Cystic Fibrosis

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Author Disclosure
Drs Paranjape and Mogayzel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Practice Gap

1. The median survival of individuals affected with cystic fibrosis is currently 41.1 years. Whereas standard treatments in cystic fibrosis optimize lung health and nutritional status, treat chronic respiratory infection, and enhance quality of life, newer therapies that target the basic genetic defect hold significant promise for continued improvement in overall health and survival.
2. Pediatric clinicians should be familiar with the clinical presentation, diagnosis, and current management of cystic fibrosis and some of the common disease-related concerns and complications.

Objectives

After completing this article, readers should be able to:

1. Describe the current recommendations for the clinical, laboratory, and genetic analysis tools needed to confirm a diagnosis of cystic fibrosis.
2. Describe the current recommendations for the long-term medications and therapies for maintenance of optimal lung health and nutritional status in children with cystic fibrosis.
3. Recognize the clinical presentations of common cystic fibrosis–related complications.

Introduction

Cystic fibrosis (CF), among the most common of life-shortening genetic diseases, is characterized by chronic, progressive obstructive lung disease along with other systemic manifestations, such as nutrient malabsorption and malnutrition due to pancreatic insufficiency, liver disease and cirrhosis, and CF-related diabetes mellitus (CFRD). Median survival has improved steadily from less than 2 years (1)(2) at the time of the initial description of the disease in 1938 (3) to 41.1 years currently. (4) This improvement in survival largely results from early diagnosis and implementation of therapies to optimize lung health and nutritional status, treat chronic respiratory infection, and improve quality of life. Although there is currently no cure for CF, newer therapies target the basic genetic defect and hold significant promise for continued improvement in overall health and survival. Because the role of the primary care physician is vital to the well-being of children with CF, this review covers the clinical presentation, diagnosis, and current management of CF and some of the common disease-related concerns and complications.

Abbreviations

CF: cystic fibrosis
CFLD: cystic fibrosis liver disease
CFRD: cystic fibrosis–related diabetes mellitus
CFTR: cystic fibrosis transmembrane conductance regulator
DIOS: distal intestinal obstruction syndrome
IRT: immunoreactive trypsinogen

Epidemiology

On the basis of 2012 statistics from the Cystic Fibrosis Foundation, there are approximately 30,000 affected individuals in North America, with a predicted median survival of 41.1 years, and 49.1% are adults 18 years or older. (4) Approximately 1000 new cases are diagnosed annually; 70% of affected children are diagnosed by age 2 years, largely as a result of newborn screening, which was implemented in all 50 states by 2010. The incidence varies by race and ethnicity and is estimated to be 1:3200 in whites, (5) 1:15,000

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in people of African descent, 1:35,000 in people of Asian descent, and 1:9200 to 1:13,500 in Hispanics. (6) Early disease diagnosis, treatment of chronic infection and malnutrition, and other interventions, such as lung transplantation for end-stage lung disease, have had a significant effect on survival during the past 40 years.

Pathogenesis

The disease results from genetic mutations located on chromosome 7q31.2, which codes for a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR), which functions as an apical epithelial chloride channel. To date, more than 1900 mutations have been identified and categorized into 6 distinct classes that reflect abnormalities of CFTR synthesis, structure, and function (7)(8) (Figure 1). Class I mutations result in no functional CFTR protein being produced because of absent or defective protein biosynthesis. Class II mutations lead to protein variants that are improperly processed or transported to the apical cell membrane. For example, the most common and best characterized CFTR mutation, F508del, is a class II mutation. One copy of F508del is present in 70% of the affected population, and 2 copies are present in approximately 50%. Class III mutations affect CFTR activation and hinder chloride movement through channels at the cell surface. For example, G551D is a class III gating mutation targeted by the medication ivacaftor, which improves chloride conductance in individuals with CF with at least one copy of this mutation. Class IV mutations result in defects that produce a normal or diminished amount of CFTR with decreased function at the apical epithelial cell membrane. Class V mutations result from decreased amounts of fully active CFTR. A sixth mutation class is characterized by diminished stability of a fully processed and functional CFTR at the cell surface and often results in the truncation of CFTR toward the carboxyl terminus. (9)

The disease results from 2 *CFTR* mutations; however, they need not be from the same class. The amount of functional CFTR present at the cell surface, which is determined by genotype, partially accounts for the wide spectrum of CF phenotypes and, to some extent, correlates with the degree of organ involvement and disease severity. Class I, II, and III mutations are typically

