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Drs Montgomery and Howenstine 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.

Objectives

After completing this article, readers should be able to:

1. Describe the underlying genetic disruption that leads to the pathophysiologic changes seen in cystic fibrosis (CF).
2. Interpret newborn screening results and other tests used to diagnose CF.
3. Recognize the complications that may arise in various organ systems of patients who have CF.
4. Discuss a range of treatments for CF.
5. Understand the philosophies of care that have improved the outcomes of those who have CF.

Introduction

CF is the most common fatal inherited disorder among whites, with more than 30,000 affected individuals living in the United States. CF recently has been recognized more commonly within many nonwhite populations. The defect causing CF is found in a single gene that changes the function of mucosal epithelial cells in the airways, pancreatic ducts, biliary tree, intestines, vas deferens, and sweat glands. Such impairment within any of these organ systems results in manifestations of CF disease that can vary both in complexity and severity. Classic CF disease is notable for an elevated sweat chloride concentration, progressive obstructive lung disease, and pancreatic insufficiency, which has associated protein and fat malabsorption that leads to clinically significant malnutrition.

Genetics and Epidemiology

CF is an autosomal recessive disorder caused by mutations of both alleles of the large, 250,000-base-pair gene located on chromosome number 7 called the cystic fibrosis transmembrane conductance regulator (*CFTR*). The CFTR protein is a cAMP-regulated chloride channel that usually resides within the apical portion of mucosal epithelial cells. The most common defect, named deltaF508, is caused by a deletion of three base-pairs and results in the absence of phenylalanine at codon 508. The mutation is present in 70% of those who have CF. One in 3,500 newborns is affected by CF. Whites are affected most frequently, followed by the Hispanic population. CF occurs infrequently in the African American population, with 1 in 17,000 infants affected. Approximately 4% to 5% of all whites in North America are carriers of the CF gene.

To date, more than 1,500 mutations have been described in the *CFTR* gene. Twelve of the most common mutations account for 85% of CF genotypes in North American patients and include deltaF508, G542X, G551D, W1282X, W1303K, and R553X.

A classification system categorizes CF mutations into five groups according to the specific cellular location of the protein-processing defect. Class I, II, and III mutations are associated with severe defects in CFTR production and usually are associated with severe progressive pulmonary

Abbreviations

ACT:	airway clearance therapy
CF:	cystic fibrosis
CFTR:	cystic fibrosis transmembrane conductance regulator
CFRD:	cystic fibrosis-related diabetes
DIOS:	distal intestinal obstruction syndrome
FEV_1:	forced expiratory volume in 1 second
FEF_{25-75}:	forced midexpiratory flow
IRT:	immunoreactive trypsinogen
NBS:	newborn screening
NPD:	nasal potential difference

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disease and pancreatic insufficiency. Class IV and V mutations often cause milder, atypical, or even no evidence of disease. Despite these broad classifications, no relationship between genotype and phenotype has been established definitely. Current investigations are analyzing other modifying genes that may influence CFTR production or function and influence the genotype-phenotype association further in CF patients.

Diagnosis

CF Foundation Center data note that 53% of patients are diagnosed with CF by 6 months of age and 74% by 2 years of age. More than 1,000 individuals are newly diagnosed with CF in the United States annually. Physicians should test for CF in children who have recurrent or persistent episodes of cough, pneumonia, or sinusitis (Table 1). CF diagnostic testing also should be pursued in any child manifesting unexplained poor weight gain or overt failure to thrive. Other clinical findings in children that strongly suggest CF diagnostic testing include nasal polyps, rectal prolapse, hypochloremic alkalosis, or a known family history of the disease.

Additional testing for CF may be prompted through routine state-organized newborn screening (NBS) programs that are being implemented throughout the United States. NBS for CF currently is in place in more than two thirds of the states in the United States and is expected to be universal within the next decade. Infants identified through NBS have changed the diagnostic paradigm for CF because they are identified prior to the occurrence of clinical manifestations. Such early diagnosis allows for important early intervention and treatment.

