REVIEW

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Cystic fibrosis in adults: An overview for the internist

ABSTRACT

The care of patients with cystic fibrosis (CF) has improved over the past 30 years, and most patients now survive well into adulthood. As a result, clinicians other than pediatricians are more likely than in the past to see CF patients and manage their respiratory, gastrointestinal, pancreatic, and reproductive complications.

KEY POINTS

CF patients are prone to chronic lung infections. The choice of antibiotic is difficult because many CF patients are infected with multiple strains of resistant pathogens.

Abdominal pain in CF patients can be due to simple constipation; however, distal intestinal obstruction, intussusception, appendicitis, colonic strictures from pancreatic enzyme supplements, hypotonic colon, and cholelithiasis do occur with increased frequency.

Pancreatic insufficiency can lead to malabsorption of fat, fat-soluble vitamins, and protein. Diabetes is common.

Most men with CF are infertile owing to obstruction and resorption of the vas deferens during gestation. Most women with CF have only modest reduction in fertility.

The Cystic Fibrosis Foundation recommends a program of surveillance for complications of CF, with regularly scheduled follow-up visits, pulmonary function tests, respiratory cultures, and measurements of the serum creatinine, plasma glucose, and liver enzyme levels.

*Dr. Budev has indicated that she has served as an advisor/consultant for the Chiron corporation.

CYSTIC FIBROSIS (CF) is no longer a purely pediatric disease: with current management, almost 80% of patients with CF reach adulthood.[1–3] In fact, CF patients born in the 1990s are predicted to survive a median of more than 40 years.[2]

It was not always so. When CF was recognized as a distinct clinical entity in 1938, it was thought to be invariably fatal during infancy.[4] Over the last 30 years, the average life span of CF patients has increased, possibly owing to more sensitive diagnostic techniques and better supportive treatment in multidisciplinary CF care centers.

In this paper we review the prevalence, pathophysiology, and management of CF for general internists, who are now more likely to see CF patients than in the past.

MORE COMMON IN WHITES

CF, an autosomal-recessive disease, occurs predominantly in whites, in whom the rate is 1 in 2,500 to 3,500 live births and in whom it is the most common autosomal-recessive, life-limiting disease.[5,6] Two to five percent of white people are CF carriers (having one normal and one abnormal gene) but have no overt sign of disease.

CF does occur in African Americans, but at the much lower frequency of approximately 1 in 17,000 live births.[7] In general, mutations of the CF gene are most prevalent in people of Northern and Central European and Ashkenazi Jewish descent and are rare in Native Americans, Asians, or native Africans.[8]

All together, approximately 30,000 children and adults in the United States have CF. Males and females are equally affected.

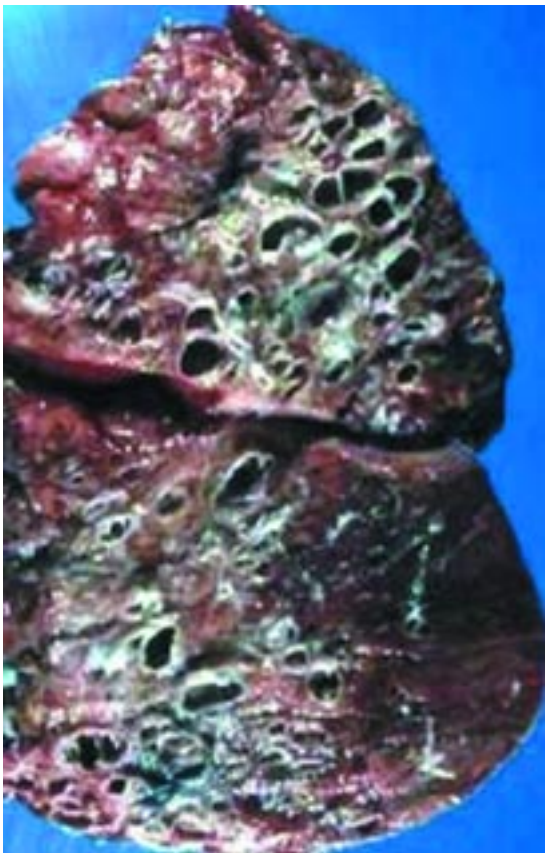

FIGURE 1. Cystic fibrosis of the lung.