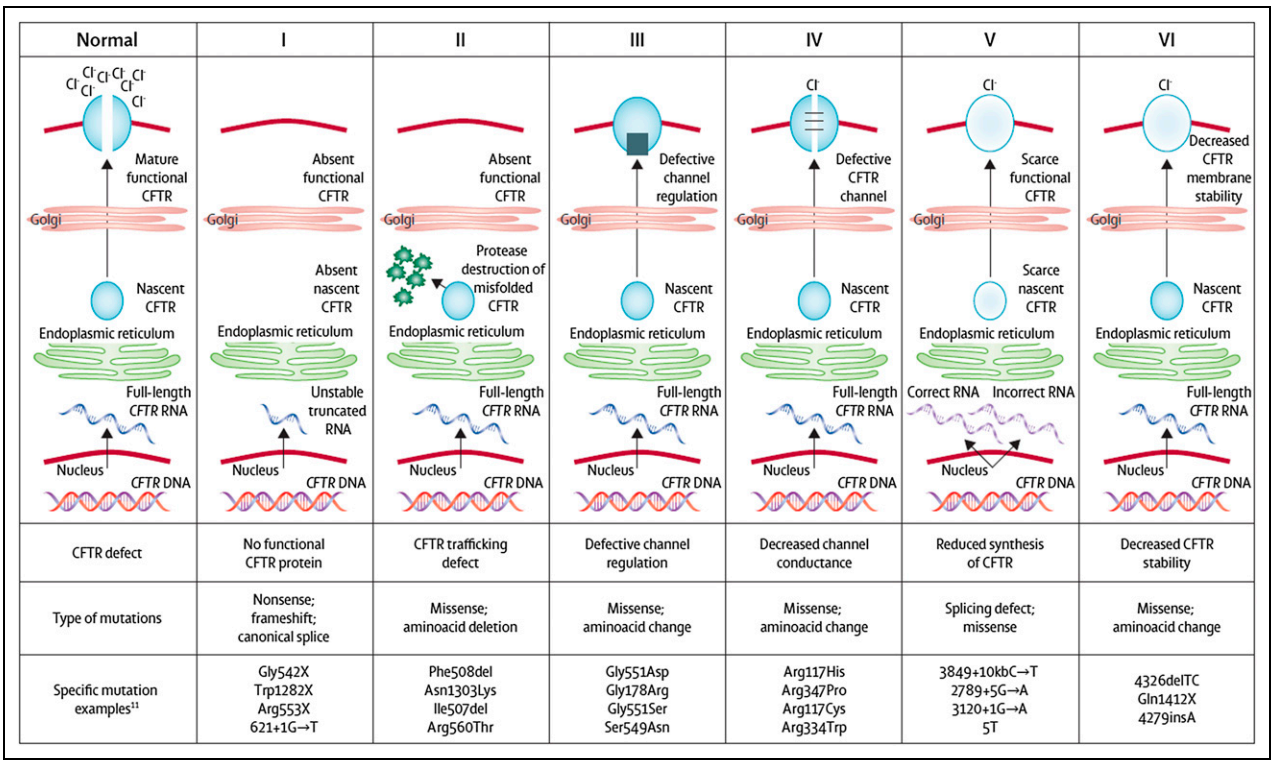

Figure 1. Cystic fibrosis transmembrane conductance regulator (CFTR) mutation classes. CFTR mutations have been grouped into 6 distinct classes based on abnormalities of CFTR synthesis, structure, and function. Reprinted from *The Lancet Respiratory Medicine*, Vol. 1, Issue 2, Boyle MP, DeBoeck K, "A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect," pages 158–163, (C) April 2013, with permission from Elsevier.

associated with early involvement of respiratory and digestive manifestations (ie, chronic cough, recurrent sinopulmonary infections, and exocrine pancreatic insufficiency). Class IV and V mutations are generally associated with milder or later-onset lung disease and exocrine pancreatic sufficiency.

Diminished or absent chloride channel function results in dehydrated, viscid secretions that contribute to organ dysfunction (Figure 2). In the lungs, mucous plugging leads to inflammation, chronic infection, progressive small airways obstruction, and bronchiectasis. In the exocrine pancreas, intestinal tract, and liver, inspissation of viscid secretions leads to pancreatic insufficiency and results in the malabsorption of fat and protein, intestinal obstruction, and cholestasis. Other clinical manifestations include chronic pansinusitis, nasal polyposis, and reduced fertility. In the sweat gland, abnormal chloride channel function results in excessive salt loss in sweat and forms the basis of the gold standard pilocarpine iontophoresis sweat test for CF diagnosis. (10)

Diagnosis

In 2008, a Cystic Fibrosis Foundation Consensus Panel established diagnostic criteria (11) that include the following: (1) the presence of one or more characteristic phenotypic features of chronic, recurrent sinopulmonary disease, nutritional and gastrointestinal abnormalities, male urogenital abnormalities (eg, absence of vas deferens), and salt depletion syndromes; (2) a family history of CF in a sibling; and (3) a positive newborn screening test result associated with laboratory-demonstrated evidence of CFTR dysfunction, such as elevation of sweat chloride concentration, identification of 2 disease-causing *CFTR* mutations, or demonstration in vivo of characteristic ion transport abnormalities across the nasal epithelium. Approximately 2% of cases are known as nonclassic, (12)(13) in which the genotype-CFTR functionality-phenotype correlations are less clear-cut and result in wide disease variability, which in turn is exaggerated further by the large number of identified mutations. A more appropriate diagnostic term for these individuals is *CFTR-related disorder*. Although the diagnosis of these cases can be challenging, the established diagnostic criteria should be used.

The gold standard for diagnosis of CF remains the pilocarpine iontophoresis sweat test developed by Gibson and Cooke in 1959, (10) which measures the chloride concentration in sweat that is typically elevated in those with CF. To maintain quality control, testing must be performed by experienced personnel using standardized

