Gastrointestinal, Pancreatic, and Hepatic Manifestations of Cystic Fibrosis in the Newborn

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Education Gap

Advances in newborn screening have led to earlier diagnoses of many patients with cystic fibrosis. Despite these advancements, some patients are not detected by newborn screen, and early recognition of clinical manifestations of cystic fibrosis remains critical. For most patients with cystic fibrosis, gastrointestinal signs and symptoms represent the earliest indication of disease. Furthermore, even for those in whom early detection is achieved, early manifestations of disease, such as reflux, dysbiosis, meconium ileus, poor weight gain, and cholestasis, present unique clinical and therapeutic challenges. Finally, it is imperative that providers recognize that early therapeutic interventions may impart a lifelong impact among patients with cystic fibrosis.

Abstract

Gastrointestinal, pancreatic, and hepatic signs and symptoms represent the most common presentation of early disease among patients with cystic fibrosis and may be the initial indication of disease. Regardless of whether cystic fibrosis is diagnosed early by newborn screening or later by clinical course, the impact of gastrointestinal, pancreatic, and hepatic manifestations on early life is nearly ubiquitous. Conditions strongly linked with cystic fibrosis, such as meconium ileus and pancreatic insufficiency, must be recognized and treated early to optimize both short- and long-term care. Similarly, less specific conditions such as reflux, poor weight gain, and cholestasis are frequently encountered in infants with cystic fibrosis. In this population, these conditions may present unique challenges in which early interventions may have significant influence on both short- and long-term morbidity and mortality outcomes.

Objectives After completing this article, readers should be able to:

1. Recognize and treat common, early gastrointestinal, pancreatic, and hepatic manifestations of cystic fibrosis.
2. Understand that early interventions can have a long-lasting effect on the morbidity and mortality of patients with cystic fibrosis.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
AST	aspartate aminotransferase
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
EGD	esophagogastroduodenoscopy
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GGT	γ-glutamyl transferase
H2RA	histamine-2 receptor antagonist
MII-pH	multichannel intraluminal impedance and pH measurement
PERT	pancreatic enzyme replacement therapy
PPI	proton pump inhibitor
SIBO	small intestinal bacterial overgrowth
ULN	upper level of normal

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, multisystem disease affecting 1 in 2,000 to 1 in 4,000 newborns in the United States, with incidence varying by race and ethnicity. (1) It is caused by genetic mutations resulting in abnormal synthesis, structure, and/or function of the cystic fibrosis transmembrane regulator (CFTR) protein. The CFTR is a cyclic adenosine monophosphate-induced anion channel that transports chloride and bicarbonate across the apical surface of epithelial cells and may also regulate other important cellular functions. (2) Deficient CFTR function leads to altered mucus secretions in the luminal environment that can then lead to inflammation, obstruction, and dysfunction of various organs. (3)(4)

Respiratory disease remains the most frequent cause of morbidity and mortality in patients with CF, but gastrointestinal, pancreatic, and hepatobiliary disease are more commonly encountered in the first year of life. The widespread use of newborn screening has resulted in earlier diagnosis and improved outcomes for patients with CF, with many patients now diagnosed before the onset of clinical manifestations. Despite earlier diagnoses occurring in most patients, nutritional deficiencies, weight deficits, pancreatic dysfunction, steatorrhea, and meconium ileus remain common for patients with CF during the newborn period. (5)(6) Timely recognition and intervention are critical, as early therapies and outcomes in CF have been shown to have profound long-term effects on nutritional and pulmonary health. (7)(8)(9) Early exposure to antibiotics and other medications may also have long-term negative implications on a patient's health. It is, therefore, necessary that neonatologists be able to recognize and appropriately manage the early clinical manifestations of CF.

GASTROINTESTINAL MANIFESTATIONS

Gastroesophageal Reflux Disease

Gastroesophageal reflux (GER) is a common physiologic condition characterized by passive retrograde flow of gastric contents into the esophagus that affects more than 50% of infants. Typically, GER does not require any intervention and resolves by ~1 year of age. This clinical course is similar in patients with CF and GER. Gastroesophageal reflux disease (GERD) occurs when complications of GER occur, such as respiratory compromise or esophagitis. (10) The incidence of GERD in infants with CF is ~25%. (11)(12) The most frequent clinical manifestations of GERD in patients with CF are emesis and posseting, followed by parental-perceived irritability in the infant. However, it is important to note that these are common symptoms in the newborn period and have been shown to have a poor positive predictive value for GERD in infants with CF. (12) Although GERD has been shown to be associated with worse pulmonary outcomes in older patients, (13) respiratory manifestations of GERD in infancy are rare and typically are limited to wheezing. Failure to thrive has not been associated with GERD in infants with CF. (12)