Immunoreactive trypsinogen (IRT) is a measurable fraction of pancreatic enzymes that normally is released at extremely low concentrations into the systemic circulation. Results of an NBS test for CF are considered positive when IRT concentrations in the serum of a screened newborn are elevated, suggesting underlying acinar pancreatic dysfunction. The amount of IRT elevation beyond a critical "positive" threshold is associated with an increased incidence of CF but does not correlate with the severity of CF disease. In most states, an elevated IRT measurement triggers subsequent DNA testing to assess for the presence of *CFTR* genetic mutations (IRT/DNA method). Alternatively, some states repeat the IRT measurement 2 weeks later before proceeding with other diagnostic evaluations (IRT/IRT method).

NBS is believed to provide 90% to 95% sensitivity for detection of CF disease. Both methods (IRT/IRT and IRT/DNA) identify most at-risk newborns. Most positive CF NBS results by the IRT/DNA method detect a single *CFTR* mutation, but only 1 in 20 of such infants actually have CF diagnosed after additional testing. Infants who possess two *CFTR* mutations are presumed to have CF. It is important to note that NBS is not diagnostic and only identifies patients at risk for CF. A negative NBS result does not definitively exclude the presence of CF. In all cases, receipt of a positive CF NBS by a primary care practitioner should lead to prompt (within 1 week) evaluation of the infant and additional testing. A confirmatory test (sweat chloride) should be performed in those patients who have a one-mutation positive NBS result or a second elevated IRT. Infants who have a two-mutation positive NBS result should be referred to a CF center for evaluation and definitive testing.

The sweat chloride test is the most discriminatory test for CF and remains the gold standard for diagnosis. The

Table 1. Clinical Manifestations of Cystic Fibrosis

Respiratory
• Chronic productive cough
• Lower airways bacterial colonization
• Endobronchial infection
• Exercise intolerance
• Hypoxemia
• Bronchiectasis
• Pneumothorax
• Hemoptysis
• Pulmonary hypertension/heart failure
Gastrointestinal
• Protein and fat malabsorption
• Malnutrition/failure to thrive
• Meconium ileus
• Distal intestinal obstruction syndrome
• Obstructive jaundice
• Focal biliary cirrhosis
• Rectal prolapse
• Recurrent pancreatitis
Upper Airway
• Chronic pansinusitis
• Nasal polyposis
Other Systemic
• Diabetes mellitus
• Digital clubbing
• Hyponatremic dehydration
• Hypochloremic alkalosis
• Vitamin A, D, E, and K deficiencies
• Zinc deficiency dermatitis
• Male infertility

test is performed by using the method of quantitative pilocarpine iontoelectrophoresis, a technique that requires careful attention to detail and protocol. The sweat test involves stimulation of the sweat gland with pilocarpine, careful collection and weighing of the sweat, and analysis of the sweat chloride concentration by titrametric analysis. The CF Foundation assesses laboratory proficiency in sweat chloride testing and certifies qualified laboratories through an accreditation process that rigorously reviews sweat collection and analysis techniques. Values of chloride greater than 60 mEq/L (60 mmol/L) in a child are considered positive. Indeterminate results range from 40 to 60 mEq/L (40 to 60 mmol/L) and usually require additional diagnostic testing. Infants younger than 2 months of age, including those identified through NBS, are considered to have indeterminate results if the sweat chloride value is 30 mEq/L (30 mmol/L) and greater (Table 2). Such infants should be referred to a CF Foundation-accredited center for additional investigation.

CF also can be diagnosed by DNA analysis to identify specific *CFTR* mutations. CF can be diagnosed if two CF-causing mutations are identified. Interpretation of the CF genotype requires an understanding of the criteria for defining CF-causing mutations versus common *CFTR* polymorphism variations, as well as an understanding of the phenotypic variability of *CFTR* mutations. Currently available commercial panels can identify more than 90% of *CFTR* mutations. Despite the availability of expansive profiles and DNA sequencing, almost 10% of CF patients in the CF Foundation registry have at least one unidentified mutation. The absence of two distinct CF-causing alleles does not necessarily exclude the diagnosis of CF. Identification of CF mutations may be more difficult in Hispanic, African American, and Asian populations because mutation prevalence in these populations often differs from the panel of mutations commonly analyzed by most commercially available CF genetic tests.