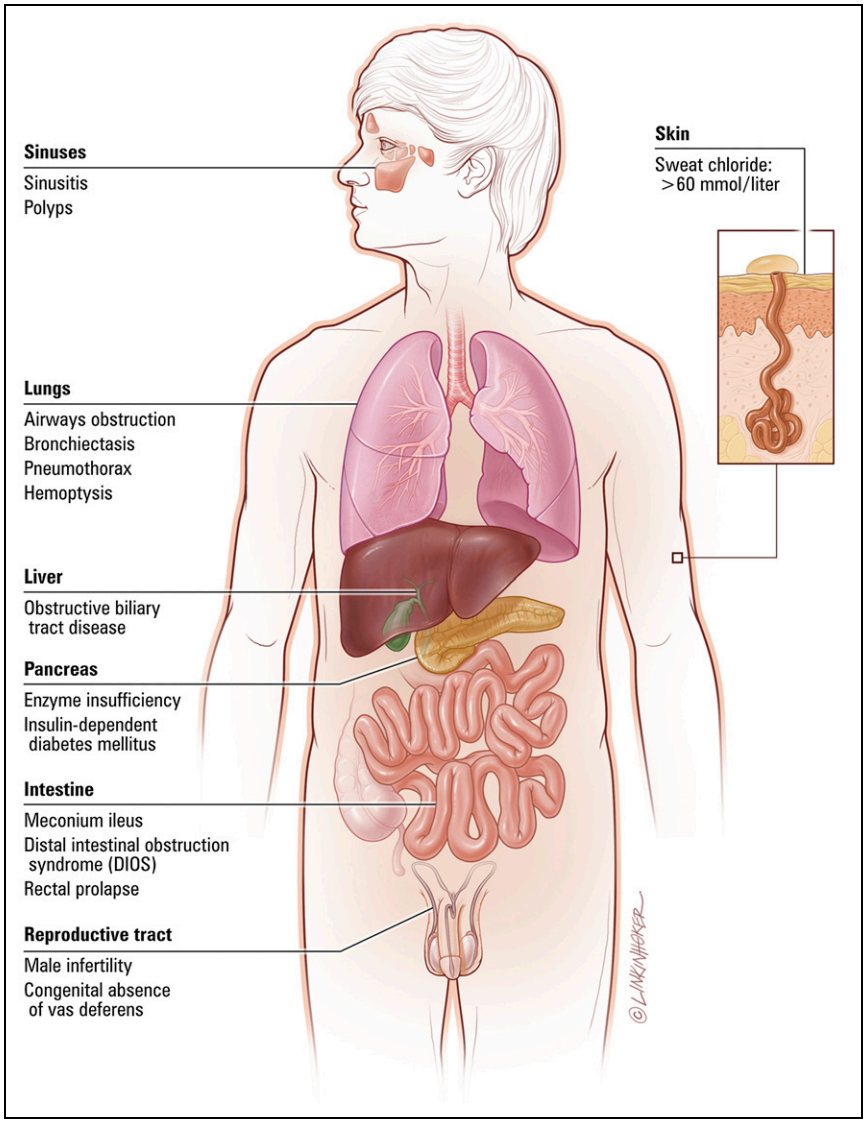

Figure 2. Common clinical manifestations of cystic fibrosis. Reproduced with permission from Link Studio LLC.

Table. Interpretation of Sweat Chloride Concentration

Group	Interpretation
Infants age 0–6 months	
Sweat chloride concentration (mEq/L)	
0–29	CF is unlikely[a]
30–59	Intermediate
≥60	Indicative of CF
Infants age >6 months, children, and adults	
Sweat chloride concentration (mEq/L)	
0–39	CF is unlikely[a]
40–59	Intermediate
≥60	Indicative of CF

CF=cystic fibrosis.
SI conversion factor: To convert chloride to mmol/L, multiply by 1.
[a]There are individuals with CF who have sweat chloride concentrations in this range.

methods in accredited laboratories. Normal sweat chloride values are age dependent, but a chloride concentration ≥60 mEq/L (60 mmol/L) is indicative of CF in individuals of all ages (Table). Additional sweat testing or genetic testing should be performed to confirm abnormal sweat chloride test results.

Genetic analysis is often helpful to confirm diagnosis, particularly for cases that present with indeterminate sweat chloride measurements. The genotypic criteria for diagnosis (11) include identification of 2 disease-causing mutations on distinct chromosomes. *CFTR* mutations should meet at least one of the following conditions: (1) alteration of the CFTR sequence with the result of affecting protein structure and/or function; (2) introduction of a premature stop codon, such as with an insertion, deletion, or nonsense mutation; (3) alteration of intron splice sites; and (4) creation of a novel amino acid sequence that does not occur in the normal *CFTR* genes of the affected individual's ethnic group. Commercial laboratories test for the most common *CFTR* mutations (often referred to as CF carrier testing), which will identify most individuals with CF. Complete sequencing of the *CFTR* gene is also available and can be helpful for confirming diagnosis of clinically atypical cases. Information about the clinical features associated with individual *CFTR* mutations can be found in the CFTR2 database sponsored by the Cystic Fibrosis Foundation (www.cftr2.org).

Nasal potential difference measurements can be beneficial in establishing a CF diagnosis, especially in clinically atypical cases. (14)(15)(16) However, this test is not considered to be a standard diagnostic method and is only performed at a limited number of CF centers. Cystic fibrosis is caused by abnormalities in salt transport that result from a defective CFTR protein, which is a chloride channel that regulates the salt content in the fluid that covers the surface of the nasal passages and airways. Transport of ions, such as sodium and chloride, creates an electrical potential difference across the airway lining. This potential difference can be measured by placing an electrode on the lining of the nose. Because individuals with CF do not have normal CFTR function, the epithelial nasal potential difference responds differentially to administration of the various salt solutions to the nasal epithelium.

Newborn screening was pioneered in the United States in the 1980s and by 2010 was implemented in all 50 states. (17) The benefits of newborn screening include early diagnosis, slowing of lung disease progression, prevention of malnutrition, and provision of psychosocial and extended medical support, such as genetic counseling, for individuals with CF and their families. Potential risks of newborn screening include increased medical interventions and increased risk for complications (ie, early treatment of bacterial infection, leading to antimicrobial resistance), earlier exposure to pathogenic bacteria, financial considerations given the high costs of therapies, and psychosocial repercussions stemming from false-positive screening results. (18)

Newborn screening for CF is performed by measuring the amount of immunoreactive trypsinogen (IRT) in the newborn blood spots typically obtained by heelstick. State laboratories either perform 2 IRT measurements (IRT/IRT) or perform *CFTR* mutation testing (IRT/DNA) if the IRT level is elevated. Positive screening results indicate that IRT levels remain persistently elevated by the time the neonate is ages 7 to 14 days or that at least one CFTR mutation has been identified. This result will trigger notification of the primary care physician and the infant's family. At this point, the infant should be referred to an accredited facility for definitive evaluation with a sweat test. A normal sweat chloride result (<30 mEq/L [<30 mmol/L]) means that CF is unlikely. An elevated (≥60 mEq/L [≥60 mmol/L]) sweat chloride measurement confirms the diagnosis, leading to further diagnostic measures (ie, genetic analysis to identify one or both CFTR mutations, depending on the type of newborn screen performed) and clinical assessment at a CF center accredited by the Cystic Fibrosis Foundation. Indeterminate sweat chloride levels (30–59 mEq/L [30–50 mmol/L]) require further genetic analysis and clinical assessment. With the current practices for newborn screening, the possibility exists for identification of a CFTR abnormality at birth that

does not immediately produce clinical manifestations, a syndrome known as CFTR-related metabolic syndrome. (19) (20) It is also important to remember that newborn screening for CF can have false-negative results as well, especially in infants with meconium ileus. Therefore, sweat testing should be performed if there is a clinical suspicion of CF regardless of the individual's age, even if he or she had a normal newborn screen result.

