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Helping patients with cystic fibrosis live longer

Lung and pancreas dysfunction are just part of the CF picture. Managing this “full-body disease” requires timely testing, traditional therapies, and familiarity with newer agents.

PRACTICE RECOMMENDATIONS

› Prescribe inhaled dornase alpha and inhaled tobramycin for maintenance pulmonary treatment of moderate to severe cystic fibrosis (CF). **A**

› Give aggressive nutritional supplementation to maintain a patient’s body mass index and blood sugar control and to attain maximal forced expiratory volume in one second (FEV₁). **B**

› Consider prescribing cystic fibrosis transmembrane conductance regulator modulators, which have demonstrated a 5% to 10% improvement in FEV₁ for CF patients. **A**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

Thanks to improved therapies and medical care in the last 3 decades, the treatment of cystic fibrosis (CF) is on the threshold of a new era, and the median age of survival has reached 40 years.¹ The hope of further extending survivability is now very real because of a new class of medications that act to modulate the primary pathology.

■ The focus of treatment. CF is not limited to the classic picture of lung and pancreas destruction with subsequent loss of function. The underlying pathology can occur in body epithelial tissues from the intestinal lining to sweat glands. These tissues contain cystic fibrosis transmembrane conductance regulator (CFTR), a protein that allows for the transport of chloride across epithelial cell membranes.² In individuals homozygous for mutated CFTR genes, chloride transport can be impaired. In addition to regulating chloride transport, CFTR is part of a larger, complex interaction of ion transport proteins such as the epithelial sodium channel (ENaC) and others that regulate bicarbonate secretion.² Decreased chloride ion transport in mutant CFTR negatively affects the ion transport complex; the result is a higher-than-normal viscosity of secreted body fluids.

■ Reason for hope. It is this impairment of chloride ion transport that leads to the classic phenotypic features of CF (eg, pulmonary function decline, pancreatic insufficiency, malnutrition, chronic respiratory infection), and is the target of both established and emerging therapies³—both of which I will review here.

When to consider a CF diagnosis

Cystic fibrosis remains a clinical diagnosis when evidence of at least one phenotypic feature of the disease (**TABLE 1**) exists in the presence of laboratory evidence of a CFTR abnormality.⁴ Confirmation of CFTR dysfunction is demonstrated by an ab-

TABLE 1

Phenotypic features of cystic fibrosis and usual treatments⁴

Respiratory system
Chronic cough
Chronic sputum production
Nasal polyps
Chronic sinusitis
Persistent chest x-ray abnormalities
Colonization with known CF pathogens: <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>
Treatments: Inhaled hypertonic saline, inhaled dornase alpha, inhaled antibiotics, intranasal steroids, nebulized albuterol, oral anti-inflammatories, mechanical airway clearance by exercise/therapy vest/laminar airflow devices, CFTR modulators
Gastrointestinal system
Pancreatic insufficiency
Recurrent pancreatitis
Focal biliary cirrhosis
Malnutrition
Vitamin deficiency
Greasy stools
Frequent abdominal pain, cramping with constipation, or obstruction
GERD
Treatments: Pancreatic enzymes replacement, vitamin supplementation, balanced nutritional supplements, histamine-2 blockers, proton pump inhibitors, polyethylene glycol, CFTR modulators
Reproductive system
Male infertility
Absence of the vas deferens
Other
Salt loss syndromes, especially when exercising
Treatments: Sodium supplementation and replacement

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

normality on sweat testing or identification of a CF-causing mutation in each copy of CFTR (ie, one on each chromosome).⁵ All 50 states now have neonatal laboratory screening programs;⁴ despite this, 30% of cases in 2012 were still diagnosed in those older than 1 year of age, with 3% to 5% diagnosed after age 18.¹

A sweat chloride reading in the abnormal range (>60 mmol/L) is present in 90% of patients diagnosed with CF in adulthood; this test remains the gold standard in the diagnosis of CF and the initial test of choice in suspected cases.⁴ Newborn screening programs identify those at risk by detecting persistent hypertrypsinogenemia and referring those

with positive results for definitive testing with sweat chloride evaluation. Keep CF in mind when evaluating adolescents and adults who have chronic sinusitis, chronic/recurrent pulmonary infections, chronic/recurrent pancreatitis, or infertility from absence of the vas deferens.⁴ When features of the CF phenotype are present, especially if there is a known positive family history of CF or CF carrier status, order sweat chloride testing.