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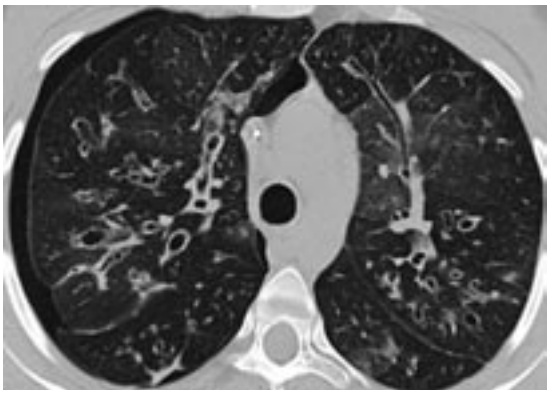

FIGURE 2. Computed tomographic image of cystic fibrosis of the lung with right pneumothorax.

2%–5% of whites are CF carriers

PATHOPHYSIOLOGY: AN AUTOSOMAL-RECESSIVE DISEASE

Thick, sticky mucus

CF patients inherit two defective copies of a gene on the long arm of chromosome 7. This gene codes for a protein called the cystic fibrosis transmembrane conductance regulator (*CFTR*). This protein, 1,480 amino acids long, spans the cell membrane of epithelial cells[9,10] and normally regulates the transport of chloride and other electrolytes.[11]

More than 1,000 mutations of the *CFTR* gene associated with the CF phenotype have been described to date.[12] The most common of these mutations, delta F508, results from the deletion of three base pairs that together code for phenylalanine at position 508 of the protein. The mutant protein does not fold properly and is removed to a lysosome.

Without enough functional copies of the *CFTR* protein in their cell membranes, epithelial cells cannot pump enough water into the mucus and other products they secrete. Therefore, the secretions are too dry, thick, and sticky, and they tend to obstruct the ducts of various organs and the small airways of the lungs. This obstruction sets the stage for chronic infection or inflammation or both, and eventually tissue destruction.

Chronic lung infections

The hallmark of CF, and the cause of death in more than 90% of patients, is chronic pulmonary infection with specific bacteria; in order of prevalence these are[3]:

- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Haemophilus influenzae*
- *Stenotrophomonas maltophilia*
- *Burkholderia cepacia*.

Emerging pathogens include *Alcaligenes xylosoxidans*, nontuberculous mycobacteria, and opportunistic fungi.

Patients with CF are prone to colonization with *S aureus* and mucoid types of *P aeruginosa*. The latter bacterial colonies are created by the transformation to a biofilm-encased form protecting the microorganisms from normal host defenses and antibiotics.[13]

Another organism with a significant impact on CF lung disease is *B cepacia*, which is actually a cluster of closely related species (a "genomovar"). Invasive pulmonary infection and rapid clinical deterioration is associated with acquisition of an epidemic genomovar of this pathogen, prompting CF care centers to "cohort" patients with this infection (ie, place

them in isolation when they are in the hospital) in an attempt to prevent its spread.[14]

CF lung disease progresses from bronchiolitis and bronchitis to bronchiectasis as a consequence of the persistent obstruction and infectious insult. Bronchiectasis is more severe in the upper lobes. Bronchiectatic cysts are present at autopsy in more than 50% of lungs in patients with end-stage CF and may contribute to the 3% to 19% reported incidence of spontaneous pneumothorax (**FIGURE 1, FIGURE 2**).[15,16]

Pancreas, liver, and gallbladder disease

Ninety percent of CF patients have pancreatic insufficiency.