The present diagnostic methods take into account the wide clinical spectrum of disease and permit diagnosis of milder cases earlier in life. Early diagnosis has been found to have a profound effect on preventing lung disease progression and optimizing nutrition, which have had significant effects on survival and quality of life.

Clinical Presentations

The clinical diagnosis of CF in most individuals not detected by newborn screening is based on a triad of (1) recurrent sinopulmonary infections, (2) steatorrhea, and (3) failure to thrive. Exocrine pancreatic insufficiency is present in 85% of affected individuals. In infancy and early childhood, particular manifestations are strongly suggestive of a CF diagnosis. For example, the prenatal ultrasonographic finding of hyperechoic bowel is suggestive of intestinal obstruction; CF is present in approximately 10% of fetuses with this finding. Delayed meconium passage, meconium plug syndrome, or meconium ileus are present in approximately 15% to 20% of neonates with CF and result from abnormal meconium with a high protein concentration. Meconium ileus results from inspissation in the small intestine, leading to bowel obstruction; is associated with the clinical findings of abdominal distension and dilated bowel loops on imaging studies; and is complicated by intestinal perforation and peritonitis in approximately 50% of cases. Treatment generally involves surgical intervention. Rectal prolapse occurs in 20% of untreated children with CF between ages 6 months and 3 years and results primarily from malabsorption, malnutrition, and the elimination of bulky stools. Other less common clinical presentations in infancy include the following: (1) salt depletion syndrome, which results in a hyponatremic, hypokalemic, and hypochloremic metabolic alkalosis; (2) prolonged neonatal jaundice, resulting from intrahepatic biliary stasis or extrahepatic bile duct obstruction; (3) edema, hypoproteinemia, and acrodermatitis enteropathica, resulting from malabsorption; and (4) hemorrhagic disease of the newborn secondary to vitamin K deficiency.

In older children, adolescents, and adults, clinical findings suggestive of a CF diagnosis include both respiratory and gastrointestinal presentations. Chronic and recurrent infections of the sinuses and respiratory tract, poorly controlled or refractory asthma, and the findings of nasal polyposis, bronchiectasis, and digital clubbing are typical of respiratory involvement. Alternatively, individuals in this age group may also present at diagnosis with gastrointestinal features, such as poor weight gain and growth, steatorrhea, rectal prolapse, intestinal obstruction, chronic constipation, or liver disease. Pancreatitis can be seen in individuals with pancreatic sufficient CF. These clinical presentations will become less common because most children diagnosed as having CF are now identified by newborn screening.

Therapies to Maintain Optimal Lung Health and Nutritional Status

Cystic fibrosis results in inspissation of mucous secretions in the airways, leading to chronic obstruction, infection, and inflammation that eventually lead to bronchiectasis and parenchymal destruction (Figure 3). As lung disease progresses, chronic respiratory symptoms such as cough and sputum production develop. The major aims of the treatment of respiratory disease focus on optimizing lung function and preventing disease progression and other disease-associated complications. The overall goals of treatment of CF gastrointestinal disease are to optimize nutritional status and attain age-appropriate growth and weight gain. For both pulmonary and gastrointestinal manifestations, treatment is lifelong and generally begins at the time of diagnosis. In the United States, individuals with CF require routine quarterly visits at a care center accredited by the Cystic Fibrosis Foundation, which provides multidisciplinary, patient- and family-centered care.

The treatment of CF lung disease includes the control of chronic airways infection, particularly with bacterial agents against organisms such as *Pseudomonas aeruginosa*, airway clearance of secretions, and the use of anti-inflammatory therapies. In 2007, the Cystic Fibrosis Foundation's Pulmonary Clinical Practice Guidelines Committee developed recommendations that were based on a systematic review of the literature and assessment of the available evidence based on an established grading scale. (21) These guidelines were updated in 2013 (22) to review the latest evidence on long-term therapies to maintain optimal lung health and included newer therapies.

Chronic Airways Infection

Management of chronic airways infection includes routine surveillance cultures of respiratory secretions for bacterial pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Figure 4). Other organisms, including atypical mycobacteria and fungal pathogens, can have a significant effect on CF lung disease. Treatment of

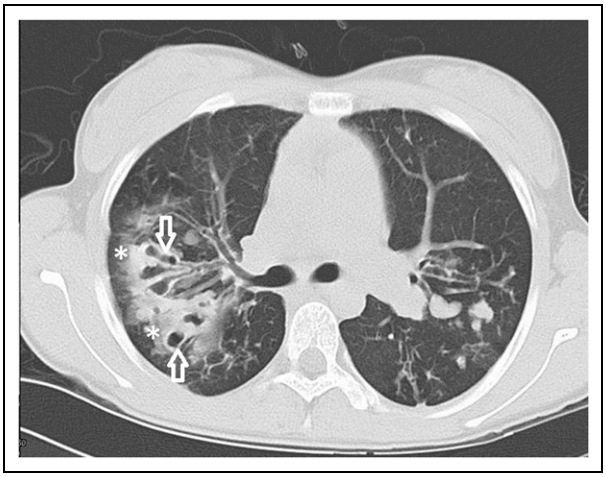

Figure 3. Chest computed tomographic (CT) findings. A CT image of an adolescent girl with cystic fibrosis demonstrates significant bronchiectasis (white open arrows) and mucous plugging (white asterisks).

newly acquired *P aeruginosa* typically uses inhaled tobramycin with the goal of eradication of initial infection. Individuals with chronic infection with *P aeruginosa* and other gram-negative species can benefit from regular use of inhaled antibiotics, such as tobramycin or aztreonam, typically used every other month.

