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ADVANCES IN PEDIATRICS

Advances in the Diagnosis and Treatment of Cystic Fibrosis

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Keywords

• Cystic fibrosis • CFTR • Newborn screen • Bronchiectasis • CFTR modulators • Ivacaftor

Key points

- Cystic fibrosis (CF) is an autosomal recessive disorder that leads to chronic multisystem disease consisting of chronic sinopulmonary infections, malabsorption, and nutritional abnormalities.
- Current therapies for CF lung disease primarily target the progressive cycle of mucus obstruction; chronic, persistent infections; and excessive inflammatory response to reduce progressive airway damage and dilatation, known as bronchiectasis.
- CF care is provided with a multidisciplinary approach. Team members commonly include a CF provider, nurse, respiratory therapist, dietician, social worker, and a primary care physician.
- CF transmembrane conductance regulator modulators, small molecule pharmaceuticals that target the basic defect in CF, are available for a limited group of people with CF, and offer the hope of improved treatment options for many more people with CF over the next decade.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder that leads to chronic multisystem disease consisting of chronic sinopulmonary infections, malabsorption, and nutritional abnormalities. It is the most common autosomal recessive life-shortening disease among white people in the United States. Although multiple organ

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systems are affected in this disease, lung involvement is the major cause of morbidity and mortality. From a pulmonary perspective, a cycle of chronic, persistent infections with CF-related pathogens and an excessive inflammatory response progressively damages the airways and lung parenchyma, resulting in widespread bronchiectasis and early death from respiratory failure [1,2].

CF is caused by mutations in a gene on chromosome 7 that encodes the CF transmembrane conductance regulator (CFTR) protein, a cyclic adenosine monophosphate–regulated ion channel. CFTR functions primarily as a chloride channel and controls the movement of salt and water into and out of epithelial cells lining the respiratory tract, biliary tree, intestines, vas deferens, sweat ducts, and pancreatic ducts. More than 1500 mutations in CFTR have been identified. The most common mutation in the United States, F508del, is a deletion of 3 base pairs encoding for phenylalanine at amino acid position 508 in the normal protein. This gene mutation as well as others leads to defects or deficiencies in CFTR, causing problems in salt and water movement across cell membranes, resulting in abnormally thick secretions in various organ systems and critically altering host defense in the lung.

Since its initial pathologic description 75 years ago [3], life expectancy in CF has improved, with a median predicted survival now approaching 40 years [4]. The improved survival in CF is one of the great success stories in pediatrics. Over these 75 years, CF has changed from an early fatal childhood disease, in which most afflicted infants died at a young age, to a chronic disorder in which most patients with CF are expected to live well into adulthood. There are myriad reasons for this improved survival, summarized in recent reviews (Fig. 1) [5,6], which include pancreatic enzyme replacement therapy; advancements in airway clearance techniques/devices; development of antimicrobial agents, including inhaled antibiotics targeting CF-specific pathogens; and

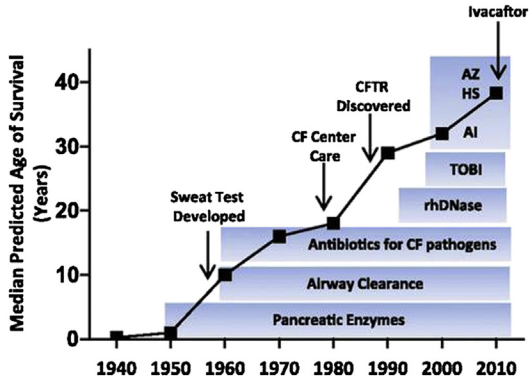


Fig. 1. Survival in CF since 1940. CF survival over time (*line*), associated CF therapies (*bars*), and milestones (*arrows*). AI, inhaled aztreonam; AZ, azithromycin; HS, hypertonic saline. (*Reprinted* with permission of the American Thoracic Society. Copyright © 2014 American Thoracic Society. Clancy JP, Jain M. Personalized medicine in cystic fibrosis: dawning of a new era. Am J Respir Crit Care Med 2012;186:594. Official Journal of the American Thoracic Society.)

inhaled mucolytic agents. Along with these therapeutic approaches, other developments that have had a positive impact on health outcomes and survival in CF include a network of accredited CF care centers with multidisciplinary specialized teams, dedicated quality improvement efforts, and early diagnosis through the nationwide implementation of newborn screening for CF.

This article reviews advances in both the diagnosis and treatment of CF. Based on recommendations from the Centers for Disease Control and Prevention [7] and the CF Foundation (CFF) [8], all states are now performing newborn screening for CF, which provides the opportunity for early intervention and improved outcomes. As a result, most individuals with CF are diagnosed through newborn screening. From a therapeutic perspective, the CF community has historically focused on treatments that counteract downstream manifestations of CF lung disease including mucus obstruction, infection, and inflammation. In an effort to address the root cause of CF, defective CFTR, the CFF established collaborations with biopharmaceutical companies to develop novel drugs targeting mutant CFTR. These efforts have led to the recent approval of one compound, ivacaftor (Kalydeco), for patients with CF with the G551D gating mutation. Drugs targeting F508del and other mutations are currently undergoing clinical trials. Development of CFTR-targeted drugs represents a new era in CF treatment, one that is expected to revolutionize the care of patients with CF.

