Cystic Fibrosis

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PRACTICE GAPS

1. In light of the significant increase in the median survival age for individuals with cystic fibrosis (CF), both pediatric and adult providers should be familiar with the current recommendations related to optimization of lung health and nutritional status.
2. Providers should also be aware of the development of modulator therapies that target the different basic genetic defects of the disease, which have allowed for personalized therapies that promise continued improvement in outcomes. As of 2019, approximately 90% of individuals with CF have mutations that would benefit from modulator therapy.
3. Clinicians should be familiar with the clinical presentation, diagnosis, and current management of CF as well as the more common disease-related morbidities.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the common clinical manifestations of cystic fibrosis (CF) as well as the laboratory and genetic studies needed to diagnose CF.
2. Recognize the most common presentations of CF-related morbidities.
3. Describe the current recommendations for long-term maintenance of optimal lung health, nutritional status, and other involved organ systems in children with CF.

ABSTRACT

Cystic fibrosis (CF) is one of the most commonly diagnosed genetic disorders. Clinical characteristics include progressive obstructive lung disease, sinusitis, exocrine pancreatic insufficiency leading to malabsorption and malnutrition, liver and pancreatic dysfunction, and male infertility. Although CF is a life-shortening disease, survival has continued to improve to a median age of 46.2 years due to earlier diagnosis through routine newborn screening, promulgation of evidence-based guidelines to optimize nutritional and pulmonary health, and the development of CF-specific interdisciplinary care centers. Future improvements in health and quality of life for individuals with CF are likely with the recent development of mutation-specific modulator therapies. In this review, we will cover the current understanding of the disease manifestations, diagnosis, and management as well as common complications seen in individuals with CF.

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ABBREVIATIONS

ACT	airway clearance therapy
ABPA	allergic bronchopulmonary aspergillosis
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFRD	cystic fibrosis–related diabetes mellitus
CFTR	cystic fibrosis transmembrane conductance regulator
DIOS	distal intestinal obstruction syndrome
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
IRT	immunoreactive trypsinogen
NBS	newborn screening
PERT	pancreatic enzyme replacement therapy
PEx	pulmonary exacerbations

INTRODUCTION

Cystic fibrosis (CF) is a common life-shortening autosomal recessive genetic disorder characterized by pulmonary manifestations, specifically chronic and progressive obstructive lung disease, sinusitis, malabsorption due to pancreatic exocrine insufficiency leading to malnutrition, liver disease (biliary cirrhosis), and CF-related diabetes mellitus (CFRD). Earlier diagnosis through newborn screening (NBS), improved therapies to optimize lung health and nutritional status, as well as aggressive treatment of chronic respiratory infections and lung transplant for end-stage lung disease have led to significant improvements in survival. CF was a uniformly fatal disease in childhood at the time of its initial description in 1938, (1) but the predicted median survival is currently 46.2 years. Currently, more than 50% of people living with CF are 18 years and older, (2) resulting in the evolution of the disease from exclusively a disease of childhood to a disease where affected individuals transition to adulthood and adult providers. With the advent of newer therapies targeting the basic genetic defect that causes the disease and the expansion of the age and genetic variants for which these therapies are indicated, there is promise of continued improvement in quality of life as well as overall health and survival. Individuals with CF benefit from coordination of care between their primary care providers and their interdisciplinary CF care team, in addition to routine visits with both. This review covers the current understanding of the disease manifestations, diagnosis, and management as well as common complications seen in individuals with CF.

EPIDEMIOLOGY

CF is one of the most common genetic disorders among white people, with an incidence of 1:3,200 individuals. (3) The incidence does vary significantly by race/ethnicity, with an incidence of 1:13,500 in people of Hispanic background, 1:15,000 in people of African descent, and 1:35,000 in people of Asian descent. (4) It is estimated that 1 in every 35 Americans is a carrier of CF. (5) Based on statistics from the 2019 Annual Data Report published by the Cystic Fibrosis Foundation (CFF), there are an estimated 31,000 affected individuals in the United States living with CF. (2) Worldwide, there are an estimated 70,000 affected people, with the highest prevalence in North America, Europe, and Australia. Annually, approximately 1,000 new cases are diagnosed in the United States (although the rate of new cases may be declining related to preconception screening), (6) and the incidence is equal in males and females. Since 2010, all 50 states screen neonates for CF, (7) and, as a result, >60% of new diagnoses occur via NBS. (2)

PATHOGENESIS

CF is a multisystem disorder that results from deleterious genetic variants in the *CFTR* gene located on chromosome 7q31.2, which encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Defects in this protein lead to absent or malfunctioning chloride channels in the apical membranes of the lung surface epithelium, resulting in the formation of thick and sticky mucus, leading to chronic lung infections, pancreatic and liver dysfunction, and reduced fertility. CF also results in abnormal chloride channel function in the sweat glands, resulting in excessive salt loss in sweat, an observation first made by Dr Paul di Sant'Agnese after caring for infants with CF presenting with dehydration during a heat wave in New York City in 1948. (8) This clinical observation paved the way for the pilocarpine iontophoresis sweat test for CF diagnosis. (9)

CF is an autosomal recessive disorder, and for individuals to have CF they must inherit 2 deleterious *CFTR* variants. To date, there are more than 2,000 different *CFTR* variants reported, some of which are confirmed to cause CF and others with more putative links to the disease. (10)(11) They are classified into 6 distinct groups that reflect abnormalities of CFTR protein synthesis, structure, and function (Fig 1). The most common CF-causing variant is *F508del* (p.Phe508del). *F508del* is a class II mutation, meaning that the CFTR protein is created, but misfolding prevents it from reaching the cell surface (trafficking defect). Overall, 44.4% of individuals with CF are homozygous for *F508del*, an additional 40.9% have 1 copy of *F508del* and another variant, and 14.7% have 2 non-*F508del* variants. (2) The specific *CFTR* variants that an individual carries determine the amount of functioning CFTR protein present and are partially correlated with phenotypic severity and organ involvement. (12)

CLINICAL PRESENTATIONS

The classic manifestations of CF include a triad of recurrent sinus and pulmonary infections, steatorrhea, and malnutrition, which in its most severe form presents as failure to thrive. In the lungs, mucous plugging from dehydrated thick secretions results in inflammation, chronic infection, progressive obstruction of the small airways, and the development of bronchiectasis, which is an abnormal, permanent enlargement of the bronchi (Fig 2). Bronchiectasis leads to