Abnormal *CFTR* function in the pancreatic ducts causes a decreased volume of pancreatic secretions with reduced bicarbonate concentration. Autoactivation of retained digestive proenzymes leads to destruction and fibrosis of pancreatic tissue. Consequently, absorption of lipids and fat-soluble vitamins (A, D, E, and K) is reduced, which can lead to steatorrhea and malnutrition.

Clogging of the biliary ducts may lead to liver involvement and biliary cirrhosis, which is present at autopsy in 25% of patients with CF. Hepatic steatosis may result from malnutrition, and congestion of the liver may result from hypoxia-induced cor pulmonale.[6] Only about 5% of CF patients develop clinical cirrhosis, however.

Fecal loss of bile acids is increased in CF, leading to a reduction in the bile-salt pool. Approximately 30% of adult CF patients have a hypoplastic, poorly functioning gallbladder and may develop gallstones.[6,9]

Diabetes is common, due to pancreatic duct obstruction

Over time, obstruction of the pancreatic ducts causes amyloid deposition and diabetes.[17,18]

CF-related diabetes usually develops after the second decade of life and rarely before the age of 10 years, due to sparing of Langerhans cells. The incidence of diabetes requiring chronic insulin therapy in CF patients older than 13 years has been reported as 16.9%.[19] Ketoacidosis is very rare in CF-related diabetes.

Male infertility is almost universal in CF

Ninety-five percent of young men with CF are infertile because of bilateral absence of the vas deferens, abnormalities of the seminal vesicle, or both.[20] It is believed that the vas deferens becomes plugged with secretions and is reabsorbed during gestation.

TABLE 1

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SIGNS AND SYMPTOMS

CF is a multisystem disease with clinical manifestations in the respiratory, gastrointestinal, and reproductive tracts (**TABLE 1**).

Productive cough, dyspnea, wheezing, chest pain

Pulmonary symptoms of CF include a chronic or persistent cough that is productive of purulent and/or bloody sputum, dyspnea, wheezing, and chest pain. Clinically, pulmonary exacerbations of CF are manifested as an increase in respiratory symptoms with associated systemic symptoms such as malaise, anorexia, and weight loss.[21] Rarely do patients have fever and leukocytosis.[7]

The upper respiratory tract is also involved in CF, with most patients suffering from acute

and chronic sinusitis caused by hypertrophy and hyperplasia of the secretory components of the sinus tract.[22] Another common feature is pedunculated nasal polyposis.

Gastrointestinal symptoms: Pain, malnutrition, constipation

Gastrointestinal symptoms in CF may present soon after birth. Meconium ileus, an acute bowel obstruction caused by thick, inspissated gastrointestinal secretions, sometimes requires immediate surgical intervention.

Children with exocrine pancreatic insufficiency typically present with steatorrhea and malnutrition from fat and protein malabsorption. Chronic fat malabsorption can lead to loss of fat-soluble vitamins, resulting in neuropathy, coagulopathy, and osteoporosis.

In patients with pancreatic insufficiency, CF is usually diagnosed in childhood. Patients in whom CF is diagnosed in adulthood are usually pancreatic-sufficient and may instead present with chronic or recurrent abdominal pain from pancreatitis due to intermittent ductal obstruction.

Chronic lung infection is the cause of death in > 90% of CF patients

Other causes of abdominal pain in CF patients include the distal intestinal obstruction syndrome (DIOS, also called the "meconium ileus equivalent"), simple constipation, intussusception, appendicitis, colonic strictures associated with high doses of pancreatic enzyme supplementation, and hypotonic colon. CF patients with DIOS usually present with abdominal pain and may have a palpable mass in the right lower quadrant. Associated symptoms may include anorexia, nausea, vomiting, and obstipation.

Symptomatic cholelithiasis can also be a cause of abdominal pain in CF. While this complication is quite common, symptomatic liver disease due to cirrhosis is not.

Patients with pancreatic endocrine insufficiency (ie, diabetes mellitus) are more likely to present with weight loss and deteriorating pulmonary function than polyuria or polydipsia.