Individuals manifesting symptoms suggestive of CF or CFTR dysfunction (eg, bronchiectasis, recurrent pancreatitis, or obstructive azoospermia) who have indeterminate sweat chloride concentration results or identification of no or one CF-causing *CFTR* mutation may benefit from additional assessment performed at a CF Foundation-accredited center to clarify the diagnosis. Testing should include a clinical evaluation as well as appropriate evaluations for pulmonary, gastrointestinal, and other systemic manifestations of CF disease (Table 3). Patients who continue to manifest symptoms despite equivocal diagnostic testing results are considered to have an uncertain diagnosis of CF and should be followed on a regular basis at a CF center.

Some children and adults who have clinical features of CF, indeterminate sweat chloride testing results, and uninformative DNA testing may benefit from the evaluation of the nasal potential difference (NPD). This test, usually performed at specialized research centers, detects biochemical abnormalities in the nasal epithelium caused by the *CFTR* defect. The test, performed in vivo, measures baseline NPDs and subsequently washes the membrane with chemicals such as amiloride and isoproterenol. With chemical washing, individuals who do not have CF show a change in the measured electrical potential across the nasal epithelium; those who have *CFTR* abnormalities, such as CF patients, do not respond. The assessment of NPD changes is used primarily for older children and adults needing a definitive diagnosis.

Lung Disease

The most recognized hallmark of CF disease is progressive obstructive lung disease. This process evolves from early thickening of airway mucus to subsequent colonization with pathogenic bacteria and, ultimately, the presence of diffuse airway inflammation that destroys the conducting airways and surrounding lung parenchyma. Studies of lower airway samples in infants who have CF and are evaluated within several months of birth suggest that the onset of inflammation and infection may occur early in life. Computed tomography scan and infant lung function data also suggest that infants who have CF may have considerable pulmonary dysfunction despite an asymptomatic appearance.

Bacterial colonization and associated inflammation in CF occurs primarily within the conducting and respiratory airways, with much less direct effect on the distal alveolar units. The combination of a desiccated mucosal surface, infection, and the host's inflammatory response leads to inspissation of air-

Table 2. Cutoff Values for Sweat Chloride Concentration

	Normal (mEq/L or mmol/L)	Indeterminate (mEq/L or mmol/L)	Cystic Fibrosis (mEq/L or mmol/L)
Infant (<2 months)	<30	30 to 60	>60
Child/Adult	<40	40 to 60	>60

Table 3. Diagnostic Evaluations for Suspected Cystic Fibrosis (CF)

Definitive Assessments	Comments
Sweat chloride concentration	Gold standard
CFTR gene mutation analysis	Negative analysis does not exclude disease
Additional Considerations in Indeterminate Cases	**Comments**
Exocrine pancreas assessment	Fecal elastase measurement, ultrasonography
Respiratory culture for CF pathogens	Throat swab, sputum, or bronchial lavage
Radiography	Chest radiograph or computed tomography scan
Presence of vas deferens evaluation	Ultrasonography
Pulmonary function testing	Forced spirometry maneuvers
Epithelial chloride conductance	Nasal potential difference measurement

way debris and progressive endobronchial destruction. These events result in mechanical obstruction of the airway, associated regional mismatch of ventilation and perfusion, and ultimately, to destruction of the surrounding lung parenchyma. The latter can lead to fibrotic cavitations, typified by diffuse cystic changes on chest radiographs (Figure).

Such physiologic changes may prompt characteristic physical findings, including the presence of coarse crackles focally or throughout the lung fields, decreased or absent air movement, tachypnea, use of accessory respiratory muscles, and evidence of air trapping with an increased anterior-posterior chest diameter. These findings may be apparent during an exacerbation of underlying CF disease or in more advanced disease at baseline. Other signs that typify CF lung disease include hypoxemia, exercise intolerance, weight loss, and decreased pulmonary function (as measured by spirometry). Routine lung function tests in CF may include assessment of forced expiratory volume in 1 second (FEV_1), forced midexpiratory flow (FEF_{25-75}), and lung volume measurements. Acute or progressive changes in findings should prompt additional evaluation and escalation of care, which may include increasing the frequency of airway clearance therapies and the addition of antibiotic therapy. Interestingly, some European CF centers have advocated regularly scheduled intravenous antibiotic therapy over time, independent of clinical status. The general practice in the United States is to initiate hospitalization and antimicrobial therapy in response to a decline in clinical status or lung function.