The evaluation of potential GERD in infants with CF is not different than that in the general population. During the newborn period, it is important to evaluate for any anatomical abnormalities that could be contributing to GERD and would require surgical intervention. An upper gastrointestinal fluoroscopy series is the preferred imaging modality and allows for the evaluation of esophageal abnormalities, hiatal hernias, malrotation, and other anatomical abnormalities of the upper gastrointestinal tract. (10) Although an upper gastrointestinal fluoroscopy series is helpful to diagnose anatomical abnormalities, it cannot diagnose GERD. Radiotracer may be seen infrequently in the lungs, and careful interpretation is required to determine whether this finding is due to primary aspiration, due to aspiration of refluxed contents, or of no clinical significance. Combined multichannel intraluminal impedance and pH measurement (MII-pH) is the preferred test in the evaluation and diagnosis of GERD, having been shown to be superior to other common investigations, including 24-hour pH testing, barium meal, pepsin assay, and even esophagogastroduodenoscopy (EGD). (14) MII-pH may be performed with or without an EGD, with both evaluations typically reserved for patients who do not respond to baseline empirical therapy. If MII-pH is being considered, it is strongly urged that a gastroenterology consultation is obtained to assist in the decision making regarding whether to pair with EGD, timing of MII-pH, and interpretation of results.

Similar to the evaluation of GER and GERD, the management of these conditions in infants with CF is similar to that of the general population. As per the American Academy of Pediatrics (AAP) guidelines, younger infants may benefit from an upright position after feeding, whereas the benefit of side positioning is not as clear. Although placement of an infant in the prone upright position has been theorized to help decrease reflux events in infants, it is critical to remember the associated increased risk of sudden infant death syndrome in infants placed in this position. This position might be preferred if the provider believes that the risk of death from GERD is greater than the risk of sudden infant death syndrome. (15)

Postural draining and percussion is another positional consideration in patients with CF. This technique is performed

on infants and children from the time of diagnosis until they can actively participate in their own pulmonary treatments. This method helps to move mucus out of the lungs, but it has been associated with an increased risk of GER. Two approaches have been studied: the standard 15° to 40° head-down tilt versus the 15° to 30° head-up tilt. Although limited evidence exists, there may be some benefit with a 30° head-up tilt approach because it might decrease the number of GER events, especially those that reach the upper esophagus. (16) Additional noninvasive and nonpharmacologic strategies to treat GER and GERD should likewise follow the previously referenced AAP guidelines. (15)

Pharmacologic management, which focuses on acid suppression, should be reserved for infants with GERD. Although histamine-2 receptor antagonists (H2RAs) are a reasonable first choice, proton pump inhibitors (PPIs) are typically preferred owing to superior efficacy and as adjunct therapy with pancreatic enzyme replacement therapy (PERT) to potentially improve nutritional status. (17)(18) These medications may be used empirically for suspected GERD in infants, but other pharmacologic interventions (eg, prokinetics) and more invasive therapies (eg, fundoplication) should be considered only in patients with extremely severe GERD and in consultation with a gastroenterologist. Although fundoplication may potentially help to protect the patient from aspiration, it has significant potential comorbidities (eg, gas, bloating, retching, and dumping); nearly 50% of patients will develop GERD symptoms after fundoplication. (10) It is reasonable to infer that this risk is likely greater if fundoplication is performed during infancy.

The use of PPIs for infants with GER and GERD has become commonplace, with the 2016 CF Registry reporting that more than 50% of patients with CF were prescribed a PPI during the calendar year. (19) This is despite evidence showing that PPI use is significantly associated with an increased number of hospitalizations for pulmonary exacerbations, as well as a small risk of developing hypocalcemia, hypomagnesium, osteopenia, and *Clostridium difficile*. (17)(20) It is not clear whether these associations are causative, simply reflect worse disease, or a combination of both. In addition, prolonged acid suppression with either H2RAs or PPIs has been associated with the development of small intestinal bacterial overgrowth (SIBO). (21) With these long-term CF-specific associations established, combined with the known increased risk for the development of necrotizing enterocolitis and late infections in all infants receiving acid suppression medications, cautious consideration should be practiced before prescribing infants with CF either H2RAs or PPIs. If H2RAs or PPIs are initiated, they should not be considered long-term medications, and providers should frequently assess whether they need to be continued and weaned once clinically appropriate.

Dysbiosis

A variety of gastrointestinal manifestations of CF are believed to predispose this population to dysbiosis and SIBO, including delayed intestinal transit time, frequent antibiotic exposure, prolonged use of acid suppression medications, pancreatic insufficiency, intestinal inflammation, and high rates of constipation. (21) A difference in intestinal bacterial composition and lack of diversity has been well-established in patients with CF but was largely felt to develop over the course of a patient's life. Recent data, though, suggest that CFTR dysfunction affects the near sterile gut at birth and influences the acquisition of the gut microbiome, with stool samples as early as 15 days of age showing altered composition compared with controls. (22) Specific findings include expansion of *Escherichia coli*, increased *Enterococcus* species, decreased *Clostridiales* species, and an overall decrease in alpha diversity.

There is no evidence to support a protocol to treat or prevent dysbiosis and/or SIBO in infants with SIBO. Breastfeeding has been shown to improve microbial diversity in the respiratory and intestinal tracts in samples taken from infants with CF from birth through 34 months of age. Furthermore, in the same cohort, improved intestinal, but not respiratory, microbial diversity was associated with longer time until both the first pulmonary exacerbation and initial colonization with *Pseudomonas aeruginosa*. (23) Although longer-term follow-up is required to understand the true impact of early dysbiosis on the health of patients with CF, we strongly encourage providers caring for infants with CF to be mindful of the possible implications of unnecessary exposure to antibiotics and/or acid suppression medications during this time of their life and to ensure that an adequate indication is present before initiating these medications.