Reproduction and fertility

Since many more CF patients are surviving into their reproductive years, issues of having children and raising a family have gained more attention. Men with mild CF phenotypes may present after an infertility workup has uncovered azoospermia due to bilateral absence of the vas deferens. Libido and sexual performance are typically not affected.

Overall, women with CF and normal nutritional status have only a modest reduction in fertility; hence, birth control should be discussed with female patients reaching sexual maturity.

DIAGNOSIS: A FEW WOMEN HAVE UNDIAGNOSED MILD CF

Adults with a *CFTR* mutation who present to an internist typically have already been diagnosed with CF. However, a small subset of CF patients are diagnosed at a later age. These patients, typically female with milder disease, can pose a diagnostic challenge.[23] Frequently, they have received inaccurate diagnoses of asthma, chronic bronchitis, or emphysema. Clinicians should suspect undiagnosed CF in patients with chronic respiratory tract infections, unexplained bronchiectasis, congenital bilateral absence of the vas deferens, or pancreatitis without obvious cause. Internists should be familiar with the diagnosis of CF on account of such cases.

In 1998, the Cystic Fibrosis Foundation issued a consensus statement on the diagnosis of CF.[5] The expert panel recommended that diagnosis of CF be made if the patient has any of the following:

- One or more typical phenotypic features of CF
- A family history of CF in a first-degree relative
- A positive newborn screening test.

In addition, the diagnosis requires a physiologically or genetically demonstrable abnormality in *CFTR*. The *CFTR* abnormality can be established either by an abnormal sweat chloride test, identification of mutations known to cause CF, or in vivo demonstration of an ion transport abnormality across the nasal epithelium (**FIGURE 3**).

In 2001, the median age at diagnosis of the 1,000 or more infants born yearly with CF was 6 months. Of note, 5% of cases are diagnosed after age 16.

Sweat chloride testing

Evaluation of sweat chloride content by pilocarpine iontophoresis is still the most com-