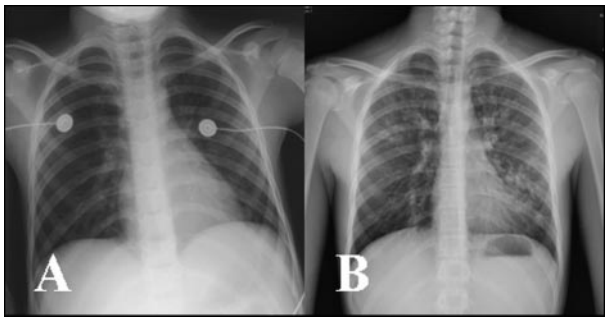

Figure. Despite aggressive antibiotic and airway clearance therapies, lung disease in CF progresses over time, as demonstrated by change from a near-normal chest radiograph at 8 years of age (A) to a radiograph in the same patient that shows evidence of mucous plugging and bronchiectasis at 15 years of age (B).

Organism colonies within the CF lung evolve throughout a patient's lifetime. During the first year after birth, a wide variety of bacteria, including enteric organisms, may be isolated. Over time, children who have CF may acquire one or more of the pathogenic bacteria *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* within their airways. According to CF Foundation registry data, approximately 60% of affected children ages 6 to 10 years are colonized with *S aureus* and nearly 80% of those ages 25 to 34 years are colonized with *P aeruginosa*. Some clinical studies have suggested that nearly 80% of 10-year-old patients are colonized with *P aeruginosa*, suggesting even earlier acquisition.

With advanced CF disease, patients may acquire *Burkholderia cepacia* within their airways. This bacterium is associated with worsening lung function and poor overall outcome in some patients who have CF. *B cepacia* has several subspecies, some of which are known to have greater propensity for transmission or poor outcome. Episodes in which *B cepacia* was transmitted by patient-to-patient contact among CF patients have been documented. Strict isolation procedures should be enforced for individuals colonized with *B cepacia*, and these patients should not be allowed to have direct contact with uninfected CF patients. This policy may require scheduling these patients at the end of the day or on separate days from other CF patients.

Rare but life-threatening pulmonary complications in CF include episodes of severe pulmonary hemorrhage or spontaneous pneumothorax. Pulmonary hemorrhage in CF occurs due to progressive outward erosion of the airway by the inflammation processes until an adjacent bronchial artery is eroded. Massive hemoptysis (500 mL of hemorrhage in 24 hours) may require acute arterial embolization or aggressive surgical intervention and, therefore, should prompt immediate medical evaluation. Spontaneous pneumothorax is a result of small airway mucus plugging, with distal air trapping and bleb formation that results in a focal area of excessive intraparenchymal pressure and subsequent rupture into the adjacent pleural space. Although not a common complication, there is a considerable incidence of pneumothorax recurrence in CF.

Pulmonary Therapies

Therapies used to combat acute and chronic manifestations of CF lung disease focus on the varied facets of the chronic airway inflammatory process. Multiple classes of antimicrobial medications are directed at colonizing bacteria. CF clinicians make appropriate antimicrobial medication selection based on sensitivity data derived from culture of sputum or oropharyngeal or bronchoalveolar lavage cultures. Although commonly used, oropharyngeal cultures do not correlate well with lower airways infection. The goal of antibiotic therapy in CF (oral, intravenous, or inhaled) is to suppress the bacterial infection of the major airways rather than to complete bacterial eradication. Exceptions to this approach may include aggressive antimicrobial therapy aimed at "eradication" of initial *P aeruginosa* cultures in young children and multidrug therapies focused on elimination of atypical organisms such as *B cepacia* and nontuberculous *Mycobacterium* species.

It is important to note that the pharmacokinetics of antibiotics such as the aminoglycosides may differ in patients who have CF compared with that of the general population. CF patients usually clear aminoglycosides (and penicillins and cephalosporins to a lesser extent) more rapidly, necessitating higher-than-normal per kilogram dosing regimens. This phenomenon may be related partly to relatively larger volumes of distribution and decreased amounts of adipose tissue in CF, but the true mechanisms of increased renal clearance in CF are not completely understood. Serum concentrations of aminoglycosides and other antimicrobials, therefore, must be monitored closely during routine administration. Consideration also should be given to additional investigation of potential adverse effects of these medications (ie, hearing loss) in CF patients who receive antibiotics frequently.