Intussusception

Symptomatic intussusception is a rare manifestation of CF, affecting ~1% of patients. There is a male predominance (2:1) and a bimodal distribution, which includes an initial peak in infancy, with the second peak occurring at approximately 10 years of age. (24) Presentation in infancy typically includes colicky pain/discomfort, vomiting, and, rarely, bloody stools. (25) Diagnosis is typically made by ultrasonography, although air and contrast enema can be both diagnostic and therapeutic, if clinically suspected. Surgery to manually reduce and assess for a potential lead point or

lesion is rarely required but should be considered if contrast enema fails to resolve the intussusception. (24)

Meconium Ileus

Meconium ileus is an intestinal obstruction caused by thick, adhesive meconium that typically involves the terminal ileum and is most often associated with CF, occurring in 12.5% to 25.9% of newborns with CF, depending on genotype. (19) Meconium ileus initially develops in utero and is frequently the first clinical manifestation of CF.

Both CFTR and non-CFTR genetic factors are thought to contribute to the pathophysiology of meconium ileus, supported by epidemiologic studies and animal models. Meconium ileus is more common in those with class I-III CFTR mutations, which are typically associated with lower CFTR function. (19) Abnormal CFTR protein in the small intestine results in diminished bicarbonate and chloride excretion, which is needed to promote water secretion. (26) With loss of CFTR function, an acidic and dehydrated luminal environment ensues, and the resultant compacted, viscous mucus and other factors combine to form abnormally sticky and tenacious meconium that occludes the intestinal lumen. (3)(4)(27)

Approximately 3% of patients affected by meconium ileus are identified prenatally. (28) Antenatal ultrasonography may identify hyperechoic masses, corresponding to inspissated meconium; this is in contrast to normal fetal meconium, which generally appears more hypoechoic or isoechoic to adjacent bone or liver. (3) A hyperechoic bowel is associated with both meconium ileus and CF but is a nonspecific finding with a broad differential diagnosis that includes normal variant. (29)(30) Other potential sonographic findings of meconium ileus include peritoneal calcifications, dilated bowel proximal to the obstruction, and polyhydramnios. (29)(31)

Algorithms have been developed to guide assessment of fetal risk for CF and meconium ileus after detection of hyperechoic bowel. Parental carrier status should ideally be assessed, with genetic counseling offered thereafter, regardless of outcome, given the limitations of testing and other diseases or syndromes associated with echogenic bowel. (31) Because the finding often subsequently resolves, antenatal ultrasonography should be repeated at least every 6 weeks. (3)(30) Referral to a perinatologist is recommended for coordination of multidisciplinary care around delivery should the findings persist, with access to a center with an experienced NICU team and specialist support, including pediatric surgery. (31)

Newborns with meconium ileus typically have symptoms within the first 48 hours after birth; these symptoms vary depending on the presence or absence of complications. (21) In simple, or uncomplicated, meconium ileus, luminal obstruction by inspissated meconium may occur anywhere from the distal ileum to the proximal colon, leading to proximal bowel distention by additional viscid meconium, gas, and fluid. The distal, unused colon is frequently small in caliber (termed *microcolon*). This leads to nonspecific signs and symptoms of lower gastrointestinal tract obstruction, which may include bilious vomiting, abdominal distention, or failure to pass meconium. (28) Approximately 50% of cases are complicated by segmental volvulus, intestinal atresia, ischemic necrosis, or perforation. Rarely, perforation can lead to pseudocyst formation from encapsulation of meconium into an intestinal membrane. This can lead to meconium peritonitis or giant meconium pseudocyst formation. (24)

Initial management of newborns with meconium ileus is similar to treatment of patients with a suspected small-bowel obstruction. This includes nil per os status, adequate intravenous access, evaluation for an infection, and placement of a nasogastric tube. An abdominal radiograph is the typical first imaging choice and often shows dilated loops of bowel with or without air-fluid levels. In addition, the presence of air in the rectum may vary depending on the "completeness" of the obstruction. The radiograph may show the classic soap bubble sign in the distal small intestine, attributed to meconium that is mixed with swallowed air, and abdominal calcifications as a result of an intrauterine intestinal perforation. (31)

In stable newborns, a contrast enema may be beneficial to detect a microcolon and exclude other anatomical abnormalities, as well as help determine whether surgical intervention is required (Fig 1). The success of medical management with hyperosmolar enemas performed under fluoroscopic guidance to ensure penetration to the terminal ileum has been reported to be 30% to 80%. Although perforation rates of 3% to 23% have been reported with contrast enemas, the goal remains to avoid surgery unless medical management is unsuccessful or the patient has a distended abdomen and peritoneal signs consistent with complex meconium ileus. (31) An algorithm for the treatment of meconium ileus is shown in Fig 2.

