected component while endocrine function also may be deranged. Parenchymal damage as acute or chronic pancreatitis can develop.

Cystic fibrosis is named for the fibrocystic lesions in the pancreas discovered by Dr. Dorothy Andersen in a seminal report on pediatric autopsy cases.[33] Malfunction of CFTR leads to impaired Cl- and HCO3- transport, which causes protein-rich, viscous exocrine fluid inspissated in the proximal pancreatic duct, leading to duct obstruction that interfere secretion of pancreatic enzymes and causes exocrine PI. It also causes autolysis and progressive destruction of pancreatic islets and

patients develop cystic fibrosis associated diabetes (CFRD).

Pancreatic insufficiency (PI):

Pancreatic insufficiency is the most common gastrointestinal complication of cystic fibrosis. About 2/3 of infants with CF[33] and 85% of patients will be affected at some point in their lives[35] CFTR genotype is more closely related to the severity of pancreatic exocrine dysfunction. Whether a patient has an adequate or insufficient pancreas depends on the type of genetic mutation, although 85% of patients aged 1 to 2 years are PI.[36] Fat malabsorption results from PI, secondary to decreased production of pancreatic enzymes. Thus, patients are at risk for steatorrhea, malnutrition, and deficiency of fat-soluble vitamins. Nutritional effects of PI include growth failure, deficiencies in fat-soluble vitamins, and bone disease. Pancreatic function tends to deteriorate over time. Clinically recognizable signs do not appear until 90% of pancreatic function has been lost. Patient with pancreatic insufficiency present with frequent, bulky, foul-smelling, oily stools that are difficult to flush, weight loss, bloating, abdominal distension may present. Exocrine PIs can develop with or without symptoms or by failure to thrive in infants and children or unexplained weight loss in adults.

Individuals with CF, regardless of age, should be screened for pancreatic insufficiency, which is generally performed by fecal elastase, a useful indicator of exocrine pancreatic function. Fecal elastase < 200 mcg/g indicates pancreatic insufficiency.[37]

Pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment for pancreatic insufficiency in CF. The initial dose children <4 years - 1000 lipase U/kg body weight/meal. Children > 4 years: 500 lipase U/kg body weight/meal.[36] Smaller dose often with snacks eaten between meals. Dosing is escalated based on symptoms of pancreatic insufficiency to a maximum dose of 2500 lipase units/kg body weight/meal to avoid fibrosing colonopathy. Infant on formula milk: The dose starts at 2000 lipase units/120 ml formula/per breastfeed. The dose can be adjusted up to 2500 lipase units per kg body weight/feeding with a maximum daily dose of 10,000 lipase units per kg.[37]

CFTR modulator therapy (ivacaftor, tezacaftor) can restore pancreatic function in young children - preliminary evidence suggests. In older children, the potential improvement of exocrine pancreatic insufficiency with ivacaftor has also been noted. Nichols et al. studied cases of older children on long-term treatment with ivacaftor and found significant improvements in Fecal elastase-1.[38]

Pancreatitis

About 15–20% of CF patients with pancreatic sufficient (PS) develop pancreatitis[39] and rarely occur with pancreatic insufficiency. It is typically present during late adolescence or early childhood. An increased prevalence of CFTR mutations has been observed in patients with acute pancreatitis, acute recurrent pancreatitis, or chronic pancreatitis. The consequences depend on the severity of the mutation. CF children should be monitored for pancreatitis if they have abdominal pain, even if it is suspected to be exocrine pancreatic insufficiency. CF patients with recurrent pancreatitis can be better treated with highly potent CFTR modulators.

Cystic fibrosis-related diabetes (CFRD)

Cystic fibrosis-related diabetes (CFRD): It is a distinct form of diabetes mellitus and an important complication of cystic fibrosis. The main cause is a relative lack of insulin associated with the destruction of pancreatic cells. 30% of patients develop CFRD in adolescence.[40] In a pediatric-specific epidemiological study on CFRD from 2000-2016, Perrem et al. identified a CFRD prevalence of 8.5% in 10 to18-year-old children in Canada.[41] Risk factors for CFRD include female gender, pancreatic insufficiency, Delta 508 genotype. Annual screening for CFRD is recommended from the age of 10.[42] OGTT should be used as a screening test. Subcutaneous insulin is the standard medical therapy for CFRD.

Hepatobiliary disease

Cystic fibrosis-associated liver disease:

CF-related liver disease as a distinct disease entity is a complication of CF. CFLD has been increasingly reported with increased life expectancy in CF patients.[43] According to various sources, the prevalence of CFLD is 2-37% in children and young adults.[44] Currently, CFLD is the third leading cause of death in patients with cystic fibrosis, the percentage is about 2–4%.[44]

CFLD is a broad term that has been used to define a spectrum of liver involvement in CF, ranging from mild asymptomatic hypertransaminosemia to cirrhosis with portal hypertension. (Table 2).

Decreased or absent CFTR function in the bile duct, resulting in impaired Cl-, HCO3-, and water transport into the bile,leading to viscus and inspissated bile causing ductular obstruction and hepatotoxicity from retained bile components, leading to inflammation and subsequent fibrosis and cirrhosis.[45,46,47]

CFLD more common in patients with SERPINA1 Z allele, H/O of PI, H/O of MI, CF-related diabetes, or male gender.