Clearance of Airway Secretions

In the management of CF lung disease, airway clearance therapy serves to remove airway secretions and lessen the burden of infection through the removal of bacteria and other irritants and thus improve gas exchange, reduce airway resistance, correct ventilation-perfusion mismatch, and decrease proteolytic activity. Commonly used airway clearance techniques include postural drainage and percussion, active cycle of breathing, autogenic drainage, positive expiratory pressure (high pressure or oscillating), high-frequency chest wall oscillation, and exercise. Airway clearance maneuvers are typically used in conjunction with inhaled mucous-altering therapies designed to thin viscous mucus and facilitate their removal from the airways. Inhaled mucous-altering agents include recombinant human DNase (dornase alfa) and hypertonic saline. Airway clearance therapies are typically performed twice daily as maintenance therapy and increased in frequency as treatment of acute lung disease exacerbations. (23)

Disease-Modifying Therapies

Ivacaftor is an oral pharmacologic potentiator that activates defective CFTR at the cell surface caused by the class III mutation G551D. Randomized, placebo-controlled trials demonstrated improvements in lung function, weight, quality of life, and sweat chloride levels and reduction in exacerbation frequency. Ivacaftor is currently approved by the US Food and Drug Administration for individuals with CF due to at least one class III *CFTR* mutation such as G551D. Clinical trials on the effects of ivacaftor in combination with other *CFTR* mutation–specific therapies for individuals the most common mutation, F508del, are in progress. (24)(25)

Chronic Airways Inflammation

Cystic fibrosis lung disease is caused in part by chronic airways inflammation. Currently used anti-inflammatory therapies include high-dose ibuprofen and oral azithromycin. (21)(22) The routine use of oral or inhaled corticosteroids as long-term maintenance therapy is not recommended for individuals with CF unless the treatment is for other coexisting inflammatory conditions, such as asthma or allergic bronchopulmonary aspergillosis. High-dose ibuprofen has been reported to decrease neutrophil migration in CF individuals between ages 6 and 17 years when serum ibuprofen levels are between 50 and 100 μg/mL (242–485 μmol/L). Although clear benefit of this anti-inflammatory therapy has been demonstrated in clinical trials, treatment in clinical practice with high-dose ibuprofen is not widely used in clinical practice because of the small increased risk of gastrointestinal bleeding and need for drug level monitoring. (26)

Oral azithromycin, typically dosed 3 times a week, has been found to improve lung function and reduce the frequency of pulmonary exacerbations in individuals with and without evidence of chronic *P aeruginosa* infection. There is concern that long-term azithromycin use in individuals who have occult atypical mycobacterial infection will lead to mycobacterial resistance and further complicate treatment. Individuals with CF should be screened for atypical mycobacterial infection before starting oral azithromycin therapy. However, recent data suggest that long-term azithromycin therapy may in fact decrease the risk of acquiring an atypical mycobacterial infection. (27)

Pancreatic Enzyme Replacement Therapy

Pancreatic insufficiency is seen in 85% of the CF population and results in the malabsorption of fat and protein. The clinical consequences of malabsorption include bulky, malodorous stools, poor weight gain, and failure to thrive. Pancreatic insufficient individuals require lifelong replacement of pancreatic enzymes with capsules that must be taken with every meal and snack. The usual dosage ranges from 2000 to 2500 U/kg of lipase per meal