In patients with meconium ileus who have not yet been diagnosed as having CF, a full diagnostic assessment should be performed, including serum immunoreactive trypsinogen (if newborn screen has not been performed), as well as a sweat chloride test. A sweat chloride test may be performed 48 hours after birth in term infants assuming that the patient is well hydrated and not edematous. It is

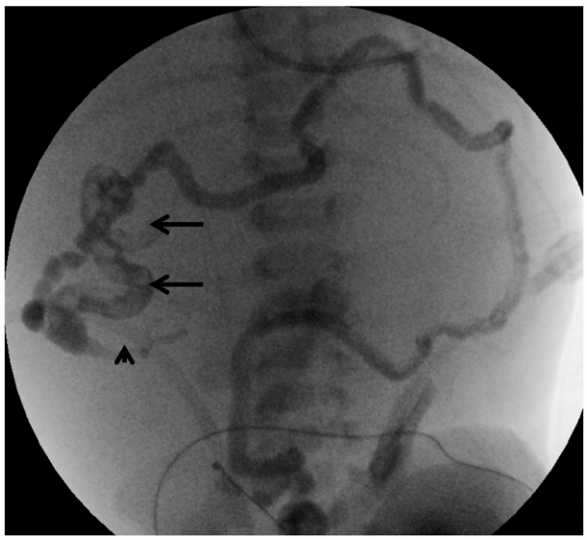

Figure 1. Barium enema in a 2-year-old boy diagnosed as having cystic fibrosis showing filling defects of the terminal ileum (arrows) distal to the appendix (arrowhead) with prominent microcolon diagnostic of meconium ileus.

important to know that false-negative serum immunoreactive trypsinogen results have been reported in infants with CF and meconium ileus and does not exclude the diagnosis. (32) In patients unable to have a sweat test performed or in whom confirmatory diagnosis is sought, CFTR genetic testing should be performed from an accredited laboratory. For patients with meconium ileus and known CF, pancreatic insufficiency should be presumed and the patient started on PERT unless a fecal elastase level is reported as normal (see the Pancreatic Insufficiency section later herein). (33)

For patients requiring surgical correction of the meconium ileus, there are 2 surgical choices, both of which require close postoperative management. An enterotomy with washout and primary anastomosis may be considered and has the benefit of potentially preventing subsequent surgery. However, it has been associated with a high 30% postoperative complication rate. (34) As such, many providers prefer the creation of an ostomy (such as a Bishop-Koop or Santulli) to prevent re-accumulation of stool and allow for bowel irrigation, if needed. Ostomies, though, especially if proximal, risk excessive water and salt loss, which may have a negative influence on the patient's short- and long-term nutritional status and must be monitored closely. (35) A total body deficit of sodium can occur, which may lead to metabolic acidosis and poor weight gain. Total body sodium level can be monitored by measuring a spot urine sodium/creatinine ratio (goal for adequate growth is ratio of 17:52) or a spot urine sodium amount; the patient should be started on sodium supplements if either value is low. (36) Both surgical approaches are associated with a risk of adhesions and increased risk of distal intestinal obstruction syndrome, both of which may also impair long-term intestinal motility. (35)

As soon as clinically indicated, enteral nutrition should be resumed in patients with simple or complex meconium ileus. If total parenteral nutrition is required, an anti-

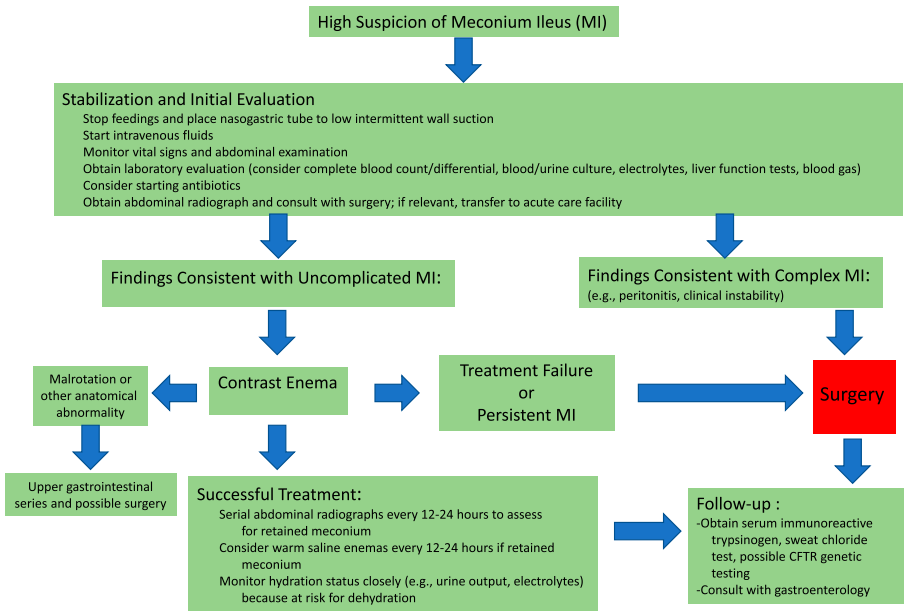

Figure 2. Treatment algorithm for meconium ileus. (Derived from Sathe M, Houwen R. Meconium ileus in cystic fibrosis. *J Cyst Fibros*. 2017;16(suppl 2): S32–S39.)

inflammatory lipid choice should be considered, including medium-chain triglycerides and fish oils to decrease the risk of cholestasis. In Europe, Smoflipid® (Fresenius Kabi USA LLC, Lake Zurich, IL) has routinely been used in affected patients, but it has not routinely been used in the United States for this indication. (31)