DIAGNOSIS OF CF

A diagnosis of CF has historically required clinical evidence of typical phenotypic features in combination with laboratory confirmation. In 1996, a CFF consensus panel recommended that the diagnosis of CF should be based on the presence of one or more characteristic clinical features (Box 1), a history of CF in a sibling, or a positive newborn screening test, plus laboratory evidence of an abnormality in the CFTR gene or protein [9]. Acceptable evidence of a CFTR abnormality includes biological evidence of protein dysfunction (ie, abnormal sweat chloride concentration or nasal potential difference) and/or identification of 2 disease-causing CFTR mutations. Widespread implementation of newborn screening has now changed the diagnostic paradigm from one in which individuals are diagnosed from clinical features suggesting CF, to one in which most infants are referred for diagnostic testing after a positive newborn screen, many of whom do not have overt clinical manifestations. To this end, the CFF convened another meeting of experts in CF diagnosis in 2007 and a consensus report on updated CF diagnostic criteria was issued [10]. The recommendations involve a combination of clinical presentation, laboratory testing, and genetics to confirm a diagnosis of CF. The various laboratory methods to diagnose CF are discussed in this article.

Newborn screening for CF

Colorado was the first state to implement newborn screening for CF in 1982 [11]. Because of the published benefits of earlier detection afforded by newborn screening, many of which came from the Colorado and Wisconsin newborn

Box 1: Phenotypic features consistent with a diagnosis of CF

1. Chronic sinopulmonary disease, manifested by:
   - Airway infection with typical CF pathogens, including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*
   - Chronic cough and sputum production
   - Persistent chest radiograph abnormalities (eg, bronchiectasis, atelectasis, infiltrates, or hyperinflation)
   - Airway obstruction, manifested by wheezing and air-trapping
   - Nasal polyps; radiographic or computed tomography abnormalities of the paranasal sinuses
   - Digital clubbing
2. Gastrointestinal and nutritional abnormalities, including:
   - Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
   - Pancreatic: pancreatic insufficiency, recurrent acute pancreatitis, chronic pancreatitis, pancreatic abnormalities on imaging
   - Hepatic: prolonged neonatal jaundice, chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis
   - Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and edema, complications secondary to fat-soluble vitamin deficiencies
3. Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis
4. Genital abnormalities in male patients, resulting in obstructive azoospermia

Adapted from Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 1998;132:590; with permission.

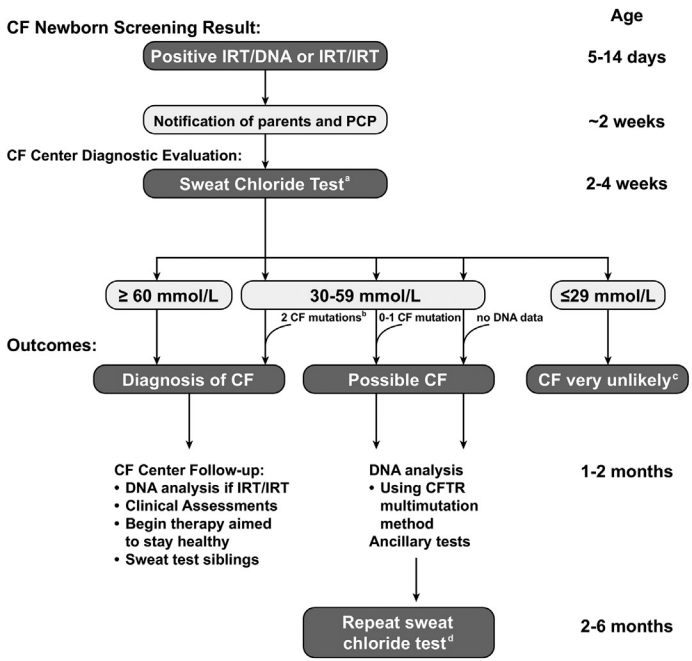
screening programs, the Centers for Disease Control and Prevention and the CFF issued guidelines in 2004 supporting the clinical usefulness of newborn screening for CF [7]. As of 2010, all 50 states are performing newborn screening for CF and most new diagnoses are now made through this diagnostic approach [4].

All newborn screening methods for CF begin with the measurement of immunoreactive trypsinogen (IRT) in dried blood spots collected from newborn infants. IRT is a pancreatic enzyme precursor that serves as a biomarker of pancreatic injury. IRT is increased in most newborns with CF because of in utero blockage of pancreatic ducts. Newborn screening protocols vary by state and individual states set the specific cutoff value that defines an increased IRT. After a high IRT value is identified, the next step involves either DNA mutation analysis (IRT/DNA) or obtaining a second IRT (IRT/IRT) to assess for persistent increase. Those infants with a positive IRT who have at least one CFTR mutation and those with persistently increased IRT

values are referred for a confirmatory sweat test. Thus, the sweat chloride test remains the fundamental test for diagnosing CF and completing the newborn screen process. An algorithm published by the CFF Consensus Committee provides a detailed, time-based description of the process from newborn screen to diagnosis, including the expectation that the initial sweat chloride test will be performed at 2 to 4 weeks of age (Fig. 2) [10].