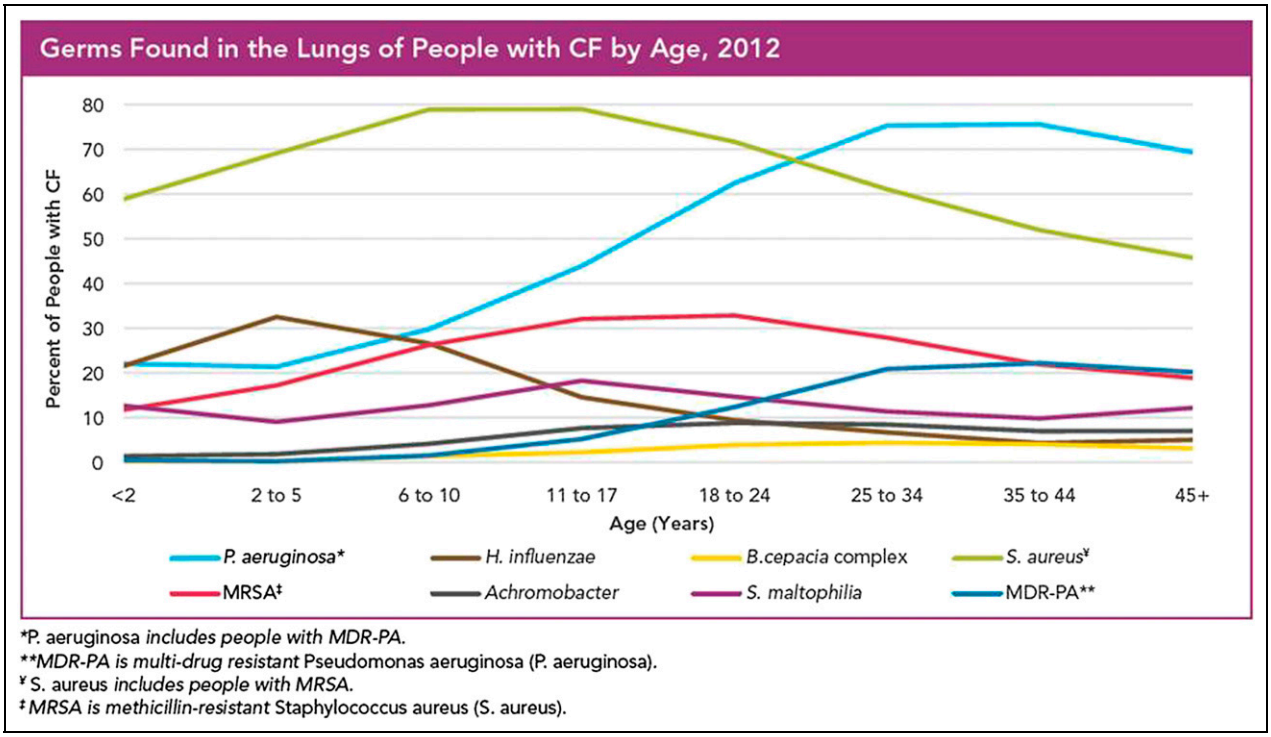

Figure 4. Prevalence of bacterial pathogens in cystic fibrosis. Cystic Fibrosis Foundation Patient Registry (C) 2013 Cystic Fibrosis Foundation. (4)

or feeding to a maximum of 10,000 U/kg of lipase per day. (28)(29) Higher pancreatic enzyme dosages are generally not needed to achieve adequate nutrient absorption. In fact, exceedingly high pancreatic enzyme dosages (>6000 U/kg of lipase per meal) are associated with fibrosing colonopathy, a rare but serious complication, in a small proportion of individuals. Optimal pancreatic enzyme replacement therapy can significantly decrease fecal fat excretion and steatorrhea, allowing individuals with CF to achieve age-appropriate growth and weight gain. (30)

Fat-Soluble Vitamin Replacement Therapy

Another consequence of fat malabsorption in pancreatic insufficient individuals is deficiency of the fat-soluble vitamins A, D, E, and K. Vitamin A deficiency results primarily in ocular consequences, such as night blindness and conjunctival and corneal xerosis. Skin involvement, such as follicular hyperkeratosis, is also associated with vitamin A deficiency. Vitamin D is integral in calcium homeostasis and bone mineralization, as well as immunomodulatory processes. Vitamin D deficiency results in nutritional rickets, osteopenia, and osteoporosis and can predispose severely malnourished individuals with CF to pathologic fractures. Vitamin E deficiency results in peripheral neuropathy, myopathy, and hemolysis. Vitamin K deficiency results in coagulopathy and can contribute to bone disease in CF. Replacement of these vitamins begins at diagnosis, and monitoring of serum levels is performed annually. The usual doses are typically higher than those required for an individual without CF; commercially available vitamin combination products supply doses within the target range.

Diagnosis and Management of Common Pulmonary and Extrapulmonary Complications in CF

Pulmonary Exacerbation

Cystic fibrosis lung disease results from inspissation of mucus and chronic bacterial infection, leading to progressive airways obstruction and chronic daily respiratory symptoms. Intermittent worsening of these ongoing daily symptoms is generally termed a *pulmonary exacerbation*, which is characterized by increased respiratory symptoms, such as increased cough and sputum production, and interval worsening of objective measures, such as pulmonary function, and nonspecific constitutional

symptoms, including increased fatigue, decreased appetite, and interval weight loss. (31) Fever is not a typical symptom of pulmonary exacerbations. Treatment includes oral, inhaled, or intravenous antibiotics, depending on the severity of the exacerbation. The choice of antibiotics is guided by previous airway culture results and the prevalence of various pathogens in the airway (Figure 4). In addition, escalation of the long-term regimen of maintenance therapies, such as airway clearance, is important to clear secretions from the airways.

Hemoptysis

Hemoptysis occurs in approximately 9% of individuals with CF annually. Typically associated with advanced lung disease, it can also be a symptom of worsened airways infection. (32) CF-associated conditions, such as vitamin K deficiency, either from malabsorption of fat-soluble vitamins or from liver disease and hypersplenism, can worsen hemoptysis. The pathogenesis of hemoptysis is multifactorial and likely results from proliferation and hypertrophy of the bronchial arteries, which can then rupture into the airway as a consequence of chronic infection and inflammation. (33) Hemoptysis is characterized by the amount of blood expectorated: scant (<5 mL), moderate (5–240 mL), or massive (>240 mL). (32) The management of scant to moderate hemoptysis drugs includes medical evaluation, initiation of antibiotic therapy for treatment of pulmonary exacerbation, cessation of anti-inflammatory agents (such as nonsteroidal anti-inflammatory drugs), and consideration for limiting certain therapies, such as mucous altering agents and airway clearance, as clinically appropriate. The management of massive hemoptysis is considered a life-threatening emergency. Medical management includes clinically appropriate stabilization of cardiorespiratory status and supportive care; nonsteroidal anti-inflammatory and airway clearance measures should be limited. Bronchial artery embolization is considered for the treatment of massive hemoptysis or significant recurrent hemoptysis once the site of bleeding has been localized. (33)

Pneumothorax

Another common pulmonary complication in CF is pneumothorax, which will develop in approximately 3.4% of all individuals. Pneumothorax is more common in adults (median age, 21 years) and individuals with advanced lung disease. (32)(34) The pathogenesis of pneumothorax involves air trapping. When alveolar pressure exceeds interstitial pressure, air escapes the alveoli into the interstitium and tracks along the airways toward the hilum with eventual rupture into the mediastinal parietal pleura. The typical presentation is the acute onset of chest pain and dyspnea. Diagnosis is generally confirmed by chest radiography, although in some cases, computed tomography may better demonstrate the pneumothorax in the setting of advanced lung disease with pleural adhesions. Pneumothoraces are characterized by size: small (<5 cm) or large (≥5 cm). (32) Management is largely guided by the degree of clinical compromise. Small pneumothoraces can be managed with observation or aspiration using a small catheter, depending on clinical stability. Other measures to facilitate airway clearance can be continued, with the exception of devices that use positive pressure because these can hinder resolution of the pneumothorax. Large pneumothoraces should be managed in the hospital with placement of a chest tube. Chemical or surgical pleurodesis is reserved for recurrent large pneumothoraces. (34)