Table 2: Clinical presentation of cystic fibrosis –related liver disease.[43,48,49]

Category	Approximate frequency in individuals with CF	Typical characteristics
Neonatal cholestasis	<10%	Cholestasis is the earliest and most common manifestation of CF liver disease and often recognized by elevated conjugated/Direct bilirubin >1 mg /dl. In addition to jaundice, affected infant may have acholic stools, hepatomegaly, splenomegaly, hypoalbuminemia &/ or elevated transaminase, alkaline phosphatase &/or gamma glutamyl transferase level. Usually regresses within months. H/o of prolong TPN or surgery related to MI may be risk factor of later CFLD development.
Focal biliary cirrhosis	20 % to 40%	Usually asymptomatic and developed within first 12 years of life. May or may not be presented with hepatomegaly and persistently elevated aminotransferase level.
Multilobular cirrhosis	5 to 10%	Advance stage of focal biliary cirrhosis. May be complicated by GI bleeding, portal hypertension (causing splenomegaly, ascites and esophageal varices) and nutritional deficiencies. Hepatic synthetic function (coagulopathy and hypoalbuminemia) may impair.
Hepatic steatosis	10 to 60%	Incidental findings on USG or liver biopsy with transient hepatomegaly, can present at any age and may be associated with stunting or wasting. Steatosis is likely multifactorial resulting from long term malnutrition, CFTR dysfunction, medication, essential fatty acid deficiency.

Diagnosis

Liver disease in CF can be difficult to diagnose because patients can remain asymptomatic late in the disease course and screening tests correlate poorly with disease severity. Nonetheless, early diagnosis of CFLD can be made through comprehensive clinical examinations, biochemical tests, and imaging techniques. Biochemical markers of liver disease, such as aminotransferase levels along with biliary inflammatory markers—alkaline phosphatase and gamma-glutamyl transferase can vary and are often found to be normal despite histological evidence of liver disease.[50] Appropriate diagnostic tools are USG, transient elastography and liver biopsy. Annual CFLD screening in children with abdominal examination (hepatosplenomegaly), biochemical evaluation (bilirubin, AST, ALT, GGT, ALP, albumin, prothrombin time, platelet count), abdominal ultrasound and pulse oximetry (screening for hepatopulmonary syndrome recommended by the CF Foundation). Guideline.[43]

Management

The clinical management of CFLD depends on the patient's age and the extent of the liver disease. Currently, UDCA is the only available therapeutic option that increases bile flow, replaces potentially toxic bile acids, acts as a cytoprotective agent, and potentially stimulates bicarbonate secretion in the bile ducts to prevent or avoid progression of CFLD,[51] but there is no strong evidence of its effectiveness in the prevention of liver cirrhosis and long-term treatment should be individualized. CFLD's management emphasizes two main aspects: first, treatment of the underlying liver disease itself, and second, nutritional therapy (adequate caloric intake, fat-soluble vitamin supplementation, etc.) as well as portal hypertension and decompensated cirrhosis, both possible consequences of the underlying liver disease. Liver transplantation is the ultimate treatment for patients with end-stage liver disease.

Gallbladder disease

Up to 50% of children may develop gallbladder abnormalities including small or absent gallbladder, cholelithiasis, gallbladder hypokinesia. The micro gallbladder is benign and can mimic biliary atresia on USG findings, which can lead to diagnostic uncertainty when cholestasis is also present. In patients with cystic fibrosis, gallstones are found quite frequently, with a pediatric incidence of 3% to 25%[52] and black-pigmented stones are found more frequently, resulting from abnormal acidification of the bile, a mechanical defect created by the absence of CFTR in the bile epithelium. Cholecystectomy is indicated when complications such as cholecystitis or biliary obstruction are present.

Malnutrition

Malnutrition in cystic fibrosis is multifactorial. Malabsorption of fat, protein, and fat-soluble vitamins occurs because of insufficient production of pancreatic enzymes, which can be exacerbated by bile salt abnormalities in the presence of concurrent liver disease. Additionally, cystic fibrosis patients tend to burn more

calories due to the extra work it takes to breathe and fight infection. Other contributing factors include CF-related DM, altered GI tract motility, and SIBO. Proper delivery of nutrients and correction of maldigestion and malabsorption are critical to achieving normal growth, supporting optimal lung function, and prolonging life. Assessment of nutritional status is important for patients with CF. In children, HAZ, weight Z-score and BMI percentage should be measured.

For improved weight gain, the higher energy intake should be 110% to 200% of the RDA. Intensive behavioral and nutritional counseling is recommended for weight promotion in CF patients aged 1 to 12 years.[53,54] Supplementation with the fat-soluble vitamins A, D, E, and K should begin at diagnosis, including in asymptomatic infants and patients with pancreatic insufficiency. Omega-3 fatty acid supplementation improves several markers of lung disease. One study showed that DHA supplementation in CF patients improved markers of inflammation, but an inconsistent improvement in FEV1. CF patients are prone to salt loss due to excessive sweating, intestinal malabsorption (if an ostomy is present), and chronic inflammation. Sodium chloride supplementation is often considered in warm months/climates and in infants.[55] Table salt 2-4 mmol/kg/day is recommended. Zinc is recommended for children under 2 years old with FTT. Children with CF are prone to develop iron deficiency anemia. (56). In the case of iron deficiency, iron supplementation is necessary after the inflammation has subsided. Bone disease is common in CF patients that progress with age. Therefore, supplementation with calcium, phosphorus, vitamin K, and vitamin D is recommended to support bone health.

CONCLUSION

Patients with cystic fibrosis can present a wide range of gastrointestinal and hepatic manifestations and contribute significantly to the morbidity of CF. Therefore, it is of paramount importance to address the gastrointestinal aspect of cystic fibrosis. A holistic approach to patient care can improve life expectancy and quality of life.

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