Sweat testing for CF

The quantitative measurement of chloride in sweat (commonly called the sweat test) is the standard procedure for diagnosing CF. Despite more than 5 decades of experience with sweat testing, technical and interpretative challenges remain. Therefore, the CFF requires that sweat testing conducted at accredited CF care centers adheres to specific standards and requirements [12]. The sweat test involves transdermal administration of pilocarpine by iontophoresis to stimulate sweat gland secretion, followed by collection and quantitation of sweat onto gauze or filter paper or into a Macroduct coil (Wescor Inc, Logan, UT) and



[a] If the baby is at least 2kg and more than 36 weeks gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 µl, respectively.

[b] CF mutation refers to a CFTR mutant allele known to cause CF disease.

[c] The disease is very unlikely; however, if there are 2 CF mutations in trans, CF may be diagnosed.

[d] After a repeat sweat test, further evaluation depends on the results as implied above.

Fig. 2. The CF diagnostic process for screened newborns. IRT, immunoreactive trypsinogen; PCP, primary care provider. (*Reprinted from* 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:S6; with permission.)

analysis of chloride concentration, as described by the Clinical and Laboratory Standards Institute [12].

A sweat chloride value greater than 60 mmol/L has traditionally been considered diagnostic of CF. However, there have been instances in which individuals diagnosed with CF had lower sweat chloride values, and data emerging from newborn screening programs suggest that some infants eventually diagnosed with CF have initial sweat chloride values less than 60 mmol/L. This finding has led to recently revised reference values [10]. CF is now deemed to be very unlikely when the sweat chloride value is less than or equal to 29 mmol/L in infants up to age 6 months old or when the sweat chloride value is less than or equal to 39 mmol/L in individuals more than 6 months old (see Fig. 2). Individuals with intermediate results (30–59 mmol/L in infants up to age 6 months or 40–59 mmol/L in individuals more than 6 months of age) should undergo additional evaluation and be referred to a CF care center with expertise in diagnosing CF.

CF genotyping

DNA analysis for detection of CFTR mutations is recommended for all individuals with a sweat chloride in the positive or intermediate range [10]. Individuals with normal sweat chloride but features strongly suggesting CF should also have genetic testing performed, because, rarely, CF may still be diagnosed [13]. The most common mutation, F508del, is detected in up to 80% of people with CF in the Unites States. The detection rate of CFTR mutations varies based on mutation panel, testing method, and ethnic background. For example, targeted mutation analysis with a 23-mutation panel detects 2 CFTR mutations in more than 90% of Ashkenazi Jewish individuals, ~70% of white people, and only ~25% of Hispanic individuals [14]. The 23-mutation screening panel recommended by the American College of Medical Genetics is used for prenatal CF carrier screening and in newborn screening programs that rely on DNA analysis. Some states have implemented the use of expanded mutation panels or gene sequencing approaches in their newborn screening algorithms in order to capture individuals of more diverse ethnic backgrounds. DNA analyses that are commercially available typically include an initial panel of ~100 mutations. If no or only 1 CFTR mutation is detected, then extended full-gene sequencing and deletion/duplication testing is indicated; full-gene testing detects 2 mutations in ~97% of people with CF. In the era of CFTR modulator therapy, every effort should be made to identify 2 CFTR mutations in all persons with CF.

Genotype/phenotype correlations

Each of the CFTR mutations identified results in different functional protein consequences, ranging from complete protein absence to defective protein activity at the plasma membrane. CFTR mutations are broadly categorized into 5 classes based on the effect of the gene mutation on the CFTR protein function (Fig. 3) [15]. Class I (nonsense mutations) includes premature termination codons and frameshift mutations that result in either no significant protein