Chronic Rhinosinusitis and Nasal Polyposis

The upper airway manifestations of CF include chronic rhinosinusitis and nasal polyposis. Nearly all individuals with CF will have radiographic demonstration of chronic pansinusitis. The prevalence of nasal polyposis is variable but ranges from roughly 18% in children younger than 6 years in one report to approximately 45% in adolescents. (35)(36) The pathophysiology of chronic rhinosinusitis and nasal polyposis results from mechanical obstruction of the sinus ostia by mucous stasis, which ultimately leads to local infection and inflammation. The clinical manifestations of chronic rhinosinusitis and nasal polyposis include headache, facial pressure, and nasal obstruction that can lead to broadening of the nasal bridge and septal deformation. Medical treatment includes saline nasal irrigation and topical anti-inflammatory therapies, such as nasal steroids. Surgical treatment is necessary for severe and recurrent disease. Functional endoscopic sinus surgery is the gold standard procedure to improve sinus drainage and remove inflamed and diseased mucosa. Although safe and beneficial in terms of reducing symptoms and decreasing the burden of infection, surgery generally does not result in improvement in lung function. Further prospective studies are needed to determine the effects of functional endoscopic sinus surgery on management and recurrence of rhinosinusitis in individuals with CF.

Distal Intestinal Obstruction Syndrome

Distal intestinal obstruction syndrome (DIOS) is a common complication in both pancreatic-insufficient and pancreatic-sufficient individuals with CF characterized by accumulation of viscous fecal matter in the distal small intestine, which leads to partial or complete small bowel

obstruction that presents clinically with abdominal pain, abdominal distension, and vomiting. Because the intestinal epithelium shares similar secretory processes seen in the airways, CFTR dysfunction leads to dehydration of mucous and intestinal obstruction. Bile acid stimulation of secretion and active reuptake by the terminal ileum are dependent on both CFTR-dependent and sodium gradient–driven cotransporter mechanisms and offer a plausible pathophysiologic mechanism for the involvement of the distal ileum.

Several risk factors predispose patients to the development of DIOS, including pancreatic insufficiency, suboptimal fat absorption (ie, inadequate pancreatic enzyme replacement therapy), a history of meconium ileus, and dehydration. (37) The differential diagnosis of DIOS includes constipation, adhesions after surgery, intussusception, volvulus, appendicitis, and inflammatory bowel disease, such as Crohn disease. Management is geared toward rehydration and treatment with osmotic laxatives, such as polyethylene glycol, to achieve a clear fecal effluent and typically lead to resolution of abdominal pain and other symptoms, such as vomiting. The use of procedures such as sodium meglumine diatrizoate (Gastrografin) enemas are recommended for near-complete obstruction. Retrograde lavage with visualization of the terminal ileum should be performed by an experienced radiologist. Surgical interventions are generally not required for DIOS with early diagnosis and implementation of appropriate medical management.

Cystic Fibrosis Liver Disease

In the liver, CFTR is expressed on the apical membrane of biliary epithelium. The putative role of CFTR is to facilitate water and solute movement via chloride secretion, thus promoting bile flow. The mechanism by which abnormal CFTR leads to liver disease in CF is uncertain. The end result of liver disease in CF is the development of biliary fibrosis, leading to biliary cirrhosis that may progress to multilobular cirrhosis. Some affected individuals develop portal hypertension and its associated complications. The sequelae of portal hypertension cause enhanced morbidity and mortality of CF patients such that liver disease is the third leading cause of death in CF, accounting for 2.5% of overall CF mortality. Most of the studies of the natural history of CF liver disease (CFLD) suggest a prevalence of cirrhosis between 5% and 15%, although it is difficult to accurately assess the full extent of liver disease in the CF population.

The most common clinical presentation of CFLD is the physical examination finding of hepatomegaly. Many affected individuals are asymptomatic with respect to signs and symptoms of liver disease even after the development of multilobular cirrhosis. Because sensitive and specific tests are not available to screen for biliary and hepatic cellular dysfunction, the early diagnosis of CFLD rests on clinical examination and the use of biochemical tests and imaging techniques to evaluate for the development of cirrhosis. The gold standard of diagnosis remains tissue biopsy.

The presence of CFLD should be considered with at least 2 of the following: (1) abnormal physical examination findings (hepatomegaly and/or splenomegaly); (2) abnormalities of liver function test results above the reference range of normal on at least 3 consecutive determinations during a 12-month period; (3) ultrasonographic evidence of abnormal liver echotexture or portal hypertension; and (4) confirmation of cirrhosis by tissue biopsy. Treatment with ursodeoxycholic acid is recommended when the diagnosis of CFLD is made. Annual screening of individuals with liver disease is recommended and should include assessment of biochemical liver function, ultrasound evaluation as clinically indicated, and evaluation by a gastroenterologist for other causes and morbidities associated with liver disease (such as variceal development) and for consideration for other treatments such as liver transplantation. (38)