Long-term antibiotic use is employed in CF in a few circumstances. Scheduled antibiotic therapy with inhaled tobramycin on an alternating-month basis often is prescribed for patients chronically infected with mucoid *P aeruginosa*. Thrice-weekly azithromycin has been demonstrated to improve pulmonary function, decrease exacerbations, and improve weight gain in children and young adults who have chronic *Pseudomonas* infection. Some clinicians have advocated the use of chronic suppressive antistaphylococcal antibiotics to postpone the acquisition of *S aureus* infection in CF, but such regimens also have been linked to earlier acquisition of *Pseudomonas*.

Airway clearance therapies (ACTs) employed by CF patients and their caregivers include medications and mechanical methods that, individually or in combination, may mobilize viscous airway secretions, facilitating expectoration. The traditional means of providing ACT to CF patients involves manual chest percussive therapy with associated postural drainage; this modality remains the most common form of ACT used by affected children younger than 2 years of age. Several unique devices have been developed that allow older CF patients more independence in performing ACT, including oscillating chest vests and hand-held vibratory expiration appliances. Other patients use focused coughing and expectoration techniques.

In an attempt to improve ACT, drugs have been developed that address the intrinsic mucociliary clearance problem in CF. Hypertonic saline solution (7%) may be nebulized into the airway, providing hydration to thickened airway mucus as well as being a potent stimulus to cough. Nebulized recombinant human deoxyribonuclease fosters cleavage of nucleic material from spent airway neutrophils, aiding mucus clearance. Current research also has identified investigational compounds that promote increased airway hydration via the activation of nonCFTR electrolyte channels along the respiratory epithelium.

Despite the overwhelming inflammatory environment in the CF airway, use of inhaled corticosteroids has not been shown to be of great benefit. Systemic corticosteroids are beneficial in certain circumstances in CF, but the adverse effects of this drug class must be considered. Other novel anti-inflammatory medications have found some support in the treatment of CF lung disease, including daily oral administration of high-dose ibuprofen and thrice-weekly oral dosing of the macrolide antibiotic azithromycin. It remains unclear

whether routine azithromycin treatment gains its positive effect in CF primarily through an antimicrobial or an immunomodulating mechanism of action.

Ongoing research is addressing the primary defect in CF: the absence or impairment of *CFTR* gene function. Recent studies have identified drugs that may augment severely impaired CFTR function directly by manipulating normal cellular processing of faulty proteins. Work also continues on direct *CFTR* gene replacement therapy via delivery of normal alleles to affected cells, although results so far have been limited.

Advances in CF lung disease therapies have markedly improved the quality of life and long-term outcomes of patients. However, the obstructive lung disease in most patients continues to progress over time, ultimately leading to respiratory failure. Many patients are evaluated and listed as candidates for bilateral sequential lung transplantation as CF lung disease advances. Factors that may lead to consideration for lung transplantation include a baseline FEV_1 less than 40% predicted, increasing frequency of severe pulmonary exacerbations requiring hospitalization, progressive oxygen need, and the emergence of organisms resistant to multiple antibiotics. Nearly 200 CF patients undergo lung transplantation annually, with an expected 5-year survival of approximately 60%. Concurrent lung and heart transplants also have been performed in patients whose CF disease is severe and have advanced associated cor pulmonale.

Pancreatic Disease

Nearly all patients who have CF suffer some degree of pancreatic disease that progresses throughout their lifetimes. Pancreatic duct obstruction by thickened secretions may impede not only the excretion of pancreatic enzymes but also the bicarbonate-rich solution necessary for optimal pancreatic enzyme function. Patients who demonstrate sufficient exocrine pancreatic function early in life may slowly lose the capacity to digest nutrients adequately because of slow autodigestion of the pancreas. These patients also are at increased risk for recurrent episodes of pancreatitis.