Rectal Prolapse

Cystic fibrosis has been commonly associated with rectal prolapse, with historical data suggesting that approximately 23% of patients with CF experience rectal prolapse. (37) Not surprisingly, with widespread use and expansion of newborn screening for CF, rectal prolapse as a manifestation of the disease has decreased in incidence and was more recently estimated to be as low as 3.5%. (38) Rectal prolapse typically occurs during the toddler years, but it has been described as an early and initial presentation of CF within the first week of life, although its incidence in the neonatal period is not definitively known. (39)(40) Given the very low incidence of rectal prolapse as an initial manifestation of CF, early rectal prolapse should prompt an initial evaluation for other potential etiologies, such as anorectal abnormalities or Hirschsprung disease. (41) We recommend obtaining a sweat test to further evaluate for CF only if the patient has recurrent prolapse or if the prolapse is associated with loose, diarrheal stools (suggesting pancreatic insufficiency).

It is expected that 75% of patients with CF and rectal prolapse will respond to PERT, with full resolution of the prolapse episodes. (39) For patients not responding to PERT in the newborn period, a period of observation with appropriate constipation management would be advised because most patients will eventually outgrow this disorder. Invasive measures such as surgery or sclerotherapy would only be considered in the neonatal period for complex cases in which manual reduction was not possible and/or could lead to other complications (eg, incarceration). (41)

PANCREATIC AND NUTRITIONAL MANIFESTATIONS

Pancreatic Insufficiency

The pancreas is one of the earliest and most frequently affected organs in CF, with significant initial injury occurring in utero and initial insult seen as early as 17 weeks' gestation. (42) It is commonly believed that impaired chloride and bicarbonate transport results in pancreatic secretions, which have a lower pH, increased viscosity, and higher protein concentration, altering zymogen secretion and leading to ductal obstruction. (43) Early pancreatic histopathology shows sparing of the islets of Langerhans, and, thus, endocrine function is not expected during infancy, with onset of CF-related diabetes typically seen later in life. However, acinar plugging with inflammation, ductal injury, and adipose replacement of the pancreatic parenchyma result in pancreatic insufficiency, most notably in patients with class I-III mutations. (44) As such, ~60% of newborns with CF will have pancreatic insufficiency, with another 30% developing pancreatic insufficiency during the next 36 months. (45)

The impact of pancreatic insufficiency on nutrition in infants with CF is profound and cannot be understated. PERT treatment in patients with pancreatic insufficiency is lifelong and must be closely monitored, as described later herein. In infants with CF who are receiving adequate PERT dosing but continue to experience symptoms of pancreatic insufficiency, such as bloating, steatorrhea, diarrhea, and weight loss, alternative etiologies should be considered and evaluated for, including, but not limited to, SIBO, short bowel, and cholestasis.

Nutrition

Poor nutrition should be an ever-present concern among providers caring for patients with CF. The known combination of increased energy losses, increased resting energy expenditure, and inadequate nutritional intake are known difficulties that increase the risk of undernutrition. The extent to which these affect infants with CF is unclear. However, it is well-established that in infants with CF, poor early nutritional status that is left untreated is associated with stunted growth, impaired cognitive function, worse lung function, and poor survival. (46)

Goal nutrition specifically for infants with CF is not well-studied, but the general principles are thought to be similar to those for toddlers and children with CF. The resting energy expenditure of patients with CF is greater than that of healthy same-age children, and it is assumed to be similar among infants. Therefore, goal intake should be 110% to 200% of that expected for the healthy same-age population. Close monitoring of growth parameters should be conducted with a goal of achieving and maintaining a weight-for-length at the 50th percentile (0 SD) as healthy same-age infants on the sex-appropriate World Health Organization (WHO) growth curve. (47) It has been recommended that head circumference, weight, length, and weight-for-length all be measured a minimum of 1 to 2 times per week until the child is thriving. (48) Although protein-energy malnutrition has been described in infants with CF, (49) this is largely historical, or more prevalent in developing countries, and is unlikely to be a concern if caloric goal intake is achieved.

Human milk remains the preferred source of nutrition in infants with CF. The benefits of human milk in the general population is well known, and it may be even more important for patients with CF. Infants with CF who receive human milk as their nutritional source have been shown to have improved microbial diversity of the intestinal and respiratory tracts, longer time until their first pulmonary exacerbation, longer time to colonization with *Pseudomonas aeruginosa*, reduction in decline of pulmonary function as measured by forced expiratory effort in 1 second, and decreased number of pulmonary infections during the first 3 years after birth. (23)(50)(51) If human milk is unavailable, standard formula is the preferred alternative. Despite the high frequency of pancreatic insufficiency, formulas containing higher concentrations of medium-chain triglycerides have shown no benefit, assuming adequate PERT is provided.