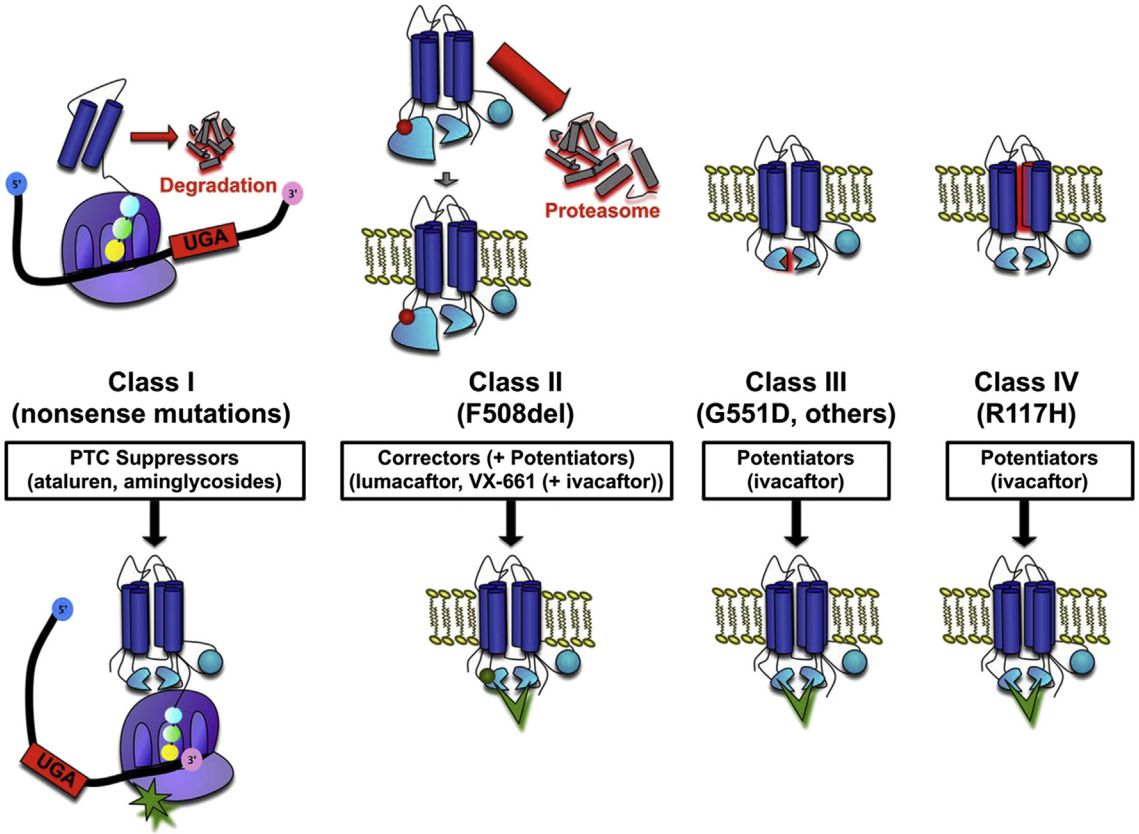


Fig. 3. CFTR gene mutation classes and therapeutic approaches. PTC, post-transciptional control; UGA, stop codon genetic code. (*From* Rowe SM, Borowitz DS, Burns JL, et al. Progress in cystic fibrosis and the CF Therapeutics Development Network. Thorax 2012;67:883; with permission.)

synthesis or low levels of truncated CFTR proteins. Class II mutations, which include the most common F508del mutant, cause folding or maturation defects, and little detectable CFTR at the plasma membrane. Class III mutations (eg, G551D) lead to the formation of CFTR proteins that reach the plasma membrane but are nonfunctional secondary to gating defects that limit channel opening. As such, classes I to III mutations typically have minimal protein function and are associated with a classic CF phenotype including pancreatic insufficiency. Class IV and V mutations are associated with either reduced chloride conductance through the CFTR protein or reduced levels of the CFTR protein at the plasma membrane, respectively. Individuals with 1 class IV or V mutation typically have residual CFTR function (ie, partial function mutations), often have sufficient pancreatic function to absorb nutrients without supplemental pancreatic enzymes (ie, pancreatic sufficiency), and may have sweat chloride values in the CF diagnostic or intermediate ranges [16]. The most commonly detected class IV mutation is R117H, which has an additional layer of clinical phenotype variability based on polymorphisms in the poly T tract in intron 8 of the CFTR gene [17]. Individuals with the R117H mutation, particularly with a 7T poly T tract, are generally expected to do well with low risk of disease progression, whereas those with a 5T poly T tract are at higher risk of developing lung disease. Although underlying CFTR mutations are strong predictors of pancreatic status, mutation class is a poor predictor of lung disease phenotype. It is thought that, in addition to the CFTR genotype, both CF modifier genes and environmental factors influence the variability of CF symptoms and comorbidities [18–20].

Although more than 1500 CFTR mutations have been identified, the functional consequence of many mutations remain unclear. The Clinical and Functional Translation of CFTR (CFTR2) is a joint venture between international researchers and the CFF [21]. The CFTR2 Web site (www.cftr2.org) provides information about specific CF mutations to patients, researchers, and the general public from a database of almost 40,000 people with CF worldwide. Because clinical phenotypes can vary, individuals with abnormal genetic testing and unclear diagnoses should be referred to an accredited CF care center for evaluation.

CFTR-related metabolic syndrome

CFTR-related metabolic syndrome (CRMS) is the diagnostic term used for infants with a positive newborn screen, sweat chloride less than 60 mmol/L, and up to 2 CFTR mutations, at least one of which is not clearly CF disease causing [22]. Infants with CRMS differ from individuals diagnosed later in life with nonclassic CF or CFTR-related disorders (eg, congenital absence of the vas deferens, recurrent pancreatitis, and bronchiectasis) because infants with CRMS are typically asymptomatic, whereas evaluation in older individuals is initiated by clinical symptoms. There is a paucity of data on the clinical course and outcomes of infants with CRMS; however, population data suggest that most

people with CRMS remain healthy. The CFF issued guidelines in 2009 for the management of infants with CRMS [22].