Traditional therapies

Both maintenance and acute therapies are directed throughout the body at decreasing



For 90% of adults with cystic fibrosis, sweat chloride will be in the abnormal range of >60 mmol/L.

The traditional CF care model

The Cystic Fibrosis Foundation (CFF) has been a driving force behind the increased life expectancy CF patients have seen over the last 3 decades. Its contributions include the development of medication through the CFF Therapeutics Development Network (TDN) and disease management through a network of CF Care Centers throughout the United States. The CFF recommends a minimum of quarterly visits to a CF Care Center, and the primary care physician can play a critical role alongside the multidisciplinary CF team.²⁰

At every CF Care Center encounter, the entire team (nurse, physician, dietician, social worker, psychologist) interacts with each patient and their families to maximize overall medical care. Respiratory cultures are generally obtained at each visit. Dual-energy x-ray absorptiometry is performed biannually. Lab work (complete blood count, comprehensive metabolic panel, glycated hemoglobin, vitamins A, D, E, and K, 2-hour glucose tolerance test), and chest x-ray are obtained at least annually (TABLE 2).⁴

Since CF generally involves both restrictive and obstructive lung components, complete spirometry evaluation is performed annually in the pulmonary function lab, with static lung volumes in addition to airflow measurement. Office spirometry to measure airflow alone is performed at each visit. FEV₁ is tracked both as an indicator of disease progression and as a measure of current pulmonary status.

The CFF recommends that each patient receive full genetic testing and encourages patient participation in the CFF Registry, where mutation data are documented among other disease parameters to ensure that patients receive mutation specific therapies as they become available.⁴ The vaccine schedule recommended for CF patients is the same as for the general population.

fluid viscosity, clearing fluid with a high viscosity, or treating the tissue destruction that results from highly-viscous fluid.³ The traditional classic picture of CF is one of lung and pancreas destruction with subsequent loss of function. However, CF is, in reality, a full-body disease.

Respiratory system: Lungs

CFTR dysfunction in the lungs results in thick pulmonary secretions as the aqueous surface layer (ASL) lining the alveolar epithelium becomes dehydrated and creates a prime environment for the development of chronic infection. What ensues is a recurrent cycle of chronic infection, inflammation, and tissue destruction with loss of lung volume and function. Current therapies interrupt this cycle at multiple points.⁶

■ **Airway clearance** is one of the hall-

marks of CF therapy, using both chemical and mechanical treatments. Daily, most patients will use either a therapy vest that administers sheering forces to the chest cavity or an airflow device that creates positive expiratory pressure and laminar flow to aid in expectorating pulmonary secretions.⁷ Because exercise has yielded comparable results to mechanical or airflow clearance devices, it is recommended that all CF patients who are not otherwise prohibited engage in regular, vigorous exercise in accordance with standard recommendations for the general public.⁷

Mechanical therapies are often preceded by airway dilation with short- and long-acting bronchodilators and inhaled steroids that open airways for optimal airway clearance.⁴ Thick secretions can be treated directly and enzymatically with nebulized dornase alpha,^{4,8} which is also best administered before mechanical clearance therapy. Finally, viscosity of airway secretions can be decreased by improving the hydration of the ASL with nebulized 7% hypertonic saline.^{4,8}

■ **Infection suppression.** Thickened pulmonary secretions create a fertile environment for the development of chronic infection. By the time most CF patients reach adulthood, many are colonized with mucoid producing strains of *Pseudomonas aeruginosa*.^{4,8-10} Many may also have chronic infection with *Staphylococcus aureus*, some strains of which may be methicillin-resistant. Quarterly culture and sensitivity results can be essential in directing acute antibiotic therapy, both in the hospital and ambulatory settings. In addition, in the case of *Pseudomonas*, inhaled antibiotics suppress chronic infection, improve lung function, decrease pulmonary secretions, and reduce inflammation.

Formulations are available for tobramycin and aztreonam, both of which are administered every other month to reduce toxicities and to deter antibiotic resistance. Some patients may use a single agent or may alternate agents every month. When acute antibiotic therapy is necessary for a pulmonary exacerbation, the inhaled agent is generally withheld. If outpatient treatment is warranted, the only available oral antibiotics with anti-pseudomonal activity are ciprofloxacin and levofloxacin.^{4,8-10} *S aureus* can