CFTR dysfunction often is severe enough that the patient has insufficient pancreatic function at the time of neonatal or early childhood diagnosis. Failure to recognize this process may lead to intestinal protein and fat malabsorption and subsequent malnutrition. Symptoms may include stools described as frequent, greasy, or foul-smelling as well as increased flatulence, abdominal distention, and cramping. Because of fat malabsorption, patients also may become deficient in the fat-soluble vitamins A, D, E, and K. Research suggests a close correlation in CF between optimization of nutritional status and maintenance of lung function. Routine use of supplemental pancreatic enzyme replacement therapy prior to meals can improve digestion and intestinal absorption of dietary protein and fat. CF patients almost universally require supplementation of calories with fortified formulas, protein-rich shakes, and even gastrostomy feedings to maintain adequate growth during childhood. Routine CF care mandates close observation of growth over time, with an overall goal of achieving a normal age-appropriate body mass index.

Patients who have CF also are at risk of developing impairment of the endocrine pancreas. Progressive sclerosis and destruction of the islets of Langerhans ultimately lead to CF-related diabetes (CFRD). The prevalence of CFRD is approximately 8% in school-age children and nearly 30% in adults in the fourth decade of life. Glycemic control may be difficult in these patients, particularly during acute pulmonary exacerbations, but ketoacidosis rarely occurs.

Intestinal Disease

Absent or impaired CFTR chloride transport in CF often leads to pathologic intestinal obstruction due to marked thickening of intestinal secretions. This event frequently is manifested as meconium ileus in newborns. Affected infants fail to pass stool within the first few days after birth and may develop symptoms of acute intestinal obstruction and even visceral perforation. Conservative therapy for meconium ileus includes aggressive lower and upper bowel regimens. Often, surgical intervention is warranted to decompress the intestinal obstruction manually and to remove necrotic bowel, if indicated.

Obstruction due to thickening of intestinal secretions is not limited to the newborn period. Liquid stool may become firm, accumulate in the distal small intestine, and become hindered at the ileocecal valve. This sequence of events often is termed distal intestinal obstruction syndrome (DIOS). Treatment for DIOS includes enteral stool softeners, osmotic laxatives, and osmotic enemas. As in meconium ileus, surgery may be required to disimpact the obstruction manually, although the need to do this is rare.

Rectal prolapse occurs rarely in patients who have CF due to a combination of intestinal disease and poor supporting musculature resulting from poor nutrition. This finding is usually amenable to simple manual reduction. Recurrence may be prevented through strict bowel regimens that promote easy stooling as well as by addressing underlying malnutrition. Evidence of rectal pro-

lapse in otherwise healthy children is an indication for sweat chloride analysis to assess for undiagnosed CF.

Hepatobiliary Disease

In CF, biliary secretions often are thick and inspissated due to widespread CFTR dysfunction along the apical biliary membrane. The severity of disease may range from poor mobility of biliary secretions to frank gallbladder disease, with or without gallstones. Histologically, the concretion of material within the bile ducts typically leads to a periportal proliferation of bile canals and associated sclerosis. Nearly one third of CF patients ultimately develop liver dysfunction. A small proportion of those patients eventually develop symptomatic cirrhosis, usually associated with hepatomegaly, splenomegaly, portal hypertension, and occasional blatant liver failure necessitating liver transplantation. In rare cases, simultaneous liver/pancreas and liver/bowel transplants have been performed at some transplantation centers.

Upper Airway Disease

Although most patients who have CF have significant opacification of the maxillofacial sinuses on radiographic evaluation, many remain asymptomatic. A subset may develop symptoms of acute sinusitis with evidence of sinus tenderness, pressure headaches, facial swelling, and posterior pharyngeal drainage. In CF, the bacteria responsible for worsening sinus disease usually are the same as those cultured from the patient's lung. Antibiotic treatment for symptomatic patients should be based on results of cultures of a recent sputum or deep throat swab. Treatment should be of sufficient length to allow for adequate penetration into the sinus cavities, often requiring greater than 2 weeks of therapy.

Nasal polyps arise from the nasal mucosa of CF patients with greater frequency than for the general population. Routine application of nasal steroids may arrest the growth of polyps in some. A small number of symptomatic patients may require surgical intervention for removal of obstructive polyps, although the incidence of polyp recurrence in these patients remains high. The presence of nasal polyposis in otherwise healthy children is an indication for sweat chloride testing.