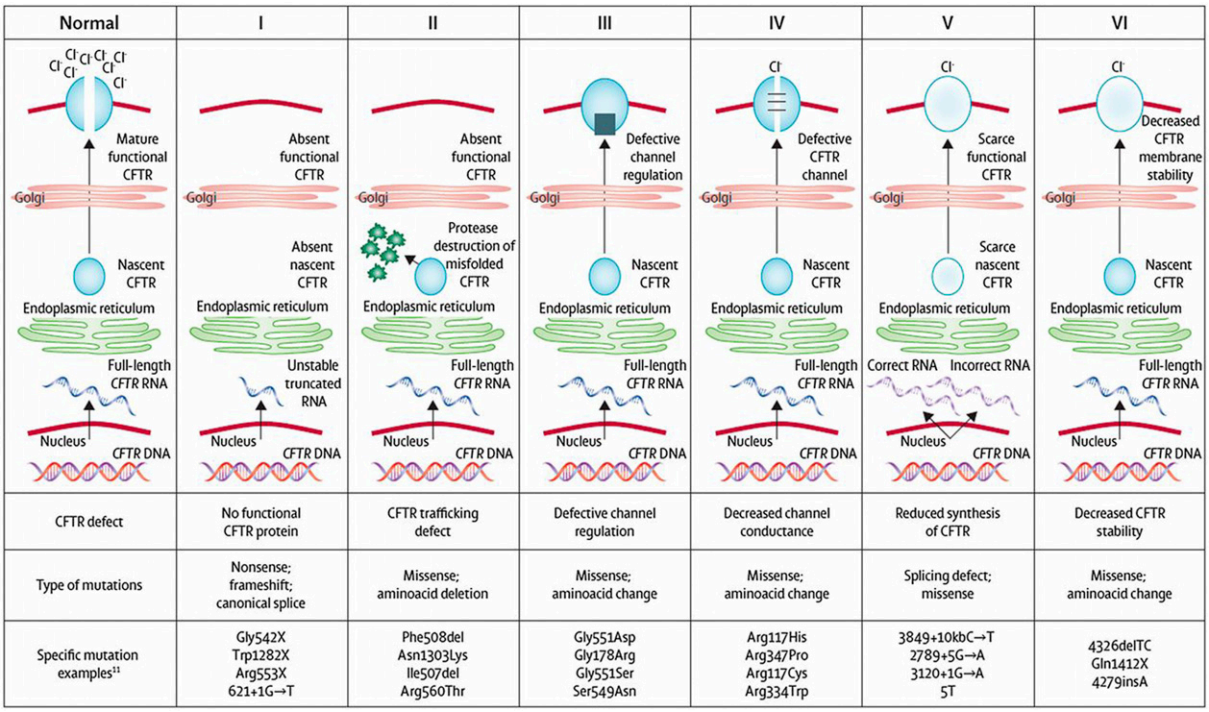


Figure 1. Cystic fibrosis transmembrane conductance regulator (CFTR) mutation classes. CFTR mutations have been grouped into 6 distinct classes based on abnormalities of CFTR synthesis, structure, and function. Reprinted with from: Boyle MP, DeBoeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med*. 2013;1(2):158–163.

decreased ability to clear secretions, causing increased rates of infections, which further dilates and damages the airways. In addition, the effects of diminished or absent chloride channel function can result in dysfunction in several other organ systems (Fig 3). Pancreatic involvement includes pancreatic exocrine insufficiency, which results in fat, protein, and carbohydrate malabsorption and subsequent malnutrition, as well as insulin insufficiency and the development of CFRD.

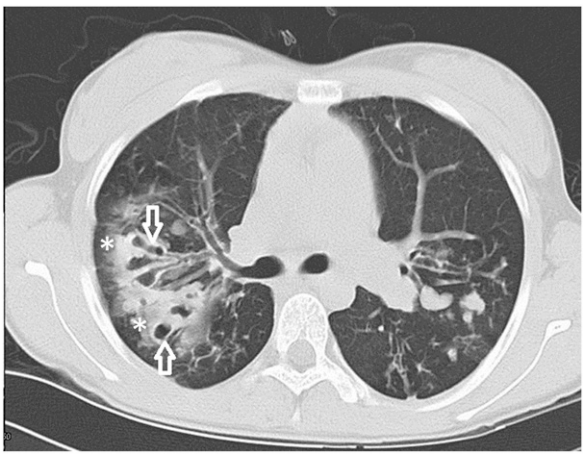


Figure 2. Chest computed tomographic scan of an adolescent girl with cystic fibrosis demonstrates significant bronchiectasis (white open arrows) and mucous plugging (white asterisks). Reprinted from: Paranjape SM, Mogayzel PJ. Cystic fibrosis. *Pediatr Rev*. 2014;35(5).

In infants and young children, other presentations may also be indicative of CF. In utero, ultrasonographic evidence of hyperechogenic or dilated bowel suggests intestinal obstruction, which has been reported in 50% to 78% of fetuses affected with CF. (13)(14) Postnatally, delayed meconium passage or meconium ileus is present in 11.9% of infants younger than 1 year with CF; (2) it results from thick gastrointestinal secretions that become adherent to the intestinal mucosa, leading to bowel obstruction. Meconium ileus is often accompanied by abdominal distention and dilated loops of bowel on imaging, and a reported 30% of cases of meconium ileus are complicated by intestinal perforation and peritonitis. (2) Approximately 20% of untreated children (aged 6 months to 3 years) have rectal prolapse, which is secondary to malabsorption, malnutrition, and bulky stools as opposed to constipation. (15) Other clinical presentations during the neonatal period may include prolonged jaundice secondary to biliary stasis or bile duct obstruction and hemorrhagic disease of the newborn owing to vitamin K deficiency. Throughout infancy and early childhood, individuals