It is critical to ensure adequate PERT in pancreatic-insufficient patients with CF. It is well-established that ~60% of newborns with CF will have pancreatic insufficiency, with another 30% developing it during the next 36 months, predominantly those with class I-III mutations. (45) Pancreatic status should be evaluated by obtaining a fecal elastase level in all infants with CF and at least 1 mutation known to be associated with pancreatic insufficiency, or if inadequate growth/nutrition occurs. Patients with a fecal elastase level less than 200 μg/g should be considered to have pancreatic insufficiency and should receive PERT. Note that fecal elastase may vary in the first year after birth in infants with CF, and those with levels between 50 and 200 μg/g should be reevaluated at 1 year of age. Recommended PERT dosing is shown in the Table. Of note, in a cohort of 205 infants with CF and pancreatic insufficiency, higher PERT dosing was not associated with improved growth parameters, but patients receiving PERT + PPIs achieved greater weight *z* scores than those receiving PERT + H2RAs. (18)

Fat-soluble vitamin deficiencies are common in patients with CF and pancreatic insufficiency, occurring in up to 35% of these children. Vitamin D has specifically been evaluated in infants and has been reported to be deficient in 22% of patients. (47) Guidelines outlining when to assess fat-soluble vitamin levels do not yet exist, but initial dosing and goal levels are shown in the Table. For patients who experienced a prolonged nursery or NICU admission, we recommend assessment of vitamin D level at least monthly until thriving, and then every 3 months.

Infants with CF are at increased risk for salt loss due to excessive sweating, intestinal malabsorption (especially if an ostomy is present), and chronic inflammation. Excessive salt loss has been associated with impaired growth in infants with CF. Likewise, zinc deficiencies have been reported in infants with CF and are associated with growth problems, increased susceptibility to infection, and ocular concerns. (47) As such, sodium and zinc supplementation is often considered in at-risk patients, with dosing guidelines shown in the Table. Currently, a monitoring protocol for sodium and zinc deficiencies does not exist. As such, the provider must maintain a high index of suspicion and monitor levels as clinically indicated.

The widespread and expanded use of newborn screening for CF has resulted in earlier diagnosis of CF and significantly improved nutritional outcomes. However, although weight and weight-for-length measures are improving, linear stunting remains a concern. (5)(51) Furthermore, there are some infants who simply cannot tolerate the increased caloric demand by mouth. In cases where it is believed that a patient cannot consume an adequate amount of calories by mouth to meet and improve on age-dependent anthropometric and growth targets despite an appropriate evaluation, enteral tube feeding should be recommended. In patients in whom less than 3 months of tube feedings are expected, nasoenteric tube placement is appropriate, with nasojejunal reserved only for those who cannot tolerate nasogastric feedings. When considering the placement of an enteral feeding tube in an infant with CF, a thorough GER evaluation should be performed (preferably with the assistance of a gastroenterologist). There is no specific method or route of delivery for PERT that is recommended during tube feeding, although continuous feedings at night are preferred. Even if surgical placement of an enteral tube is performed, airway clearance may resume 24 hours after placement. (52)

HEPATOBILIARY INVOLVEMENT

Neonatal Cholestasis

Cholestasis is the earliest and most common neonatal manifestation of liver involvement in patients with CF, often recognized by elevated serum conjugated/direct bilirubin levels greater than 1.0 mg/dL (>17 μmol/L). Its incidence in infants diagnosed as having CF in a statewide newborn screening program is considered low at ~6% but is ~140-fold greater than that in the general population of term infants. (53)(54) Patients with complicated meconium ileus are at increased risk for cholestasis, with an incidence greater than 25% in this group. (54)

In addition to jaundice, other clinical features of CF-associated neonatal cholestasis are often nonspecific. Affected

TABLE. **General Nutritional Guidelines for Infants with Cystic Fibrosis**

Growth target	Weight-for-length at 50th percentile (0 SD) for healthy same-age population
Route of nutrition	By mouth as tolerated Enteral tube to be considered if unable to tolerate caloric demands by mouth
Preferred nutrition	Human milk (standard formula if human milk not available)
Energy target	110%–200% expected energy requirements for same-age healthy infant
Pancreatic status assessment	Fecal elastase performed in any patient with ≥1 cystic fibrosis–causing mutation associated with pancreatic insufficiency or if inadequate growth/nutritional status occurs
PERT dose (if pancreatic insufficient)	2,000–4,000 U of lipase/120 mL of human milk or formula or ~2,000 U of lipase/1 g of dietary fat
Vitamin A dose	No specific dose but should be a component of a fat-soluble multivitamin provided
Vitamin D dose (as vitamin D_3)	400 IU/d (maximum 1,000 IU/d if deficient) until age 1 y Goal is minimum serum 25-hydroxyvitamin D level of 20 ng/mL (50 nmol/L)
Vitamin E dose (as α-tocopherol)	50 IU/d until age 1 y; goal is plasma α-tocopherol/cholesterol ratio >5.4 mg/g
Vitamin K_1 dose	0.3–1 mg/d
Sodium supplementation	1–2 mmol/kg per day for breastfed infants aged 0–6 mo at risk for sodium deficiency; give in small portions throughout the day in dilute water or fruit juice
	Up to 4 mmol/kg per day may be considered in infants with special needs (eg, living in hot ambient temperatures, increased fluid losses, or ostomy present)
Zinc dose	1 mg/kg per day (maximum 15 mg per day) until age 2 y