Cystic Fibrosis–Related Diabetes Mellitus

Abnormal chloride channel function leads to thick viscous secretions that cause obstructive damage to the exocrine pancreas and results in fatty infiltration and destruction of islet cell architecture, which in turn produces an insulin-insufficient state. Typically, CFRD is more common in individuals with pancreatic insufficiency and has been associated with a higher mortality rate. More recent studies suggest early diagnosis and aggressive glucose control may prevent this increase in mortality. CFRD has been associated with decreased body mass index and lung function. Unexplained decrease in these clinical parameters may be due to occult CFRD. Microvascular complications, such as retinopathy, microalbuminuria, and autonomic neuropathy, occur in CFRD, as in other forms of diabetes, and are associated with the presence of fasting hyperglycemia. Ketoacidosis is uncommon with CFRD. Typically presenting after the first decade of life, the annual incidence of CFRD increases approximately 5% per year in individuals older than 10 years and approximately 10% per year in individuals older than 20 years. (39)

According to the 2010 recommendations, annual screening using the oral glucose tolerance test is recommended for those with CF who are older than 9 years. (40) Measurement of hemoglobin A_{1C} is not an effective screening tool because it underestimates overall glycemic

control. Insulin is the treatment of choice for CFRD; oral hypoglycemic agents are not recommended. Nutritional treatment remains focused on increasing and not restricting caloric intake in this patient population. The intake of carbohydrates is not discouraged; however, avoidance of foods that are high in simple sugar content and low in nutritional value is recommended to limit glucose excursion.

Prognosis

Overall, survival is improving for individuals affected with CF. Treatment goals include early diagnosis, screening, and treatment of the disease and its associated manifestations toward optimizing pulmonary function and nutritional status. Pharmacologic interventions, including the newer, mutation-specific therapies, have had a profound effect on the overall health and well-being for individuals with CF. Effective communication among primary care physicians, subspecialists, and the patient and family are paramount to maintaining optimal health and quality of life.

Summary

- On the basis of consensus, (11) the diagnosis of cystic fibrosis (CF) is based on (1) the presence of one or more characteristic phenotypic features of chronic, recurrent sinopulmonary disease, nutritional and gastrointestinal abnormalities, male urogenital abnormalities, and salt depletion syndromes; (2) a family history of CF in a sibling; and (3) a positive newborn screening test result associated with laboratory-demonstrated evidence of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction, such as abnormal sweat chloride concentration, identification of 2 disease-causing CFTR mutations, or demonstration in vivo of characteristic ion transport abnormalities.
- On the basis of consensus, (40) 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, (21)(22) the long-term therapies to maintain optimal lung health for children and adults with CF include control of chronic airways infection and inflammation, clearance of mucous secretions, and, where clinically applicable, treatments aimed at the basic CF genetic defect.
- On the basis of strong research evidence, (24)(25) treatment with ivacaftor, the first US Food and Drug Administration–approved drug that targets the basic CF genetic defect, resulted in improvements in lung function, weight, quality of life, and sweat chloride levels and reduction in exacerbation frequency in people with CF carrying at least one G551D mutation.

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PIR Quiz Requirements

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NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

1. You have been notified by the state laboratory that a 10-day-old boy has a positive cystic fibrosis neonatal screen (immunoreactive trypsinogen test) result. You contact the family and have them return for an evaluation. They report that the infant has been nursing well and passing 5 soft bowel movements daily. They also report an occasional cough. On examination, the infant has gained 200 g and appears well hydrated. His lungs are clear, and his abdomen is soft without distension or hepatomegaly. The most appropriate next step is to:

   A. Hospitalize for intravenous antibiotics.
   B. Perform chest radiography.
   C. Refer for sweat chloride testing.
   D. Refer to a pediatric pulmonologist.
   E. Repeat immunoreactive trypsinogen assay.

2. You are asked to evaluate a newborn infant in the nursery for abdominal distension and vomiting. Prenatal ultrasonography had suggested a hyperechoic bowel. Examination confirms the abdominal distension, and the abdominal plain radiograph demonstrates dilated small bowel loops and air fluid levels suggestive of meconium ileus. A pediatric surgeon is consulted. Newborn screening for cystic fibrosis performed that day revealed a normal immunoreactive trypsinogen (IRT) level. The most likely explanation for the normal newborn screen finding is that:

   A. The infant does not have cystic fibrosis.
   B. The infant has a single *CFTR* gene mutation.
   C. The infant has meconium peritonitis.
   D. The infant has a pancreatic sufficient form of cystic fibrosis.
   E. The infant's cystic fibrosis newborn screening result is false negative.

3. You are seeing a teenager with cystic fibrosis with pancreatic insufficiency, who is receiving 2500 U/kg of lipase per meal, for a total of 10,000 U/kg of lipase per day. He is bothered by abdominal pain and excessive flatus and asks you if he can just triple his dosage of pancreatic enzymes. Which of the following is a known complication of high-dose pancreatic enzyme intake?

   A. Colonic polyps.
   B. Diarrhea.
   C. Fibrosing colonopathy.
   D. Rectal bleeding.
   E. Vomiting.

4. A 13-year-old girl with cystic fibrosis followed up at your practice has had symptoms of recurrent sinusitis, including headache, facial pain, and chronic nasal drainage. Nasal irrigation, intranasal steroids, and several courses of antibiotics have failed to clear the infection. An appropriate next step would be:

   A. Endoscopic sinus surgery.
   B. Intranasal tobramycin.
   C. Ivacaftor.
   D. Nasal polypectomy.
   E. Nebulized albuterol.

5. A 5-year-old girl with cystic fibrosis is a new patient to your practice. The family has read about the possibility of diabetes in patients with CF and asks whether she should be screened for diabetes. Which of the following is currently recommended as a screening protocol for cystic fibrosis–related diabetes?

   A. Annual fasting blood glucose measurement beginning at age 5 years.
   B. Annual fasting blood glucose measurement beginning at age 9 years.
   C. Annual glucose tolerance test beginning at age 5 years.
   D. Annual glucose tolerance test beginning at age 10 years.
   E. Annual hemoglobin A_{1C} measurement beginning at age 5 years.

Parent Resources from the AAP at HealthyChildren.org

- http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Cystic-Fibrosis.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chronic/paginas/cystic-fibrosis.aspx

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