Nasal potential difference

Transepithelial nasal potential difference (NPD) is a method of testing for CFTR activity by measuring the electrical potential difference across respiratory epithelia lining the nasal mucosa [14]. The electrical potential difference relies on active ion transport, which is abnormal in individuals with absent or decreased CFTR function. Changes in the NPD are measured by a small catheter placed in the nostril while amiloride, low ion, and beta-agonist solutions are used to bathe the nasal mucosa. NPD can be performed reliably in children as young as 6 to 8 years of age in specialized CF centers. NPD measurements are most useful in patients with inconclusive sweat chloride values and as outcome measures in clinical trials of CFTR modulators [23].

Conventional diagnosis

Before newborn screening, individuals with CF were diagnosed based on clinical presentation (including 15%–20% presenting at birth with meconium ileus) or a known family history of CF. Over the past decade there has been a dramatic increase in the number of infants diagnosed by newborn screening, from less than 10% before 2001 to almost 60% in 2011 [4]. It is expected that the number of those diagnosed conventionally will continue to decrease. Despite this, clinicians need to maintain vigilance in order to identify those with CF missed by newborn screening because of (1) false-negative results, (2) laboratory error, or (3) birth before implementation of newborn screening or in a country without a screening program. Clinical manifestations that should prompt further evaluation for CF include failure to thrive with symptoms of fat malabsorption, chronic productive cough, recurrent pneumonia, nasal polyposis, bronchiectasis, pancreatitis, digital clubbing, dehydration with hyponatremic, hypochloremic metabolic alkalosis, and male infertility (see Box 1). Patients with pancreatic-sufficient CF are at a slightly higher risk of being missed by newborn screening and may present without the nutritional deficiencies seen in pancreatic-insufficient CF.

MANAGEMENT GOALS IN CF

Management goals in CF broadly include optimizing nutritional status and lung health, and preventing and treating comorbidities (Table 1). The care of people with CF requires a multidisciplinary team approach in order to adequately address these issues. Clinical care guidelines are based on evidence from clinical trials, expert consensus, and benchmarking, a tool used by the CFF to identify health care practices associated with the best outcomes and to spread these strategies in order to improve overall care [24]. These guidelines are available for viewing and downloading from the Web site at www.cff.org/treatments/CFCareGuidelines.

Table 1
Management goals in CF

Management goals	Clinical approach	Clinical care guidelines
Nutritional:	High-calorie, high-fat diet	Stallings et al [59], 2008
• Maintain normal growth patterns in children	Nutritional supplements (oral or enteral) for growth deficits	Borowitz et al [22], 2009
◦ Goal weight for length ≥50th percentile for infants <2 y old	Behavioral and nutritional intervention as indicated	
	Pancreatic enzyme replacement therapy for patients with pancreatic insufficiency	
◦ Goal BMI ≥50th percentile for children ≥2 y old	CF vitamin containing vitamins A, D, E, and K	
• Maintain normal blood levels of fat-soluble vitamins	Salt supplementation: table salt prescribed in infants; older children salt food liberally	
• Prevent hyponatremia and hypochloremia	Frequent monitoring, particularly in infancy	
Lung health:	Avoidance of tobacco smoke	Borowitz et al [22], 2009
• Minimize lung damage caused by infection, mucus plugging, and inflammation	Seasonal influenza vaccination	Flume et al [30], 2007
	Avoid contact between individuals with CF to reduce transmission of bacteria (unless siblings or close relatives)	Flume et al [38], 2009
• Maintain lung function (age ≥6 y)		
• Prevent onset of new lung infections	Infection control procedures in CF clinic	
• Detect and treat chronic lung infections	Daily airway clearance treatments	
• Prevent and treat pulmonary exacerbations	Use of dornase or hypertonic saline	
	Early treatment with antibiotics for any increase in respiratory symptoms	
	Chronic azithromycin when indicated	
	Routine airway cultures at least quarterly	
	Routine spirometry at least twice annually	
Comorbidities	Obtain regular CF care in a CF Foundation–accredited care center (every 1–2 mo for infants, then every 3 mo after age 1 y)	Debray et al [62], 2011
• Detect and treat complications of CF including:		Moran et al [63], 2010
◦ CF liver disease	Annual screening for liver disease, fat-soluble vitamin deficiency, ABPA	Stevens et al [64], 2003
◦ CF-related diabetes	Annual oral glucose tolerance testing starting at age 10 y	Besier et al [65], 2011
◦ Nasal polyposis	Referral to ENT, GI, liver, or endocrinology specialists as indicated	
◦ Gastrointestinal complications	At least annual assessments by CF-trained social worker or psychologist	
◦ ABPA		
◦ CF-related osteoporosis		
◦ Depression		
◦ Anxiety		

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ENT, ear, nose, and throat; GI, gastrointestinal.