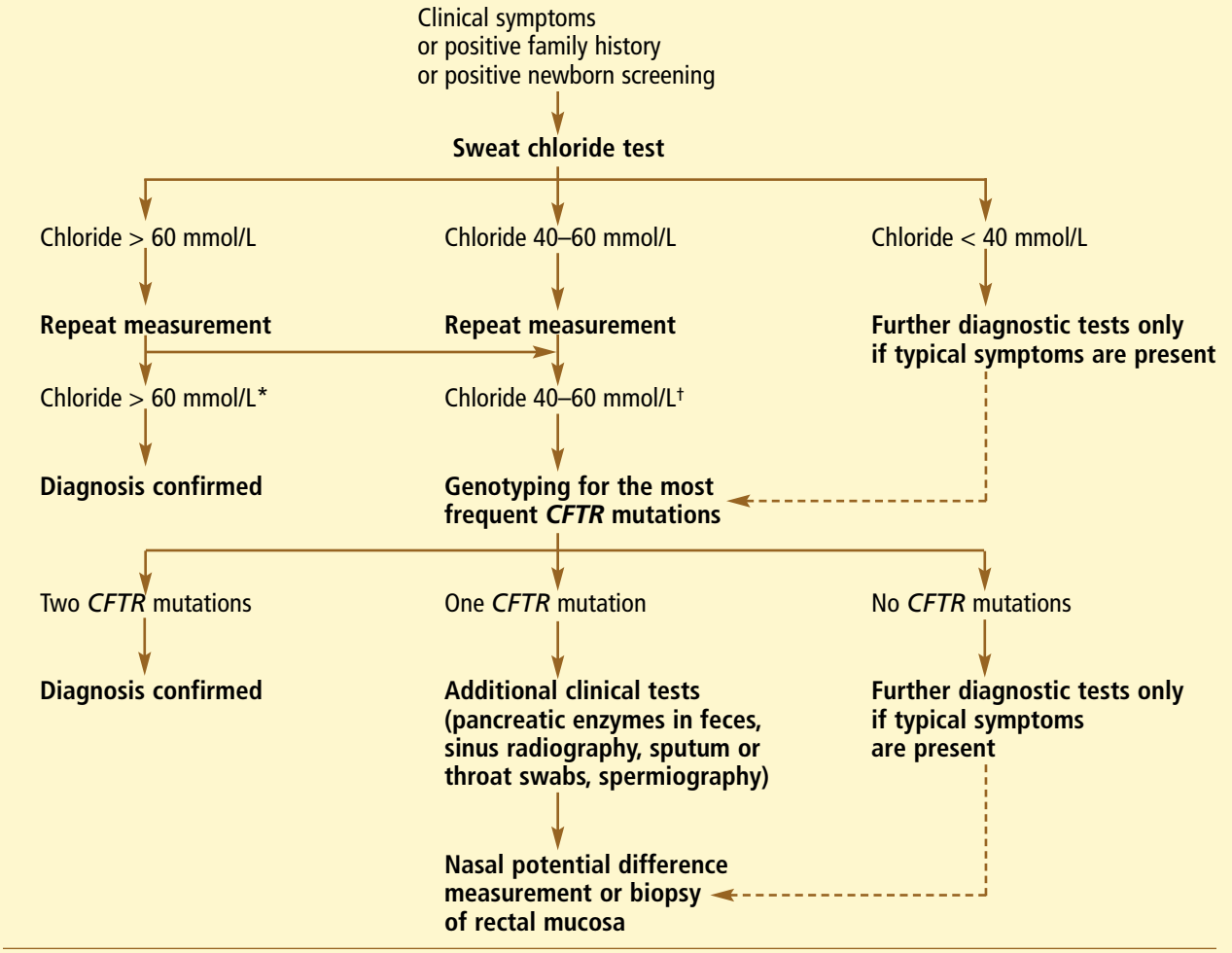

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FIGURE 3

monly used test to establish physiologic abnormalities in *CFTR* function. A positive test is constituted by a chloride concentration in excess of 60 mmol/L in children or 80 mmol/L in those over 18 years of age. The test requires at least 75 mg of sweat, and it should be repeated (two separate measurements) for confirmation at a laboratory accredited by the Cystic Fibrosis Foundation.

Genotyping

More than 1,000 *CFTR* mutations have been linked to CF; the commonly used genetic tests probe for the 70 to 80 most common of these. The sensitivity of these tests is over 85% for one mutation and about 95% for two mutations in patients with bona fide CF. Recently, Ambry Genetics (Irvine, CA) has made comprehensive sequencing of the CF locus commercially available.

Ancillary testing

In patients with atypical features, a number of clinical and radiologic tests can help evaluate for a CF phenotype; these include sputum culture, chest radiography, computed tomography of the chest, sinus evaluation, testicular ultrasonography, semen analysis, and pancre-

TABLE 2

Cystic Fibrosis Foundation guidelines for routine follow-up

SURVEILLANCE	FREQUENCY
Outpatient visits	Four or more per year
Pulmonary function tests	Two or more per year
Respiratory cultures	At least one per year
Creatinine level	Every year
Glucose	Every year if ≥ 14 years
Liver enzymes	Every year

WITH PERMISSION FROM CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY ANNUAL DATA REPORT 2004. BETHESDA, MD: CYSTIC FIBROSIS FOUNDATION, 2005.

atic functional assessment including measurements of pancreatic elastase in fecal fat and stool.

THERAPY

Health maintenance

CF lung disease progresses from bronchiolitis and bronchitis to bronchiectasis

In the early 1990s, the Cystic Fibrosis Foundation developed guidelines to help standardize the care of patients with this complex disease.[5] Their recommendations for annual screening tests are listed in TABLE 2. The emphasis is on catching disease progression early for aggressive management.

Respiratory care

Spirometry is useful for monitoring trends in pulmonary status. Lung function is normal early on in most CF patients.

Among the first pulmonary function findings to suggest CF lung disease are a low value for the forced expiratory flow at 25% to 50% of forced vital capacity (FVC) ($FEF_{25\%–75\%}$) and an increased ratio of residual volume (RV) to total lung capacity (TLC).