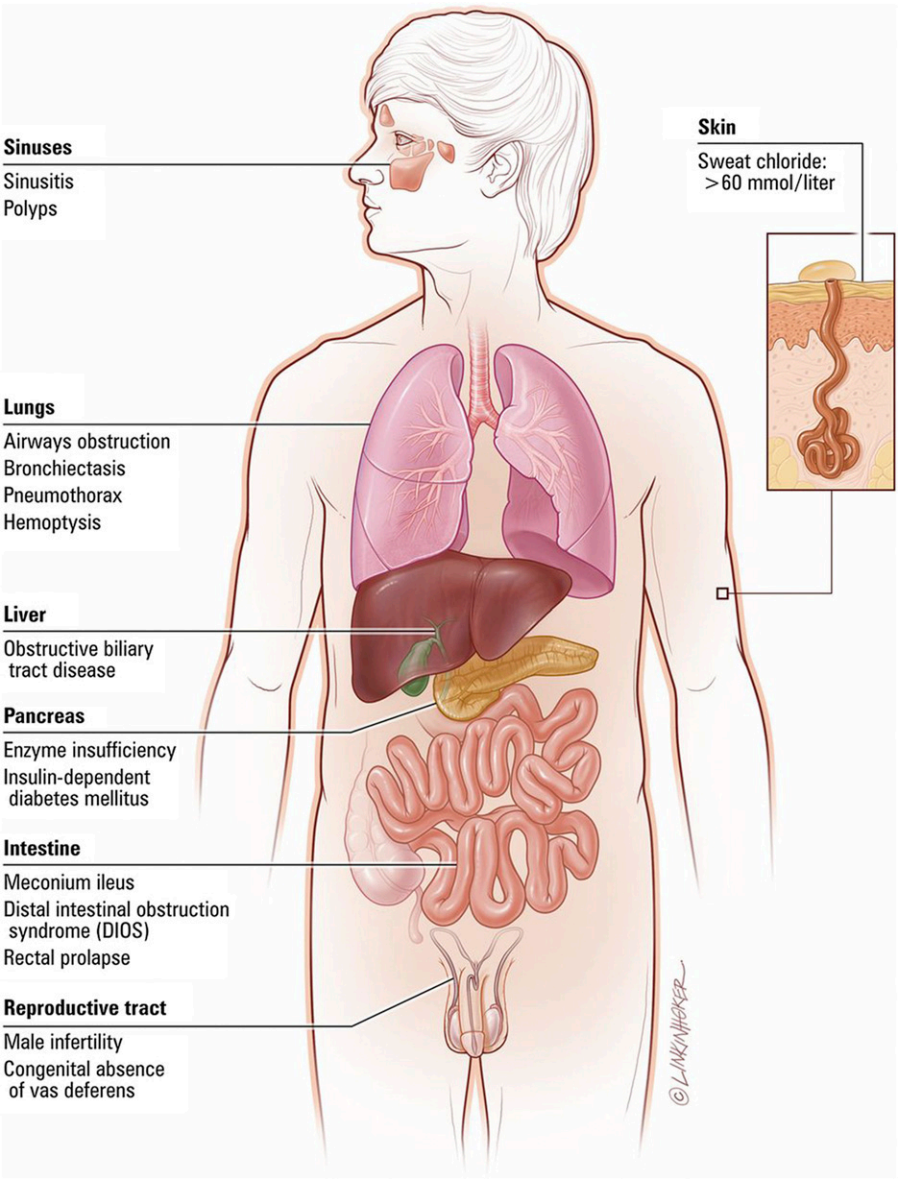


Figure 3. Common clinical manifestations of cystic fibrosis. Reprinted with permission from Link Studio LLC.

may also present with salt depletion syndrome characterized by a hyponatremic, hypochloremic, hypokalemic metabolic alkalosis and edema/acrodermatitis due to hypoproteinemia from malabsorption. (16)

Typical respiratory findings in older children, adolescents, and adults who newly present with CF may include recurrent sinusitis, bronchitis, or pneumonias; asthma that is poorly responsive to standard management; nasal polyposis or digital clubbing on physical examination; and bronchiectasis on lung imaging studies. (16) Common gastrointestinal symptoms may include malnutrition, poor growth, steatorrhea, intestinal obstruction, chronic constipation, rectal prolapse, and liver disease. (17) Individuals with pancreatic-sufficient CF (who are more likely to be diagnosed later in life due to appropriate weight gain) can present with pancreatitis secondary to progressive pancreatic inflammation, although the exact etiology is unclear. (18) Finally, more than 98% of men with CF are infertile as a result of obstructive azotemia secondary to congenital bilateral absence of the vas deferens and may be diagnosed during an infertility evaluation. (19) NBS is expected to reduce, but not eliminate, late clinical presentations given the expected rate of false-negatives associated with screening. Clinicians should include CF in the differential diagnosis for unexplained recurrent respiratory bacterial infections (pneumonia, bronchitis, persistent cough, and/or sinusitis) and/or failure to thrive.

SCREENING

NBS for CF, first introduced in the 1980s, is performed by measuring an immunoreactive trypsinogen (IRT) level in screening neonatal blood spots. In neonates with CF, mucous plugs partially block the pancreatic ducts that lead into the small intestine, preventing trypsinogen from reaching the intestine and being converted to the pancreatic enzyme trypsin, even in infants with CF who are pancreatic sufficient. If an infant has an elevated IRT level, almost all US state laboratories perform confirmatory *CFTR* variant testing (IRT/DNA), with 1 state laboratory currently repeating the IRT measurement (IRT/IRT). Screening is considered positive if the IRT level remains persistently elevated between ages 7 and 14 days or if at least 1 deleterious *CFTR* variant is identified on genetic testing. A positive NBS result will trigger notification of either a neonatal intensive care provider or a primary care provider, and the infant should be referred to a CFF-accredited center for definitive evaluation and sweat testing within 72 hours of a positive screening result. (20) Care centers may be located on the CFF website (http://www.cff.org/ccd/).