PHARMACOLOGIC AND NONPHARMACOLOGIC STRATEGIES IN CF

Therapies for CF lung disease primarily target the progressive cycle of mucus obstruction; chronic, persistent airway infections; and excessive inflammatory response in an attempt to maintain lung function, reduce pulmonary exacerbations, and slow progression of bronchiectasis and structural lung damage. The use of airway clearance, antibiotics, and nebulized medications to improve mucus clearance has led to significant improvements in survival (see Fig. 1).

Airway clearance

Airway clearance therapies (ACT) are mechanical means of assisting patients in clearing secretions and mucus obstructing the airways. Routine ACT is recommended for all patients with CF to maintain lung health [25]. No single form of ACT has been shown to be superior to others, therefore the modality is chosen based on patient age and preference [25]. The most commonly used forms of airway clearance include chest physiotherapy or percussion and postural drainage, positive expiratory pressure (PEP) or oscillatory PEP, and high-frequency chest compression with a vest device. To optimize mucus clearance, patients perform forced exhalation huff coughs in coordination with ACT to clear sections. Vigorous exercise is also considered to be a form of ACT and is recommended for this reason in addition to its other health-related benefits beyond mucus clearance. ACT is recommended to be performed at least 1 or 2 times daily and is typically increased in frequency during periods of illness.

Airway surface liquid and mucus alteration treatments

The airway surface liquid is dehydrated in CF because of defective chloride transport by the CFTR protein, which impairs mucociliary clearance. Hypertonic saline (HTS) inhalation is a treatment that theoretically helps to hydrate the airways in CF and accelerate mucus clearance and improve lung function [26,27]. HTS is typically pretreated with a bronchodilator to help prevent potential bronchospasm side effects. Inhaled dry-powder mannitol (Bronchitol) similarly is an osmotic agent that is thought to increase surface liquid in the airways [28]. Recombinant human deoxyribonuclease or dornase alpha (Pulmozyme) is a nebulized medication designed to degrade extracellular DNA that accumulates within the CF mucus, thereby reducing mucus viscosity and promoting clearance of secretions [29]. Hypertonic saline and dornase alpha are recommended for chronic use in children 6 years of age and older to improve lung function and reduce exacerbations [30]. At present, dry-powder mannitol is approved for use in Australia and the European Union, but is not yet available in the United States. These inhaled treatments are typically used in conjunction with ACT.

Antimicrobials

As part of CF care, routine surveillance cultures are obtained on a quarterly basis and often during periods of illness. Culture samples are obtained via oropharyngeal swab, collection of spontaneously expectorated or induced

sputum, or bronchoscopy with bronchoalveolar lavage. Typical CF pathogens early in life include *Staphylococcus aureus* and *Haemophilus influenzae*. *Pseudomonas aeruginosa* takes over as the primary pathogen in teen and adult years and chronic *P aeruginosa* infection is associated with lower lung function and increased pulmonary exacerbations [31]. *P aeruginosa* has the ability to convert over time to a mucoid phenotype that is more resistant to antibiotics and innate immunity [32]. Eradication of *P aeruginosa* after initial or early detection using inhaled tobramycin is effective in more than 80% of patients, and likely delays the time until chronic infection [33]. Thus, early detection and eradication therapy for *P aeruginosa* is now standard of care. In patients 6 years of age and older who are chronically infected with *P aeruginosa*, the CFF recommends chronic use of inhaled tobramycin [34] or aztreonam (Cayston) [35] every other month because this has been shown to improve pulmonary function, reduce exacerbation, and improve quality of life [30,36]. Other less common CF pathogens that are emerging and are pathogenic at times in the CF population include methicillin-resistant *S aureus*, *Burkholderia cepacia* complex, and nontuberculous mycobacteria, including *Mycobacterium avium* complex and *Mycobacterium abscessus*.

Pulmonary exacerbations

CF is characterized by progressive lung function decline with acute periods of worsened respiratory symptoms known as pulmonary exacerbations. Pulmonary exacerbations are characterized by increased cough, changes in sputum production, shortness of breath, constitutional symptoms, and/or decline in lung function to less than baseline, among other symptoms [37]. Exacerbations are treated with both increased airway clearance and courses of oral or intravenous antibiotics (either at home or in the hospital), typically targeting patients' typical CF pathogens [38]. Key questions yet to be answered include the optimal form of antibiotics to use (ie, oral vs intravenous), duration of treatment, and use of single agents versus combination therapy. Pulmonary exacerbations can lead to residual loss of lung function and decreased quality of life; recurrent exacerbations are associated with more rapid decline in lung function. Thus, detection and early treatment of exacerbations are critical.

Antiinflammatories

Neutrophil-dominated airway inflammation is a hallmark feature of CF lung disease that starts early in life. A major emphasis in CF treatment has therefore been placed on evaluating drugs that target inflammation. Corticosteroids and high-dose ibuprofen are broad spectrum antiinflammatory agents that have been studied in CF and that inhibit proinflammatory signaling. Both have shown clinical benefit [39,40], but side effects and other considerations have limited their use [41,42]. There are currently 2 routinely prescribed CF therapies that alter inflammation, although they are not considered traditional antiinflammatory agents. The first is recombinant human deoxyribonuclease, discussed in further detail earlier. Over a 3-year period, dornase alpha prevented an increase in several markers of lower airway inflammation that

was observed in untreated patients [43]. The second therapeutic agent is azithromycin, a macrolide antibiotic, which has been shown to reduce pulmonary exacerbations and improve lung function in patients with CF without significantly affecting lower airway bacterial density [44,45]. Evidence suggests that azithromycin may act as an antiinflammatory or immunomodulatory agent in patients both with and without chronic *P aeruginosa* infection [45,46]. Targeting inflammation in CF is still an attractive therapeutic approach, but optimizing antiinflammatory effects while minimizing the detrimental impact on host defense remains a key challenge.