PERT=pancreatic enzyme replacement therapy.
Summarized from Wilschanski M, Braegger CP, Colombo C, et al. Highlights of the ESPEN-ESPGHAN-ECFS Guidelines on Nutrition Care for Infants and Children With Cystic Fibrosis. J Pediatr Gastroenterol Nutr. 2016;63(6):671–675.

infants may have acholic stools, hepatomegaly, splenomegaly, hypoalbuminemia, and/or elevated serum transaminase, alkaline phosphatase, and/or γ-glutamyl transferase (GGT) levels. (55)(56)

The pathogenesis of neonatal cholestasis in CF is not well-defined, but the predominant mechanism is likely related to intraluminal bile stasis in a pattern similar to that seen in the lungs, intestine, and pancreas. CFTR is expressed in cholangiocytes (not hepatocytes), which contribute up to 40% of bile. Defective cholangiocyte chloride and bicarbonate transport results in decreased bile flow and abnormally thickened secretions, leading to bile duct plugging. Autopsy and biopsy specimens may demonstrate excess, inspissated mucus in the biliary tract with focal or diffuse plugging. (56)(57) In most cases, portal tract expansion and ductular proliferation are noted, in keeping with extrahepatic biliary obstruction, and at times is indistinguishable from biliary atresia. (55)(57)(58)

In infants with CF and cholestasis, a targeted evaluation with consideration of other etiologies is still recommended, often in concert with a pediatric gastroenterologist/hepatologist. Biliary atresia, in particular, must be considered in the presence of acholic stools, especially because contracted or absent gallbladders may occur in infants with CF as well. Conversely, term neonates with unexplained cholestasis should be evaluated for CF as part of a full evaluation. (53)(58)

In a retrospective cohort study, cholestasis in patients with CF was largely diagnosed within the first 2 months after birth, with total serum bilirubin levels peaking within the first 3 months after birth in all patients. The diagnosis and peak bilirubin level occurred significantly earlier in those with a history of meconium ileus. (54) Although cholestasis should generally resolve within the first year after birth with no sequelae, in some patients it may persist up to 5 years, and reported cases of liver failure and death are rare. (54)(55)(56) Patients with CF and early cholestasis generally have a favorable clinical course, whereas the long-term impact of early meconium ileus or cholestasis on CF-associated liver disease remains unclear.

Management of cholestasis is considered mostly supportive, warranting close monitoring of growth and fat-soluble

vitamin status. Ursodeoxycholic acid treatment may benefit patients with neonatal cholestasis, but there is insufficient evidence to justify its routine use in all infants with CF. (54)(55)(56)

Hepatic Steatosis

Hepatic steatosis is a common hepatic finding in CF at any age, with a reported prevalence of 23% to 70%, although no specific neonatal data are available. (50)(59) It has often been associated with long-term malnutrition or deficiencies of a trace element or minerals (eg, choline, carnitine, essential fatty acids); however, this is not always the case, so this finding could also be secondary to CFTR dysfunction. (50) Although hepatic steatosis may be seen in the neonatal period of patients with CF, its incidence would be expected to be quite rare and clinical implications minimal. As such, findings suggestive of steatosis on neonatal ultrasonography (such as homogenous hyperechogenicity) should prompt a broad evaluation that may include CF, but not as the primary focus.

Liver Enzyme Elevations

Elevated liver enzyme levels are common during childhood in patients with CF diagnosed predominantly by newborn screening. Approximately 90% of patients will have at least 1 serum elevation of aspartate aminotransferase (AST) or alanine aminotransferase levels, and ~40% will have at least 1 serum elevation of GGT levels during childhood. Such elevations are particularly common in the first 2 years after birth, even at health supervision visits. Liver enzyme elevations are typically mild; elevations that are greater than 3 times the upper limit of normal (ULN) are rare at any age in patients with CF and occur more commonly in children younger than 24 months and during intercurrent illnesses. (60)

Intermittent elevations of transaminase levels do not seem to predict progression to cirrhosis, whereas persistent (>6 months) elevations in AST or GGT levels greater than 1.5 × ULN have been associated with progression to clinically significant liver disease. (60)(61) In patients with a long NICU course or early hospital admission and elevated AST, alanine aminotransferase, and/or GGT levels, routine monitoring is encouraged. This should include a hepatic function panel that includes GGT every 1 to 2 weeks if clinically stable, or as clinically indicated otherwise. Levels that are 3 × ULN or higher, persistent elevation, or any suggestion of progression of disease should prompt consultation with an experienced gastroenterologist or hepatologist.

Gallbladder and Biliary Tract Involvement

Gallbladder abnormalities have been observed in 25% to 50% of patients with CF, most of which are incidentally found on imaging. (62) Of particular importance in the neonate is the finding of a micro-gallbladder. Although it is benign and does not require treatment, it can mimic the ultrasonography findings in biliary atresia, which may raise diagnostic uncertainty if there is concurrent cholestasis.