The benefits of diagnosing asymptomatic infants with CF include increased attention to early lung health to slow lung disease progression, optimization of nutritional status with early enzyme replacement and aggressive nutritional counseling, and provision of psychosocial support to families to help prevent or delay serious complications. (16) Possible risks of NBS include an increased number of medical interventions, earlier exposure to respiratory pathogens through attending a CF clinic, financial hardships given the cost of CF-related therapies, possible iatrogenic complications (eg, early exposure to therapies with adverse effects), and caregiver anxiety or guilt stemming from false-positive screening results due to perinatal asphyxia or other perinatal problems. (16)(21) False-positive rates may also be higher in African American children because they have higher IRT levels than white children, (22) but a much lower risk of CF. NBS can also be falsely negative, particularly in neonates with meconium ileus (23) or those screened via IRT/DNA because this testing may be less sensitive for picking up mutations in minority populations. (22) With current NBS practices, the possibility exists for a positive NBS and the identification of *CFTR* variants that do not meet clinical criteria for CF diagnosis in individuals with normal or intermediate sweat chloride testing, a syndrome known as CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis. (24)

DIAGNOSIS

The CFF published consensus guidelines in 2017 establishing that a diagnosis of CF can be made if an individual has a clinical presentation consistent with the disease, ie, 1) a positive NBS result, 2) clinical features consistent with CF (the presence of characteristic phenotypes such as of chronic, recurrent sinus and pulmonary disease, nutritional and gastrointestinal abnormalities, urogenital abnormalities in males [eg, absence of the vas deferens], and/or salt depletion syndromes), or 3) a positive family history of CF and evidence of CFTR dysfunction (eg, a sweat chloride concentration ≥60 mEq/L[≥60 mmol/L]). (24)(25)

Although prenatal screening and NBS have allowed for earlier detection of CF in asymptomatic individuals, the quantitative pilocarpine iontophoresis sweat test remains the gold standard for the diagnosis of CF. The sweat test, developed by Drs Lewis Gibson and Robert Cooke in 1959, (9) specifically measures the amount of chloride in a person's sweat. Sweat chloride testing should be performed as soon as possible after a positive NBS result. It can be performed as early as 48 hours after birth (because sweat sodium levels are transiently elevated in the first 24 hours) (26) but should be undertaken as soon as possible after 10 days of age and ideally by 4 weeks of age. Infants should weigh more than 2 kg or be corrected to 36 weeks' gestation to increase the likelihood of adequate sweat collection. (24) Infants with meconium ileus and infants and children with symptoms suggestive of CF, such as recurrent bacterial respiratory infections and/or failure to thrive, should receive sweat chloride testing regardless of age or NBS results. Any sweat test with an abnormal result should be repeated on a separate date or confirmed with genetic testing.

Results from sweat chloride testing can be categorized into diagnostic, intermediate, and unlikely. Diagnostic sweat chloride values are 60 mEq/L or greater (≥60 mmol/L) and require a confirmatory second sweat test or 2 identified CF-causing genetic variants to make the diagnosis. Intermediate values are between 30 and 59 mEq/L (30-59 mmol/L); sweat chloride testing should be repeated periodically in these individuals, and further evaluation at a CF center should be considered. A diagnosis of CF can still be made in an individual with an intermediate value if the individual has 2 identified CF-causing genetic variants. Individuals with an intermediate sweat chloride value of 30 to 59 mEq/L (30-59 mmol/L) and 0 to 1 CF-causing genetic variants may be diagnosed as having a CFTR-related disorder depending on clinical presentation and family history. Individuals with sweat chloride values less than 30 mEq/L (<30 mmol/L) are unlikely to have CF, but if 2 CF-causing genetic variants are identified, they should still be diagnosed as having CF. (24)

In conjunction with sweat testing, genetic testing is now widely available to help confirm a diagnosis of CF, particularly for cases with intermediate sweat chloride values.

Identifying an individual's specific CF-causing variants is needed for prescribing CFTR modulator therapies, which are approved for particular *CFTR* variants. A diagnosis by genotype can be made with the identification of 2 known pathogenic variants on separate chromosomes. Most individuals with CF can be diagnosed through commercial laboratories, which test for the most common *CFTR* variants, (27) but complete sequencing of the *CFTR* gene may be necessary to help confirm the diagnosis in individuals with clinically atypical presentations. (16) Clinical information related to specific *CFTR* variants can be found online (http://cftr2.org).

The era of genetic testing has expanded our understanding of CFTR dysfunction but has also added complexity to the diagnosis of CF because there are individuals with CF phenotypes without known CF-causing mutations as well as individuals with detected mutations who remain asymptomatic. The limitations of sweat chloride testing and genetic testing may require performing both tests in selected patients where there is strong clinical suspicion of CF. (28)

CF Management

In the United States, individuals with CF should be evaluated a minimum of quarterly in a CFF-accredited care center, (29) which can provide interdisciplinary, patient/family-centered care. Infants younger than 6 months should be evaluated monthly and then every 1 to 2 months in the second 6 months after birth. (20) These regular visits allow for education surrounding airway clearance methods, infection prevention, monitoring of age-appropriate growth and weight gain, and, in older children, assessment of lung function.

Therapies to Maintain Optimal Lung Health

CF is characterized by viscous airway secretions that lead to chronic mucous obstruction, inflammation, and recurrent infections that result in long-term damage to the airways (bronchiectasis) and lung parenchyma. (16) Chronic cough and sputum production are characteristic symptoms. Management of respiratory symptoms focuses on maintaining lung function and preventing the development of bronchiectasis and parenchymal destruction. (30) In addition to encouraging a smoke-free environment, children with CF are often prescribed several therapies, which will likely be lifelong and should be initiated shortly after diagnosis.

Clearance of Airway Secretions. A critical aspect of maintaining lung health is airway clearance therapy (ACT). By removing airway mucus, ACT helps decrease the respiratory bacterial load along with irritants, leading to improved gas exchange and a decrease in airway obstruction. (16) Twice daily ACT as maintenance is recommended for all patients with CF, regardless of symptoms or disease severity, and is increased in frequency during acute CF pulmonary exacerbations (PEx). (31) Commonly used ACT modalities include manual percussion, positive expiratory pressure devices, and high-frequency chest wall oscillation (achieved through an inflatable vest that performs chest physical therapy by vibrating at a high frequency). No form of ACT has been demonstrated to be superior to any other form, and ACT choice should be personalized. Exercise should be encouraged as an adjunctive therapy but should not be used as a substitute for airway clearance. (31) Nebulized agents that thin the viscous mucus of CF are commonly used with ACT and include recombinant human rhDNase (dornase alfa [Pulmozyme®; Genentech Inc, South San Francisco, CA]) and hypertonic saline.