CFTR modulators

In an effort to develop drugs that target the underlying defects in the CFTR protein, the CFF established collaborations with biopharmaceutical companies to support early-stage efforts to discover new medicines for CF. This effort has led to the development and clinical trial testing of a novel class of drugs known as CFTR modulators, which target specific CFTR mutations. These drugs have the potential to be disease modifying, extending the lives of individuals with CF by years and possibly even decades.

As noted earlier, a CFTR mutation class system has been developed to help categorize the myriad of CFTR mutations into groupings with similar functional consequences (see Fig. 3) [1]. Mutations in classes I to III typically have minimal protein function, whereas members of classes IV and V retain partial function and are usually associated with lower sweat chloride levels and pancreatic sufficiency. To date, the most successful type of CFTR modulators studied have been potentiators, which open the mutant CFTR channel and augment the activity of the protein at the plasma membrane. A landmark phase II trial of the CFTR potentiator ivacaftor (Kalydeco), which was studied in 40 patients with CF with at least one copy of the G551D mutation, a class III gating mutant, showed impressive improvements in CFTR activity, detected by NPD and sweat chloride testing, resulting in significant changes in lung function [47]. This trial was rapidly followed by 2 pivotal phase III trials in which ivacaftor treatment led to rapid, dramatic, and sustained improvements in forced expiratory volume in 1 second ($FEV_{1)}$, weight, quality of life, and biomarkers of CFTR function, and reductions in pulmonary exacerbations [48,49]. As a result, in 2012, the US Food and Drug Administration approved ivacaftor for patients with CF aged 6 years and older with the G551D mutation.

Although G551D is present in only about 4% of the US CF population, the dramatic success of ivacaftor has proved that rescue of mutant CFTR is possible, preparing the way for the development and clinical trial testing of additional CFTR modulators that target most patients with CF. Ivacaftor is currently being studied in young patients with CF, aged 2 to 5 years, with the G551D mutation. Based on in vitro data that this drug shows activity in other CFTR mutations, clinical trials were performed in patients with other non-G551D class III gating mutations. In 2014, ivacaftor was approved for

use in patients with one of 8 additional class III gating mutations, benefiting an additional 1% of the US CF population.

The next class of CFTR modulators in development and clinical trial testing are correctors of F508del CFTR trafficking defects, which work by increasing F508del CFTR protein at the plasma membrane (see Fig. 3). Vertex Pharmaceuticals has developed 2 F508del correctors that have advanced to clinical trials (VX-809 or lumacaftor, and VX-661). Preclinical testing has shown that combining the CFTR corrector lumacaftor with the potentiator ivacaftor leads to enhanced F508del CFTR activity relative to lumacaftor alone [50]. This finding led to a phase II combination trial of lumacaftor and ivacaftor that showed statistically significant improvements in lung function among adults with CF with 2 copies (homozygous) of the F508del mutation (press release from Vertex Pharmaceuticals, unpublished data, June 28, 2012). These findings provided the basis for 2 large phase III trials that are currently investigating the safety and efficacy of combination therapy in patients with CF homozygous for F508del. Results from these phase III trials are expected by the end of 2014. Combination therapy with a CFTR corrector and potentiator, if successful, has the potential to benefit approximately 75% of the US CF population.

The CFTR modulator program also includes treatment strategies directed toward suppression of premature termination codons (class I mutations) (see Fig. 3), present in approximately 10% of US patients with CF. The discovery that aminoglycoside antibiotics can allow the ribosome to read through premature termination codons resulting in full-length functional protein [51] has led to investigations of the small molecule ataluren (PTC124) by PTC Therapeutics. Following a series of phase II trials that showed modest improvements in primary outcomes [52,53], a large phase III trial failed to show a significant improvement in FEV_1, the primary end point, but did show a small effect on lung function in a predefined subset of individuals who were not treated with inhaled antibiotics, which are purported to alter the efficacy of ataluren [54]. Although the clinical status of ataluren remains uncertain at present, studies involving other compounds with translational read-through properties are proceeding [55].