Fertility Issues

The vas deferens is absent in nearly all males born with CF. Only a subtle decrease in CFTR function—perhaps even the presence of a single severe allele—can lead to this common cause of male infertility. Evaluation for the presence of the vas deferens via testicular ultrasonography may be a simple confirmatory study in mature males who have an indeterminate CF diagnosis. Assisted fertilization techniques using aspiration of viable sperm from the testes provide an alternative reproductive option for male CF patients.

Some women afflicted with CF may have difficulty becoming pregnant due to mucus-associated obstruction of the cervix. Women who have CF and are considering pregnancy should be counseled on the potential negative impact that pregnancy may have on maternal pulmonary and nutritional health. There is a strong inverse correlation between baseline lung function and the incidence of complications during pregnancy in females who have CF.

All CF patients of reproductive age, as well as their extended families, should be offered the opportunity to receive genetic counseling.

Prognosis

When CF initially was described as a clinical entity by Fanconi, Andersen, and Farber in the 1930s and 1940s, life expectancy did not extend beyond the first year after birth. CF now is a disease that causes significant morbidity and early mortality, but the outlook for newly diagnosed patients continues to improve with time. CF Foundation registry data show that the median predicted survival age in 1985 was only 25 years and by 2006 had risen to nearly 37 years.

Because survival has continued to improve over time, caregivers must recognize the transformation in patients' lifestyles that has occurred since the days of early morbidity and mortality. Infants now diagnosed by NBS are expected to live well into adulthood. Children who have CF may pursue most typical childhood activities, including participating in physically demanding sports and completing any desired level of education. For example, current United States CF registry data note that 90% of patients who have CF have completed high school and more than 60% of patients older than 18 years have attended college courses.

The improvement in CF prognosis is attributable largely to the assertive multidisciplinary approach to patient care, organized and implemented through CF Foundation-accredited centers. Patients routinely followed at a center have more favorable outcomes than patients followed elsewhere. Early diagnosis, aggressive use of airway clearance therapies and antibiotics, diligent review of growth parameters, systematic assessment for common comorbidities, and sharing of outcome data are some of the philosophies among centers that have produced laudable results. Researchers are investigating other factors that may affect the prognosis in CF, includ-

ing socioeconomic stresses, environmental exposures, and the role-modifying genes.

The care required to maintain optimistic outcomes in CF is demanding on patients and their families. A single respiratory therapy may take 30 to 60 minutes to complete, and patients often may perform two or three therapies daily. Oral pancreatic enzyme supplements with meals may draw undesired attention to some children. Frequent physician visits and hospitalizations may compromise school attendance and planned family events. Insurance complications and the expense of pharmaceuticals and medical equipment may stress family finances. Resources often are available through local CF centers and national organizations such as the CF Foundation to aid families in navigating the many financial and social complexities that arise.

In addition to frequent care at a CF center, patients who have CF require an ongoing relationship with a primary pediatrician or family practitioner. CF may occupy a large extent of a child's medical care, but children who have CF are just as susceptible to many common medical maladies and injuries as are unaffected children. Caregivers should encourage adherence to established well-child evaluation schedules and employ appropriate anticipatory guidance with affected children and their families. All children who have CF should receive routine childhood immunizations according to published guidelines, including annual influenza inoculation. Importantly, primary care physicians often may be the first to recognize early exacerbations of CF lung disease or signs of nutritional failure, leading to early and more effective interventions. Each of these issues highlights the need for strong reciprocal communication between subspecialist physicians and primary caregivers to optimize patient care.

As more CF patients reach adulthood, additional complications of the disease must be considered. Osteoporosis, joint and bone pain, increased risk of CFRD, and progressive respiratory and nutritional symptoms complicate the course of CF with advancing age. In addition, patients must learn to transition from passive participant to active, self-responsible partaker in their ongoing care. Adolescent and adult CF patients must learn to take responsibility for their own medications, understand the complexities of insurance coverage, evaluate their educational and vocational options, and consider the options for beginning their own families. To address these issues, a number of centers have organized clinical programs specifically geared toward adult CF patients.