Chronic Airway Infections. In addition to patient education and infection control measures, aggressive management of chronic airway infections has been shown to prevent lung function decline. (32) Management includes frequent respiratory cultures (oropharyngeal or sputum), including surveilling for *Staphylococcus aureus* (particularly methicillin-resistant *S aureus*) and *Pseudomonas aeruginosa*. (16) Receiving microbiology laboratories should be made aware of the patient's CF diagnosis to assess for the respiratory pathogens commonly seen in CF. The initial acquisition of *P aeruginosa* is typically treated with antipseudomonal antibiotics, such as nebulized tobramycin, in an attempt to achieve eradication. (33) Nebulized antibiotics, such as tobramycin or aztreonam (Cayston®; Gilead Sciences Inc, Foster City, CA), can also be used as suppressive therapy for individuals with chronic infection or colonization with *P aeruginosa* and/or other gram-negative organisms. This suppressive therapy is administered every other month to decrease the risk of antibiotic resistance. Other organisms, including *Burkholderia cepacia* complex, nontuberculous mycobacteria (*Mycobacterium avium* complex and *Mycobacterium abscessus*), and fungal pathogens (*Aspergillus fumigatus*), are also monitored because they can have a significant effect on CF lung disease. Of note, individuals with CF are also prone to developing a hypersensitivity reaction to *Aspergillus*, known as allergic bronchopulmonary aspergillosis (ABPA), which can affect lung function and requires management with corticosteroid therapy. (34)

Chronic Airway Inflammation. Cystic fibrosis lung disease is caused by a combination of infection and inflammation. The routine use of oral or inhaled corticosteroids in CF is not indicated unless used for another inflammatory comorbidity such as asthma or ABPA. (30) Chronic airway

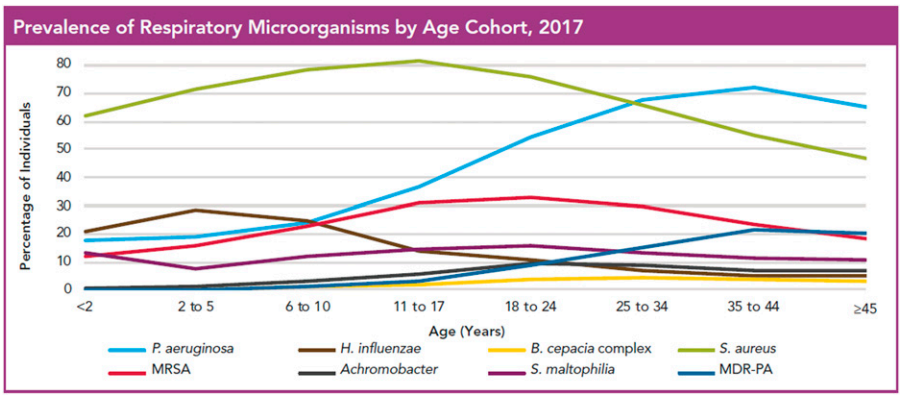


Figure 4. Prevalence of bacterial pathogens in cystic fibrosis. MDR-PA=multidrug-resistant *Pseudomonas aeruginosa,* MRSA=methicillin-resistant *Staphylococcus aureus*. Reprinted from: Cystic Fibrosis Foundation Patient Registry © 2017 Cystic Fibrosis Foundation.

inflammation is managed with either high-dose ibuprofen or azithromycin. (35) Although ibuprofen has proven benefits in CF, the risk of gastrointestinal bleeding and the need for monitoring serum levels has limited its use. (36) Azithromycin therapy has been demonstrated to result in improved lung function and a reduced number of PEx, and it is typically given orally 3 times per week. (37) However, there is concern that individuals with unrecognized mycobacterial infections receiving azithromycin long-term may develop resistance; screening using mycobacterial cultures is recommended before initiating treatment. (30)

Therapies to Maintain Optimal Nutritional Status

Decline in pulmonary status is the hallmark of CF; however, poor growth is one of its earliest manifestations. The combined effects of decreased intake, malabsorption, and increased metabolic demands contribute to the poor growth seen as early as infancy. Malnutrition has been associated with increased morbidity and mortality in CF. (38) CFF guidelines recommend that all children achieve a weight-for-length at or above the 50th percentile by 2 years old and that all children and adolescents aged 2 to 20 years maintain a BMI at or above the 50th percentile. (20)(39) Education about the role of enteral tube feeding in optimizing nutritional status should be provided to caregivers and patients throughout their lifetime. (40) Infants with CF should receive human milk if possible, and otherwise should receive standard infant formula (rather than hydrolyzed protein formulas). (20) Infants younger than 2 years should be supplemented with table salt, up to ¼ tsp per day by 6 months of age, (20) due to ongoing salt losses. Infants with CF should have their fecal elastase measured after diagnosis to assess pancreatic functional status because 85% of individuals with CF are exocrine pancreatic insufficient (fecal elastase level <200 μg/g). (2) Pancreatic insufficiency leads to malabsorption, which presents as bulky, malodorous stools; malnutrition; and, ultimately, failure to thrive.

Pancreatic Enzyme Replacement Therapy. Pancreatic enzyme replacement therapy (PERT) should be initiated in those with a diagnostic fecal elastase level or 2 *CFTR* variants associated with pancreatic insufficiency as well as those with unequivocal signs or symptoms of malabsorption. Individuals who have exocrine pancreatic insufficiency require enzyme replacement with every meal, snack, and enteral tube feeding, ranging from 2,000 to 2,500 U/kg of lipase per meal to a maximum of 10,000 U/kg per day. (29)(41) Immobilized lipase cartridges may be used for patients on continuous enteral tube feeding to help hydrolyze fats in enteral formulas. Exceeding recommended dosages generally does not result in improved nutrient absorption, and supratherapeutic dosing is associated with fibrosing colonopathy, an uncommon complication characterized by foreshortening and strictures of the right colon. (42) Individuals with CF can achieve age-appropriate growth with optimized PERT. (43)

Fat-Soluble Vitamin Replacement Therapy. Pancreatic insufficiency results in malabsorption of fat and associated fat-soluble vitamins A, D, E, and K. Vitamin A deficiency can be associated with night blindness and ocular xerosis, as well as dermatologic manifestations, such as follicular hyperkeratosis. (16) Vitamin D deficiency may result in rickets, osteopenia, and osteoporosis, which can result in fractures; recommendations for individuals with CF specify maintaining a goal serum 25-hydroxyvitamin D level of at least 30 ng/mL (≥75 nmol/L). (44) Vitamin E deficiency may result in peripheral neuropathy, myopathy, and hemolysis, and vitamin K deficiency is associated with coagulopathy and may also contribute to bone disease. (16) Supplemental vitamin therapy should begin after diagnosis, and annual monitoring of serum vitamin A, D, and E levels by CF providers is recommended. (20)