Lung transplant

Although a rare occurrence in pediatrics, bilateral lung transplant is an option to consider for patients with CF who develop severe bronchiectasis and end-stage lung disease. Referral for transplant should be considered for patients with an FEV_1 consistently less than 30% of predicted or a rapid decline in FEV_1, increased frequency or severity of pulmonary exacerbations, recurrent episodes of massive hemoptysis, and/or recurrent or refractory pneumothorax [56]. Other factors included in the pretransplant assessment include oxygen dependency, hypercapnia, and pulmonary hypertension, as well as the patients' infectious history and CF comorbidities [56]. In 2011, there were about 75 pediatric lung transplants worldwide for an indication of CF reported to the Registry for the International Society for Heart and Lung Transplantation [57]. Survival

following CF pediatric lung transplant from 1990 to 2011 is estimated to be 80% at 1 year, 50% at 5 years, and 33% at 10 years after transplantation. Median survival for pediatric CF transplant is 4.7 years [57]. Lung transplant for CF-related bronchiectasis and lung disease is more common in adults, with more than 600 transplants performed worldwide in 2011 [58]. Survival is slightly better at about 85% at 1 year, 60% at 5 years, and 45% at 10 years after transplantation. Median survival for adult CF transplant is 7.8 years [58].

Nutrition

The goal of nutritional therapy in CF is to maintain normal growth velocity throughout childhood and normal weight in adulthood [59]. Population-based studies show improved lung function and survival in those with higher weight for height and body mass index (BMI). Based on studies showing that optimal growth is associated with improved lung function, the stated goal for infants is to maintain weight for height greater than the 50th percentile and children aged 2 years and older to maintain BMI greater than the 50th percentile. In order to achieve optimal growth, children with CF require a high-calorie (typically 110%–200% of normal recommended caloric intake) and high-fat (40% of calories from fat is recommended) diet. Oral or gastrostomy tube supplements are often required in order to meet caloric goals. For patients with CF who are pancreatic insufficient (85%–90% of the CF population), pancreatic enzyme replacement therapy (PERT) is required in order to adequately absorb complex carbohydrates, fat, and protein. Enzymes are taken before all meals, snacks, supplements, and enteral feedings.

Patients with CF are at risk for fat-soluble vitamin and zinc deficiency caused by malabsorption. A CF-specific multivitamin is recommended for all people with CF. Zinc supplementation should be considered in children who are not growing adequately. Fat-soluble vitamin levels for vitamins A, D, and E are measured annually, and additional vitamin supplements are prescribed as needed. The CFF recommends a minimal 25-hydroxyvitamin D concentration of 30 ng/mL (75 nmol/L) for vitamin D sufficiency in CF [60]. Vitamin K status is more difficult to assess, but serum prothrombin time increase in a patient with CF strongly suggests vitamin K deficiency and is generally treated with additional supplementation. Daily supplementation with salt is also critical for people with CF, to prevent against hyponatremic, hypochloremic dehydration, and other electrolyte abnormalities. Chronic salt depletion can also contribute to failure to thrive, and should be considered in children with CF who are not growing adequately. A child presenting with unexplained hypochloremic metabolic alkalosis should be evaluated for CF, because this condition strongly suggests CF.

ACCREDITED CF CLINICAL CARE CENTERS AND SURVEILLANCE

The CFF is responsible for accrediting and funding the more than 110 pediatric and adult CF care centers across the United States. In addition, the CFF oversees the publication and dissemination of consensus CF care guidelines and

supporting many CF-related research efforts. Following diagnosis through newborn screen, the CFF recommends that infants be evaluated at an accredited CF care center, with the goal of an initial visit within 24 to 72 hours of diagnosis [61]. At that visit families receive comprehensive education regarding the CF diagnosis and CF-specific cares. In addition, treatments including salt supplementation, CF vitamins, and PERT are initiated. In the first year of life, there is much collaboration between the primary care provider and the CF care center, and visits are meant to complement one another. In addition to the standard pediatric visits, it is recommended that infants are followed monthly at the CF care center for the first 6 months of life, then every 1 to 2 months until 1 year. After 1 year of age, the CFF recommends that all patients with CF be followed at an accredited CF care center on a quarterly basis. Surveillance cultures are performed quarterly and, when capable, patients undergo routine spirometry for monitoring purposes at least twice annually. Care is provided with a multidisciplinary team approach, including pulmonologists trained in CF care, advance practice providers, nurses, respiratory therapists, dieticians, and social workers. Other consultants that patients may see regularly include otolaryngologists, endocrinologists, gastroenterologists, and liver specialists to assist in managing the comorbidities in CF. Mental health issues (eg, depression and anxiety) are increasingly recognized as important contributors to impaired quality of life and decreased adherence to medical therapy. Thus, the importance of mental health screening and psychiatry/psychology availability in CF care centers is becoming clear. Patients with CF should also maintain a relationship with a primary care provider for routine cares and immunizations provided on a standard schedule.

SUMMARY

CF is a genetic, life-shortening, multisystem disease that is most commonly diagnosed through newborn screen performed in all 50 states in the United States. In the past, therapies for CF lung disease have primarily targeted the downstream effects of a dysfunctional CFTR protein. Newer CFTR modulator therapies, targeting the basic defect in CF, are available for a limited group of people with CF, and offer the hope of improved treatment options for many more people with CF in the near future. Best practice is directed by consensus clinical care guidelines from the CFF and is provided with a multidisciplinary approach by the team at the CF care center and the primary care office.

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