Later, decreases are noted in the forced expiratory volume in 1 second (FEV_1) and FVC, almost always in an obstructive pattern. In general, a 10% decrease in FEV_1 is considered a sign of significantly worsening lung function and pulmonary exacerbation.[24] Patients with an FEV_1 less than 30% of predicted are at high risk of nocturnal hypoxia and hypercapnia, and one should consider measuring their arterial blood gases and their nocturnal oxygen saturation by pulse oximetry.

Supplemental oxygen. Oxygen saturation should be monitored routinely in patients with moderate to severe disease to assess the need for supplemental oxygen. Although no data show that supplemental oxygen confers a survival advantage in CF, most clinicians use the guidelines suggested by the Nocturnal Oxygen Therapy trial for COPD.[25]

Inhaled beta-agonists. No studies show that routine use of inhaled beta-agonists improves pulmonary function in the long term, but these drugs are often used. They are thought to be most effective in the subset of CF patients with airway hyperreactivity as documented by bronchodilator responsiveness on pulmonary function tests (an increase in FEV_1 of 200 mL after therapy).[26]

Inhaled hypertonic saline, either a 3% or a 6% solution, has been shown to reduce sputum viscoelasticity and to increase cough clearance in CF patients.[27] A recently published study showed that inhaled 7% hypertonic saline reduces pulmonary exacerbations and improves both FEV_1 and FVC.[28]

Dornase alfa (recombinant human deoxyribonuclease I; Pulmozyme) is thought to improve mucociliary clearance by hydrolyzing extracellular DNA, which is present at high levels in CF mucus as it is released from sloughed epithelium, inflammatory cells, and respiratory pathogens. In a multicenter, placebo-controlled study, patients treated with dornase alfa had about a 6% improvement in FEV_1 after 24 weeks compared with the control group.[29,30] In addition, the risk of respiratory exacerbations was reduced by 37% in the treatment group.

Side effects of dornase alfa include hoarseness, change in voice, and mild pharyngitis.[2]

Chest physiotherapy. Although data are lacking to support chest physiotherapy as an effective treatment to forestall pulmonary decline in CF, daily airway clearance therapy is recommended for all CF patients.[31] Since these therapies promote coughing, they should be performed before eating or administration of inhaled corticosteroids and antibiotics. In addition, because the airways have fewer secretions following physiotherapy,

deposition of inhaled medication may be enhanced.

Chest percussion (clapping) and postural drainage is the time-honored approach to the clearance of secretions in CF. With cupped hands or a clapping device, the chest wall is percussed and vibrated to aid mucus clearance; during postural drainage, the patient is positioned so that gravity assists the drainage of mucus from nondependent areas of the lung.

A similar technique, high-frequency chest wall oscillation (HFCWO), is performed using a pneumatic compression vest that percusses the entire chest at once. This device is appealing to independent CF patients because they can apply it themselves.[32]

Controlled breathing techniques that utilize sequential increases in tidal breath volumes starting close to residual volume may assist mucus clearance. Examples are called "active cycle of breathing" and "autogenic drainage." Like HFCWO, they do not require an assistant.[33] These techniques are often coupled with forced exhalation ("huffing") after inhalation to medium or high lung volumes to help move mucus out of the lungs.[34]

The application of positive expiratory pressure (PEP) by valve devices or intrapulmonary percussive ventilation (IPV) may prevent bronchiectasis-related, dynamic airway collapse that blocks mucus movement in CF. Expiratory valves such as TheraPEP (Smiths Medical Inc, Carlsbad, CA) or oscillation PEP valves such as the Flutter (Scandapharm, Birmingham, AL) or Acapella (DVD Healthcare, Wampsville, NY) devices are relatively easy to use, portable, and inexpensive.[32] IPV provides frequent, small, and low-pressure breaths in an oscillatory manner. IPV is limited by its cost and lack of portability.[24]

Some of the contraindications to chest physiotherapy techniques include poorly controlled gastroesophageal reflux disease, massive hemoptysis, and pneumothorax.