TABLE 2

Recommended tests and testing intervals⁴

Quarterly
Cystic fibrosis sputum culture and sensitivity
Office spirometry
Oxygen saturation
Temperature
Heart rate
Respiratory rate
Weight
Body mass index
Biannually
Dual-energy x-ray absorptiometry
Annually
Full spirometry in pulmonary function lab to include static lung volumes
Chest x-ray
Cystic fibrosis sputum acid fast bacilli culture
Cystic fibrosis sputum fungal culture
Complete blood count
Comprehensive metabolic panel
Glycated hemoglobin
Prothrombin time/international normalized ratio
Immunoglobulin E
Vitamins A, D, E, and K
2-hour oral glucose tolerance test

be treated with trimethoprim/sulfamethoxazole or doxycycline.^{4,8-10}

■ **Inflammation reduction** is addressed with high-dose ibuprofen twice daily, azithromycin daily or 3 times weekly, or both. Children up to age 18 benefit from ibuprofen, which also improves forced expiratory volume in one second (FEV₁) to a greater extent than azithromycin.⁸ Adults, however, face the risk of gastrointestinal bleeding and renal dysfunction with ibuprofen, which must be weighed against its potential anti-inflammatory benefit. Both populations, however, benefit from chronic azithromycin, whose mechanism of action in this setting is believed to be more anti-inflammatory than bacterial suppression, since it has no direct bactericidal effect on the primary colonizing microbe, *P aeruginosa*.^{4,11}

Gastrointestinal system: Pancreas

Cystic fibrosis was first comprehensively described in 1938 and was named for the diseased appearance of the pancreas.¹² As happens in the lungs, thick pancreatic duct secretions create a cycle of tissue destruction, inflammation, and dysfunction.² CF patients lack adequate secretion of pancreatic enzymes and bicarbonate into the small bowel, which progressively leads to pancreatic dysfunction in most patients.

■ **As malabsorption of nutrients advances**, patients suffer varying degrees of malnutrition and vitamin deficiency, especially of the fat-soluble vitamins A, D, E, and K. Over 85% of CF patients have deficient pancreatic function, requiring pancreatic enzyme supplementation with all food intake and daily vitamin supplementation.²

■ **Ensuring adequate nutrition.** Most CF patients experience a chronic mismatch of dietary intake against caloric expenditure and benefit from aggressive nutritional management featuring a high-calorie diet with supplementation in the form of nutrition shakes or bars.² There is a well-documented linear relationship between BMI and FEV₁. Lung function declines in CF when a man's body mass index (BMI) falls below 23 kg/m² and a woman's BMI drops below 22 kg/m².² For this reason, the goal for caloric intake can be as high as 200% of the customary recommended daily allowance.²

■ **Watch for CF-related diabetes.** Since the pancreas is also the major source of endogenous insulin, nearly half of adults with CF will develop cystic fibrosis-related diabetes (CFRD) as pancreatic deficiency progresses.¹³ Similar to the relationship between BMI and FEV₁, there is a relationship between glucose intolerance and FEV₁. For this reason, annual diabetes screening is recommended for all CF patients ages 10 years and older.¹³ Because glycated hemoglobin (HbA1c) may not accurately reflect low levels of glucose intolerance, screen for CFRD with a 2-hour 75-g oral glucose tolerance test.¹³ Early insulin therapy can help maintain BMI and lower average blood sugar in support of FEV₁. Once CFRD is diagnosed, the goals and recommendations for control are largely the same as those recommended by the Ameri-

➤ **Because exercise has yielded comparable results to mechanical or airflow clearance devices, CF patients should engage in regular, vigorous exercise.**

can Diabetes Association for other forms of diabetes.¹³

**Gastrointestinal system:
Alimentary canal**

CF is often mistakenly believed to be primarily a pulmonary disease since 85% of the mortality is due to lung dysfunction,⁷ but intermittent abdominal pain is a common experience for most patients, and disorders can range from gastroesophageal reflux disease (GERD) to small bowel bacterial overgrowth (SBBO) to constipation. Up to 85% of adult patients experience symptoms of reflux, with as many as 40% of cases occurring silently.² Proton pump inhibitors are a first-line treatment, but they can also contribute to intestinal bacterial overgrowth and pulmonary infections.

In SBBO, gram-negative colonic bacteria colonize the small bowel and can contribute to abdominal pain and malabsorption, weight loss, and malnutrition. Treatment requires antibiotics with activity against gram-negative organisms, or non-absorbable agents such as rifamycin, sometimes on a chronic, recurrent, or rotating basis.²

Chronic constipation is also quite common among CF patients and many require daily administration of poly-ethylene-glycol. Before newborn screening programs were introduced, infants would on occasion present with complete distal intestinal obstruction. Adults are not immune to obstructive complications and may require hospitalization for bowel cleansing.