CFTR Modulator Therapies

CFTR modulators are the first therapies to target the basic defect in CF by directly acting on the CFTR protein. They are categorized into 3 types: potentiators, correctors, and amplifiers. (45) Ivacaftor (Kalydeco®; Vertex Pharmaceuticals Inc, Boston, MA), the first approved modulator therapy, is a potentiator, which helps improve chloride flow through the CFTR protein at the cell surface for patients with class III-V mutations. Correctors such as lumacaftor and tezacaftor help the CFTR protein to form correctly and allow the protein to move, or traffic, to the cell surface. When added to potentiators, correctors such as lumacaftor/ivacaftor (Orkambi®; Vertex Pharmaceuticals Inc) or tezacaftor/ivacaftor (Symdeko®; Vertex Pharmaceuticals Inc) work to improve the amount of protein that reaches the cell surface for patients with class II mutations. Kalydeco is currently Food and Drug Administration (FDA)–approved for individuals 6 months and older, Orkambi for those 2 years and older with homozygous *F508del* variants, and Symdeko for those 6 years and older with homozygous *F508del* or several other specific CF variants.

In 2019, the FDA approved the use of a triple-combination therapy, elexacaftor/tezacaftor/ivacaftor (Trikafta®; Vertex Pharmaceuticals Inc), for individuals 12 years and older with at least 1 *F508del* variant. This new therapy will allow nearly 90% of individuals with CF to have a highly effective therapy for the underlying cause of their disease. Trikafta has been shown in clinical trials to dramatically improve key measures of disease, including increasing lung function, reducing PEx, decreasing sweat chloride values, increasing BMI, and improving patient-reported quality of life. Amplifiers are expected to increase the amount of CFTR protein that a cell makes, but they are under development and not currently available clinically. (46)

Diagnosis and Management of Common Pulmonary and Extrapulmonary Complications of CF

Pulmonary Exacerbations. One of the most common complications of CF lung disease is episodic acute worsening of symptoms, referred to as PEx. PEx are characterized by increased respiratory symptoms, including coughing, sputum production, and/or wheezing; a decline in pulmonary function measures (specifically, forced expiratory volume in 1 second [FEV_1]); fatigue; decreased appetite; and weight loss. (47) Fevers are not commonly seen with PEx. (16) The frequency of PEx varies among individuals, but contributes to the long-term lung function decline of most people with CF. Treatment typically includes antibiotics and increased frequency of ACT to help clear secretions from the airways. Antibiotic therapy and mode of delivery (enteral, inhaled, and/or intravenous) are dictated by the severity of the exacerbation and previous/current respiratory culture results (Fig 4).

Hemoptysis. Hemoptysis is reported to occur in 3% of individuals with CF annually. (2) Although often seen with severe lung disease, it can also be a manifestation of a PEx. (48) CF-related hemoptysis is most commonly a result of chronic infection and inflammation, leading to erosion of hypertrophied bronchial arteries into the airways. (49) Vitamin K deficiency, either from malabsorption or liver disease, can contribute to hemoptysis. Managing scant to moderate hemoptysis (240 mL) includes evaluation, likely antibiotic therapy for PEx management, and consideration of limiting certain exacerbating therapies, such as ibuprofen, hypertonic saline, DNAse, and ACT. (48) Massive hemoptysis (>240 mL) is considered life-threatening, and management includes appropriate stabilization and discontinuation of anti-inflammatory and airway clearance measures. The treatment for massive hemoptysis or significant recurrent hemoptysis is bronchial artery embolization, if the site of bleeding can be identified. (48)

Pneumothorax. Pneumothoraces occur secondary to air trapping. High alveolar pressure forces air into the lower pressure interstitial spaces, leading to air leak into the pleural space, resulting in symptoms of acute chest pain and dyspnea. (16) The prevalence of having at least 1 pneumothorax is 3.4% among individuals with CF. (50) Pneumothoraces are more likely in adults and those with advanced lung disease. (50) The initial diagnostic test is chest radiography, but computed tomography may be required to define the extent of a pneumothorax in severe lung disease. (16) Small pneumothoraces may be observed or treated with needle aspiration, but large pneumothoraces require chest tube placement and hospitalization. (48) Pleurodesis is an option for recurrent pneumothoraces but may complicate later lung transplant. After development of a pneumothorax, individuals should refrain from devices that use positive pressure (including vest therapy) as well as pulmonary function testing for at least 2 weeks because these can hinder the resolution of the pneumothorax or lead to recurrence. (48)

Chronic Rhinosinusitis and Nasal Polyposis. The epithelium of the sinuses also possesses defective CFTR protein, so chronic pan-sinus disease is almost universal in individuals with CF. (51) In contrast, the prevalence of nasal polyposis is more variable and increases with age. (52) Both rhinosinusitis and nasal polyposis result from mucous obstruction of the sinus ostia. Clinical presentations may include chronic headache and facial pressure.

Long-term findings may include broadening of the nasal bridge and septal deformation from chronic nasal obstruction. (16) Medical management includes saline nasal irrigation to aid with mucus clearance and nasal steroids to decrease inflammation. Surgical treatment for severe and recurrent disease can improve mucus clearance, but may not necessarily improve lung function. (53)(54)

Distal Intestinal Obstruction Syndrome. Distal intestinal obstruction syndrome (DIOS) is a common gastrointestinal complication in CF. It presents as partial or complete small bowel obstruction secondary to viscous fecal impaction in the distal intestine. Clinical manifestations include abdominal pain and distention, emesis, and a history of decreased stooling. Pathophysiology may be related to CFTR-dependent bile acid secretion and uptake in the distal ileum. (55) Known risk factors for DIOS include dehydration, dietary changes, suboptimal fat absorption (ie, inadequate PERT dosing), immobilization, bacterial overgrowth, a previous episode of DIOS, and constipating medications. (55)(56) The differential diagnosis for DIOS includes intussusception, constipation, intestinal adhesions from previous abdominal surgery, volvulus, inflammatory bowel disease, and appendicitis. (16)(56) Abdominal radiography, history, and physical examination are usually sufficient to make the diagnosis, but other causes of bowel obstruction should be considered. Management typically includes rehydration and osmotic laxative therapy. More severe cases may require inpatient admission, intravenous fluids, complete bowel rest, and the use of large volumes of polyethylene glycol. Near-complete obstruction may require sodium meglumine diatrizoate (Gastrografin®; Bracco Diagnostics Inc, Monroe Township, NJ) enemas with retrograde lavage and visualization of the terminal ileum by an experienced radiologist. With early diagnosis and implementation of appropriate medical management, surgical interventions are generally not required for DIOS. (16)