Gallstones are more frequent in pediatric CF populations, with a reported pediatric incidence of 3% to 25%, and has been reported in the neonatal period. (62)(63) It is unclear why these patients with CF are predisposed to gallstone formation, but gallstones are more likely to be pigmented and are unlikely to dissolve after ursodeoxycholic acid treatment. 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. Recommended treatment of symptomatic cholelithiasis in patients with CF is generally similar to that in the general population. (64)

SUMMARY

- Based on evidence level A, gastrointestinal, pancreatic, and hepatic signs and symptoms are the most common initial manifestations in infants with cystic fibrosis (CF).
- Based on evidence level C, the decision to treat patients with CF and gastroesophageal reflux disease must be balanced between short-term effect on disease and nutrition with potential long-term consequences of dysbiosis and worse pulmonary outcomes.
- Based on evidence level C, early recognition of meconium ileus is critical, and management should follow an evidence-based algorithm. For those who require surgical intervention, close attention must be given to nutrition, hydration, and sodium status.
- Based on evidence level A, early nutrition is critical for patients with CF and can significantly affect long-term pulmonary, gastrointestinal, morbidity, and mortality outcomes.
- Based on evidence level B, the nutritional goal for all patients with CF is to achieve a weight-for-length at the 50th percentile (0 SD), similar to healthy same-age infants.
- Based on evidence level B, human milk is the preferred source of nutrition for infants with CF. If human milk is not an option, standard formula is appropriate.
- Based on evidence level B, early hepatic and gallbladder findings are not uncommon and typically do not require intervention.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the caloric requirements for optimal postnatal growth of preterm and term infants, accounting for caloric expenditures needed for physical activity and maintenance of body temperature.
- Know the causes, clinical manifestations, diagnosis, and management of congenital or acquired malabsorption syndromes.
- Know the clinical manifestations and pathophysiology of cystic fibrosis in the newborn infant.
- Know the diagnosis and management of cystic fibrosis in newborn infants.

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1. A female infant born at term is diagnosed as having cystic fibrosis (CF) after newborn screening. At 2 months of age she presents with colic, discomfort, and vomiting. Intussusception is suspected. Which of the following statements regarding intussusception and CF is correct?
    A. Surgery is the first line of treatment.
    B. It is more common in female infants compared with males.
    C. There is a peak occurrence in infancy, with a second peak occurring at approximately 10 years of age.
    D. Intussusception will occur in more than 10% of patients with CF during childhood.
    E. The optimal diagnostic test is magnetic resonance imaging.
2. Prenatal ultrasonography identifies hyperechoic mass, peritoneal calcifications, and polyhdramnios. Meconium ileus is suspected. Which of the following statements about meconium ileus is correct?
    A. Meconium ileus initially develops in utero and is frequently the first clinical manifestation of CF.
    B. Meconium ileus is less common in those who have class I-III CF transmembrane regulator mutations.
    C. Hyperechoic bowel is a highly sensitive and specific sign for the diagnosis of CF.
    D. The finding of meconium ileus should lead to prompt delivery of the infant, with antenatal steroids administered before delivery if gestational age is before 34 weeks.
    E. Newborns with meconium ileus typically have symptoms within the first 2 hours after birth, such as respiratory distress or bilious emesis.
3. A term newborn male infant presents with rectal prolapse. The physical examination findings are otherwise normal. Before the event, the infant had been breastfeeding well and having normal-appearing stools for his age. Which of the following is an appropriate next step for this patient?
    A. Sweat chloride test.
    B. Surgical repair under general anesthesia.
    C. Sclerotherapy.
    D. Evaluation for etiologies such as anorectal malformation or Hirschsprung disease.
    E. Sepsis evaluation and broad spectrum intravenous antibiotic therapy.
4. A 5-month-old boy has been diagnosed as having CF, with a history of meconium ileus, relatively severe gastroesophageal reflux, and frequent diarrhea. Which of the following statements regarding pancreatic insufficiency in CF is correct?
    A. The earliest potential manifestation and injury occurring from pancreatic insufficiency is with the addition of nonmilk foods.
    B. Approximately 30% of infants with CF will have pancreatic insufficiency by the time they reach the teenage years.
    C. Pancreatic acinar plugging with inflammation, ductal injury, and adipose replacement of the pancreatic parenchyma result in pancreatic insufficiency, most notably in patients with class I-III mutations.
    D. Treatment with pancreatic enzyme replacement therapy should be withheld until the infant reaches 6 months of age, and then given in short intervals of 1 to 2 weeks, to avoid complications of liver and renal dysfunction.
    E. In most patients with CF, pancreatic injury leading to diabetes will precede pancreatic insufficiency leading to gastrointestinal symptoms.

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5. A term male infant who had meconium ileus complicated by meconium peritonitis and required surgical intervention for bowel obstruction has been diagnosed as having CF. He is recovering from surgery, and nutrition is being advanced. Which of the following statements regarding nutrition for infants with CF is correct?
    A. The preferred source of nutrition in infants identified as having CF is elemental formula.
    B. Several meta-analyses have shown that the addition of probiotics, such as *Lactobacillus* and *Bifidobacterium,* during infancy is preventive for *Pseudomonas* respiratory infections in childhood.
    C. The caloric intake and expenditure of infants with CF is assumed to be the same as that of similar-age infants without CF.
    D. Fat-soluble vitamin deficiencies are common in patients with CF, particularly vitamin D.
    E. It has been well established that formulas containing higher concentrations of medium-chain triglycerides are beneficial for both gastrointestinal and respiratory symptoms, with improved growth outcomes.