Gastrointestinal system: Liver

Liver disease is relatively common in CF, with up to 24% of adults experiencing hepatomegaly or persistently elevated liver function tests (LFT).⁴ Progressive biliary fibrosis and cirrhosis are encountered more often as the median survival age has increased. There is evidence that ursodeoxycholic acid (UDCA) can be a useful adjunct in the treatment of cholestasis, but it is not clear if it alters mortality or progression to cirrhosis. Only CF patients with elevated LFTs should be started on UDCA.⁴

Other areas of concern:

Sinuses, serum sodium levels

Chronic, symptomatic sinus disease in

**Cystic fibrosis
resources**

Cystic Fibrosis Foundation
www.cff.org

**Consensus report on cystic fibrosis
management**

Yankaskas JR, Marchall BC, Sufian B, et al. Cystic fibrosis adult care. *Chest*. 2004;125:15-395.

**Consensus report on cystic fibrosis
diagnostic guidelines**

Farrell PM, Rosenstein BJ, White RB. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr*. 2008;153:S4-S14.

CF patients—chiefly polyposis—is common and may require repeat surgery, although most patients with extensive nasal polyps find symptom relief with daily sinus rinses. Intra-nasal steroids and intranasal antibiotics are also often employed, and many CF patients need to be in regular contact with an otolaryngologist.¹⁴ For symptoms of allergic rhinitis, recommend OTC antihistamines in standard dosages.

Exercise is recommended for all CF patients, as noted earlier, and as life expectancy increases, many are engaging in more strenuous and longer duration activities.¹⁵ Due to high sweat sodium loss, CF patients are at risk for hyponatremia, especially when exercising on days with high temperatures and humidity. CF patients need to replace sodium losses in these conditions and when exercising for extended periods.

There are no evidence-based guidelines for sodium replacement. The Cystic Fibrosis Foundation (CFF) recommends that patients increase salt in the diet when under conditions likely to result in increased sodium loss, such as exercise. It has been thought that CF patients can easily dehydrate due to an impaired thirst mechanism and, when exercising, should consume fluids beyond the need to quench thirst.^{16,17} More recent evidence suggests, however, that the thirst mechanism in those with CF remains normally intact and that overconsumption of fluids beyond the

➤ Because HbA1c may not accurately reflect low levels of glucose intolerance, screen for CF-related diabetes with a 2-hour 75-g oral glucose tolerance test.

level of thirst may predispose the individual to exercise-associated hyponatremia as serum sodium is diluted.¹⁵

New therapies

Small-molecule CFTR-modulating compounds are a promising development in the treatment of CF. The first such available medication was ivacaftor in 2012. Because these molecules are mutation specific, ivacaftor was available at first only for patients with at least one copy of the G551D mutation,¹⁸ which means about 5% of patients with CF.³

■ **Ivacaftor increases the likelihood** that the CFTR chloride channel will open and patients will exhibit a reduction in sweat chloride levels. In the first reported clinical trial of ivacaftor involving patients with the G551D mutation, FEV₁ improvements of 10% occurred by the second week of therapy and persisted for 48 weeks.¹⁸ The drug has now been approved by the US Food and Drug Administration (FDA) for patients 12 years of age and older with at least one of the following mutations: R117H, G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, or G1349D.¹⁹

■ **A medication combining ivacaftor with lumacaftor** is also now available for patients with a copy of F508del on both chromosomes. F508del is the most common CFTR mutation, with one copy present in almost 87% of people with CF in the United States.¹ Since 47% of CF patients have 2 copies of F508del,¹ about half of those with CF in the United States are now eligible for small-molecule therapy. Lumacaftor acts by facilitating transport of a misfolded CFTR to the cell membrane where ivacaftor then increases the probability of an open chloride channel. This combination medication has improved lung function by about 5%.

The ivacaftor/lumacaftor combination was approved by the FDA in July 2015. Both ivacaftor and the ivacaftor/lumacaftor combination were deemed by the FDA to demonstrate statistically significant and sustained FEV₁ improvements over placebo.

The CFF was instrumental in providing financial support for the development of both ivacaftor and the ivacaftor/lumacaftor combination and continues to provide significant

research advancement. According to the CFF (www.cff.org), medications currently in the development pipeline include compounds that provide CFTR modulation, surface airway liquid restoration, anti-inflammation, inhaled anti-infection, and pancreatic enzyme function. For more on CFF, see "The traditional CF care model,"^{4,20} on page 190. **JFP**

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