CF-Related Diabetes Mellitus. CF leads to disruption of both the exocrine and endocrine functions of the pancreas. CFRD results from ongoing obstructive damage to the pancreas from thick secretions, which in turn results in fatty infiltration of the pancreas and islet cell destruction. (16) CFRD typically presents after the first decade and occurs in up to 20% of adolescents and at least 50% of adults with CF. (57) CFRD is typically diagnosed in patients with pancreatic insufficiency and has been associated with increased morbidity and mortality through worse nutritional status and decreased lung function. (58)(59) CFRD is often asymptomatic, and unexplained decreases in growth, weight, or lung function may be related to occult CFRD. Annual screening conducted via 2-hour oral glucose tolerance test should be initiated at age 10 years. (60) Studies have found that fasting levels of hyperglycemia or increased levels of glycated hemoglobin are not sufficiently sensitive for the diagnosis of CFRD; therefore, hemoglobin A1c levels should not be used for screening for CFRD. (61) However, hemoglobin A1c levels can be used to monitor glucose control in individuals with CFRD. Although microvascular complications such as retinopathy, microalbuminuria, and neuropathy may occur with CFRD, similar to other forms of diabetes, ketoacidosis is uncommon. (16)(60) The management of CFRD is focused on glycemic control through insulin therapy; oral antihyperglycemic agents are not as effective as insulin in improving long-term outcomes. Nutritional management remains focused on maintaining a high-calorie diet while attempting to limit intake of processed carbohydrates to avoid hyperglycemia.

CF Liver Disease. Liver disease accounts for 3.2% of overall CF mortality. (2) Approximately 3% of individuals develop CF-related cirrhosis (primarily individuals with pancreatic insufficiency), with a median age at diagnosis of 10 years. (62)(63) Clinical manifestations include cholestasis, cholelithiasis, cirrhosis, portal hypertension, and, in severe cases, end-stage liver disease. The pathophysiology is thought to be related to the role of CFTR in promoting bile flow, with abnormal flow leading to cholestasis and biliary fibrosis. (64) Males as well as carriers of alpha-1 antitrypsin Z allele are at increased risk for advanced liver disease. (64)(65) Periodic screening and evaluation for CF liver disease is critical because many individuals remain asymptomatic even with advanced cirrhosis. Annual screening of individuals should include assessment of liver function (aspartate aminotransferaseAST, ALT, and GGT), an ultrasound evaluation and/or evaluation by a gastroenterologist for other causes of liver disease, as indicated. The presence of CFLD should be considered with at least 2 of the following(1): abnormal physical examination findings such as hepatosplenomegaly, (2) abnormalities of liver function test results above normal reference ranges on at least 3 consecutive determinations during a 12-month period, (3) ultrasound with Doppler evidence of abnormal liver echotexture or portal hypertension, or(4) tissue biopsy has ruled out other causes of liver disease. (66 While there are currently no proven therapies to prevent development or progression of CF-related cirrhosis, ursodiol is frequently used in the management of hyperbilirubinemia in CFLD.

Bone Disease. Another complication of CF is cystic fibrosis-related bone disease, which manifests as low bone density and increased rates of fractures. Poor bone health is likely

a result of a combination of factors including malabsorption of fat-soluble vitamins such as vitamin D and K, in addition to poor nutritional status and chronic lung inflammation. Prevention includes optimizing nutritional status as well as encouraging weightbearing exercise, while dual X-ray absorptiometry is used for screening at-risk patients. Treatment includes aggressive management of potential pulmonary or endocrine comorbidities, and may include bisphosphonates for those with severe osteopenia. (67)

Depression/Anxiety. Living with a chronic illness, such as CF, can be both challenging and isolating, placing individuals with CF at higher risk for mental health issues. Approximately 15% of all individuals with CF report having either an anxiety disorder or depression, and 44% of individuals with CF report having both conditions. (2) It is recommended that all children with CF who are 7-11 years old be clinically assessed for depression and anxiety when a caregiver reports clinically elevated symptoms of depression or anxiety, or when there is significant concern for the child exhibiting symptoms of depression or anxiety. Annual screening for depression and anxiety in individuals with CF should begin at 12 years old using the PHQ-9 and GAD-7, respectively. Annual screening is also recommended for caregivers of children with CF. (68) Early identification of mental health difficulties is critical to helping ensure individuals receive referrals to appropriate mental health services in order to receive treatment and maintain their overall health and quality of life.

Preventative Care. Children with CF should receive routine well-child care according to the American Academy of Pediatrics guidelines, including all vaccinations. Annual influenza vaccination is recommended for children 6 months and older, as well as for all household members. The use of palivizumab should be considered in all children with CF younger than 2 years as prophylaxis against respiratory syncytial virus. (20) Providers should encourage a smoke-free environment for all children with CF, and caregivers should be informed of the health effects associated with second-hand smoke exposure.

Transition from Pediatric to Adult CF Care Centers. Because most individuals with CF are living into adulthood, the topic of transition from pediatric care centers to adult care centers will continue to be important for patients and their families. One step identified to improve the transition process includes introducing the ideas of self-care skills and transition to adult care during the teenage years. Readiness assessments for self-management skills, including the Transition Readiness Assessment Questionnaire, (69) and transition tool sets have been used to assess patients' readiness to transition to more independent management of their disease. These discussions should also include educational/vocational plans, behavioral risk counseling, screening for depression/anxiety, and reproductive health and family planning. Finally, implementation of formal transition-focused visits may be helpful to introduce patients to their new care team in a familiar clinic setting. (70)