Improvements in quality of life have been shown in CF patients who exercise regularly.[24] The mechanism of this effect is not clear. Exercise may or may not enhance mucus clearance; however, regular exercise enhances cardiovascular fitness and improves functional capacity, and it should be advocated for CF patients.[2]

Antibiotics

Improvements in antibiotics, especially antipseudomonal therapies, have likely helped to increase the life span for CF patients.

In an effort to delay acquisition of persistent *Pseudomonas* infection, many CF centers have adopted the Copenhagen Protocol, in which oral ciprofloxacin and inhaled colistin (a polymyxin B group antibiotic) are started for a course of 14 to 21 days when *Pseudomonas* species are first isolated. This strategy was shown to significantly delay the onset of chronic *Pseudomonas* recovery from sputum cultures. Cohorting measures, where patients are placed into separate subgroups according to infection status, may limit or delay pathogen acquisition.[35]

Intravenous antibiotics are the mainstay of therapy for acute exacerbations. The choice of antibiotic is difficult because many CF patients are infected with multiple strains of resistant pathogens, some of which require double antibiotic coverage to prevent further acquisition of resistance. Therefore, the choice should be based on the most recent sensitivities of the surveillance sputum cultures.

Percussion and postural drainage is the time-honored approach to clearing chest secretions

If a recent culture is not available, antibiotic coverage should include treatment for both *Staphylococcus* and *Pseudomonas* species. Most centers choose a third-generation cephalosporin, antipseudomonal semisynthetic penicillin, or carbapenem and an aminoglycoside. Treatment lasts for 2 to 3 weeks at high dosages because of altered pharmacokinetics peculiar to CF patients.

Antibiotic aerosols can minimize systemic toxicity and are easier to use at home. Inhaled tobramycin, the most studied inhaled antibiotic in CF, has been shown to improve FEV_1, decrease the rate of hospitalization, and reduce the density of *P aeruginosa* when used in stable CF patients.[36] Because of extensive mucous plugging and airway narrowing, absorption of inhaled tobramycin is attenuated, and this treatment is therefore not a substitute for intravenous antibiotics during acute exacerbations. Limiting factors in their use include cost, taste, and deposition in severe disease and acute exacerbations.[7]

Several large randomized studies demonstrated the benefit of macrolides in CF patients. These investigations indicate that the macrolide's immunomodulatory rather than antibacterial effects are responsible for the improved outcomes. Experts have suggested giving a macrolide (azithromycin or clarithromycin) every other day for 6 months in CF patients who do not improve with conventional therapy.[37] Azithromycin has been shown to improve pulmonary function over a 6-month period in CF patients homozygous for delta F508 and not receiving dornase alfa.[38]

Nutritional care and supplementation

CF patients should follow a well-balanced diet in which at least 35% to 40% of the calories come from fat. Anthropomorphic measurements should be made every 3 to 4 months, and patients should be encouraged to maintain their weight close to their ideal body weight. Annual measurements of the complete blood cell count and serum albumin, retinol, and tocopherol concentrations are recommended.

CF patients should follow a well-balanced diet with 30%–40% of calories from fat

In patients with pancreatic insufficiency, microencapsulated pancreatic enzymes should be given with each meal and snack, in dosages that prevent steatorrhea and maintain weight or growth rate in the normal range while avoiding constipation.

Refractory fat malabsorption sometimes responds to the addition of histamine$_2$ receptor antagonists or proton pump inhibitors, as hyperacidity in the small bowel renders the pancreatic enzymes less effective.

Supplements of fat-soluble vitamins should include vitamin A 10,000 IU/day, vitamin E 200 to 400 IU/day, vitamin D 400 to 800 IU/day with adequate sunlight exposure, and vitamin K 2.5 to 5.0 mg/week.

If the body mass index decreases below the normal range, enteral feeding through a gastrostomy or jejunostomy tube should be considered.