Conclusion

CF patients suffer varying degrees of multisystem complications, including progressive pulmonary disease, pancreatic malabsorption and malnutrition, hepatobiliary disease, and upper airway disease. Although substantial progress has been made in the overall outcomes of patients who have CF, immense potential for additional improvement remains. Knowledge of the complexities of the genetics of CF, the varying clinical manifestations of the disease, and the stepwise approach to diagnostic testing are important considerations for caregivers, particularly in the current age of NBS. Early diagnosis should strengthen the benefits of early interventions. Until clinically useful therapies addressing the basic CF genetic defect are available, treatments will continue to be individualized for the unique manifestations of disease in each patient. Establishment of routine care at a CF center can allow for appropriate disease monitoring and the fostering of adherence to an increasingly complicated medical regimen.

Summary

- CF is a commonly diagnosed genetic disease caused by disruption of cellular chloride transport through abnormal function of the *CFTR* gene protein.
- CF may affect multiple organ systems severely, leading to chronic sinopulmonary infections, impairment of growth, liver disease, and diabetes.
- Positive CF NBS identifies children at risk for the diagnosis of CF and always requires additional confirmatory testing with sweat chloride or genetic testing.
- Primary therapies in CF focus on methods to promote airway clearance of mucus, suppression of bacterial growth, and optimization of nutritional status.
- The prognosis for individuals born with CF continues to improve markedly over time through coordinated use of early and aggressive therapies toward common complications.

Suggested Reading

Collins MS, Abbott MA, Wakefield DB, et al. Improved pulmonary and growth outcomes in cystic fibrosis by newborn screening. *Pediatr Pulmonol*. 2008;43:648–655

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Farrell PM, Rosenstein BJ, White TB, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153:S4–S14

Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Resp Crit Care Med*. 2007;176:957–969

PIR Quiz

Quiz also available online at pedsinreview.aappublications.org.

10. Which of the following is the *primary* test used for newborn screening for CF?

    A. DNA testing for *CFTR* genetic mutation.
    B. Immunoreactive trypsinogen in blood.
    C. Meconium trypsin concentration.
    D. Nasal potential difference.
    E. Sweat chloride concentration.

11. A 2-year-old girl is being evaluated for cough, loose stools, and failure to thrive. Which of the following tests has the highest sensitivity and specificity in establishing the diagnosis of CF in this child?

    A. DNA testing for *CFTR* genetic mutation.
    B. Immunoreactive trypsinogen in blood.
    C. Meconium trypsin concentration.
    D. Nasal potential difference.
    E. Sweat chloride concentration.

12. A 12-year-old boy who has CF is admitted for worsening cough and difficulty in breathing of 1 month's duration. Sputum cultures are obtained and intravenous antibiotic therapy begun. Presence of which of the following pathogens in his sputum poses the greatest danger to other patients who have CF with whom he has direct contact?

    A. *Burkholderia cepacia.*
    B. *Klebsiella pneumoniae.*
    C. Penicillin-resistant *Streptococcus pneumoniae.*
    D. *Pseudomonas aeruginosa.*
    E. *Staphylococcus aureus.*

13. A 4-year-old girl is being evaluated for cough, loose stools, and poor weight gain of 6 months' duration. Her parents have noticed that she craves salty foods. Two separate sweat electrolyte tests performed at a CF Foundation-accredited laboratory show chloride values of 70 mEq/L (70 mmol/L) and 64 mEq/L (64 mmol/L), respectively. Which of the following statements is *most* correct?

    A. A diagnosis of CF should be confirmed by NPD.
    B. The management regimen for CF should begin.
    C. The presence of a single *CFTR* mutation is required to confirm the diagnosis of CF.
    D. The serum immunoreactive trypsinogen assay should be performed.
    E. The test should be repeated while the girl is eating a low-salt diet.

Clarification

One of the URLs cited in the Suggested Reading list for the article "Depression and Suicide in Children and Adolescents" in the June issue (*Pediatr Rev.* 2009;30:199–206) has changed since publication. The correct URL for the GLAD-PC Toolkit is: http://www.thereachinstitute.org/files/documents/GLAD-PCToolkit.pdf.