Lung Transplant. Pulmonary disease continues to account for almost 60% of CF-related mortality. (2) Lung transplant is a surgical option that can extend and improve the quality of life of individuals with CF, but it involves extensive evaluation before transplant as well as adherence with therapies and lifestyle recommendations to optimize the success of transplanted lungs. Lung transplant confers a survival benefit, (71) with recent reports indicating that individuals with CF are experiencing 9.5-year median survival after lung transplant. (72) CF providers are recommended to discuss disease trajectory and treatment options, including risk and benefits of lung transplant, with individuals with advanced lung disease, and referral to lung transplant centers should be discussed with individuals whose FEV_1 is less than 50% predicted or is rapidly declining (>20% decline in FEV_1 over 12 months). (73) Overall, 6.3% of CF transplants performed in 2018 were in individuals younger than 18 years, (2) and criteria for referral are similar to those for adults older than 18 years. (73) Discussion about lung transplant may be viewed as another transition by individuals with CF and should be facilitated by education, communication, and support for the individual and his or her family. (73)

CONCLUSION

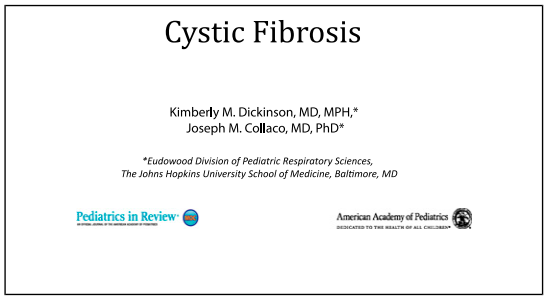
Individuals affected by CF are living longer and healthier lives, and survival is expected to continue to improve with earlier diagnosis through routine NBS, promulgation of evidence-based guidelines, interdisciplinary care centers, and the use of mutation-specific modulator therapies. The primary goals of treatment remain optimization of pulmonary function and nutritional status, and incremental advances in these therapies have had a profound effect on health and quality of life for individuals with CF. Building

partnerships with individuals and their families requires recognition of the emotional, social, and financial effects of this lifelong disease and effective communication and coordination among primary care physicians and CF care center teams.

Summary

- On the basis of consensus, (22) the diagnosis of cystic fibrosis (CF) is based on 1) a positive newborn screening; 2) clinical features consistent with CF (the presence of ≥1 characteristic phenotypic features of chronic, recurrent sinopulmonary disease, nutritional and gastrointestinal abnormalities, male urogenital abnormalities (eg, absence of the vas deferens), and salt depletion syndromes; or 3) a positive family history of CF and laboratory-demonstrated evidence of CFTR dysfunction, such as elevation of sweat chloride concentration (≥60 mEq/L [≥60 mmol/L]).
- On the basis of consensus, (50) annual oral glucose tolerance tests are recommended for people with CF older than 9 years to screen for CF-related diabetes mellitus.
- On the basis of research evidence, (25) the long-term therapies to maintain optimal lung health for children and adults with CF include control of chronic airway infection and inflammation, clearance of mucous secretions, and, where clinically applicable, treatments aimed at the basic CF genetic defect.

***To view teaching slides that accompany this article, visit* http://pedsinreview.aappublications.org/content/42/2/55.**



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1. A newborn male infant has a positive newborn screen for cystic fibrosis (CF). You prepare to meet with the parents to discuss the diagnosis. The baby is the product of full-term pregnancy with no perinatal complications. His prenatal course was unremarkable. The mother had detailed fetal ultrasonography at 20 weeks' gestation, which showed no abnormalities. In discussing the newborn screening results with the family, which of the following best describes the benefit of CF identification in an asymptomatic infant on newborn screen?

   A. Decrease in the number of medical interventions needed for the child who tests positive.
   B. Early commencement of appropriate antibiotic therapy based on the cystic fibrosis transmembrane conductance regulator (CFTR) mutation.
   C. Early implementation of optimal nutritional counseling.
   D. Less anxiety for families due to an earlier diagnosis of CF in their child.
   E. Less risk of exposure to respiratory pathogens in CF clinics because most patients in these clinics are being treated with antibiotics.

2. You are following a 2-month-old girl in your practice who had a positive newborn screen for CF and a sweat chloride level of 40 mEq/L (40 mmol/L). Which of the following is the most appropriate advice to give to the child's parents about the disease?

   A. Follow-up would be recommended for your child in a CF center with periodic monitoring, including repeating the sweat test and CFTR genetic testing.
   B. Genetic testing for CF mutations (CFTR) is not recommended at this time because your child has intermediate sweat chloride levels.
   C. It would still be recommended to prophylactically treat your child with antibiotic therapy given the diagnostic uncertainty of CF.
   D. Nutritional counseling is recommended for now. If the baby exhibits failure to thrive then she can be referred to a CF center for further management.
   E. Because the sweat chloride level in your child is below a diagnostic level of 60 mEq/L (60 mmol/L), it is unlikely that your child has CF.

3. A 12-month-old boy with CF is brought to the clinic by his parents for routine follow-up. His weight-for-length is at the 40th percentile. Which of the following is the most appropriate management plan to optimize this patient's nutritional status?

   A. Measure fecal elastase level to assess the status of pancreatic function.
   B. Place a gastrostomy tube and start enteral feeding.
   C. Place the child on hydrolyzed protein formula.
   D. Reassurance, routine follow-up, and no special intervention.
   E. Supplement with ½ tsp daily of table salt.

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4. You are following a 16-year-old adolescent boy with CF who recently had hemoptysis. He and his parents have measured his hemoptysis to be 180 mL over the past 24 hours. Which of the following is the most appropriate management plan for this patient?

   A. Admit to the ICU for close monitoring.
   B. Initiate platelet transfusion.
   C. Limit airway clearance therapy and administration of ibuprofen, DNAse, and hypertonic saline.
   D. No change in therapy is indicated because pulmonary exacerbation is unlikely.
   E. Schedule a bronchial artery embolization procedure.

5. A 17-year-old girl with CF, who is very compliant with her medications and care, is brought to the emergency department by her parents because she woke up this morning with abdominal pain and nausea. She vomited 1 hour before her presentation to the emergency department. She has had decreased bowel movements during the past 2 days. She had a similar episode 1 year ago. On physical examination her respiratory rate is 12 breaths/min, her heart rate is 90 beats/min, and her blood pressure is 110/75 mm Hg. She has dry mucous membranes and diffuse abdominal tenderness without rebound. Which of the following is the best next step in the management of this patient?

   A. Abdominal radiography, flat and upright.
   B. Exploratory laparotomy.
   C. Gastrografin enemas, retrograde lavage, and visualization of the terminal ileum.
   D. Increase her pancreatic enzyme replacement therapy dose.
   E. Upper endoscopy and duodenal biopsies.