CF patients with DIOS or partial bowel obstructions often require treatment with oral polyethylene glycol solutions and diatrizoate enemas to avoid the need for surgical intervention.

Reproductive issues

Men with CF who want to have children should be offered the option of microscopic epididymal sperm sampling, to be used in artificial insemination.

In women with CF, the success rate of pregnancy has improved since the 1960s. Maternal deaths mainly occur in patients with severe lung disease and poor nutritional status. Multiple case studies indicate that the rate of decline of lung function and the absolute FEV_1 value may be the most important factors in determining outcome.[39,40] Canny et al[39] recommended an FEV_1 of more than 70% as a requirement for a successful pregnancy, although a recent review of the Cystic Fibrosis Foundation registry did not support FEV_1 cutoffs as a predictor of success. In the patient registry, 180 women who had CF were pregnant in 2002.[3,8]

Lung transplantation improves quality of life, but not survival

In advanced CF lung disease, the options for treatment are limited. Although its ability to extend life is questionable, lung transplantation has been offered as a way to improve quality of life. In 1998, the 1-year survival rate after lung transplantation in CF patients was more than 80%, while the 5-year survival rate was approximately 60%.[41]

Based on the International Guidelines for the Selection of Lung Transplant Candidates published in 1998,[42] CF patients should be referred for transplantation when the FEV_1 declines to less than 30% of predicted, they develop hypoxia or hypercapnia, hospitalizations increase in frequency, they frequently expectorate blood, or cachexia develops (TABLE 3).

Early experiences with lung transplantation suggested that CF patients colonized with *B cepacia* were not candidates for transplantation. However, recent advances in taxonomic identification of *B cepacia* genomovars have allowed this patient population to be eligible for transplantation at many centers, including our own.[43]

Gene therapy and the future

The ultimate cure for CF would restore the function of the *CFTR*. This has been attempted with in vivo gene therapy in CF patients using adenoviral vectors and cationic liposome transfer.[44,45] These techniques have

shown some short-term physiologic effects, but lasting expression has not been noted. Although it is still far from being a standard treatment, gene therapy for CF is the subject of much ongoing research.

Many genetic diseases, including CF, have a relatively high proportion of disease-causing premature stop mutations. One study of primary human airway cells showed that relatively low-dose gentamicin exposure can lead to an increased expression of *CFTR* specifically in cells derived from CF patients with premature stop mutations.[46] An in vivo study also suggested that there is a partial restoration of *CFTR* in CF patients during treatment with gentamicin.[47]

PROGNOSIS HAS IMPROVED, BUT LIFE IS STILL SHORTER

Overall, the life expectancy in CF has risen in the last 2 decades. In 1980, the median age at death was 18 years; by 2000 it had risen to 32 years.[3] In 1990, 30% of patients in the CF registry were over 18 years old. By 2002 this value rose to 40.2%.

Although overall survival rates have improved, female patients have had consistently poorer survival rates than male CF patients in the age range from 2 to 20 years.[48] The reason is not clear.

The rate of decline in lung function over time is difficult to estimate, but CF patients often have extended periods of stable lung function. Most patients have full-time or part-time jobs and many are married and have children. Despite advances in therapies for CF, however, most patients do not have a normal life span. At the appropriate time, end-of-life options need to be addressed with patients and their families. Advance care planning should be individualized for each patient as the course of the disease is so variable. The goal of advance-care planning is to better serve each patient according to his or her wishes.[2]

TABLE 3

Indications for lung transplantation in cystic fibrosis

- Forced expiratory volume in 1 second < 30% of predicted
- Rapidly progressive respiratory deterioration
- Increasing number of hospital admissions
- Massive hemoptysis
- Recurrent pneumothorax
- Arterial partial pressure of oxygen < 55 mm Hg
- Arterial partial pressure of carbon dioxide > 50 mm Hg
- Multiresistant organisms
- Wasting
- Young female patients should be referred earlier due to overall poor prognosis

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