

Decisions in the Management of Adults with Cystic Fibrosis

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Introduction

Cystic fibrosis (CF) is a severe and common hereditary disorder, affecting about 30,000 adults and children in North America. More than 1 in 29 individuals in North America—at least 10 million people in the United States alone—are carriers of the disease.¹ Owing to this high carrier level, about 1 of every 2,000 newborns will be affected with CF^{2,3}; average lifetime costs to treat the disease are roughly \$800,000 per patient.⁴ When CF was first identified 62 years ago, the 1-year mortality rate was 70%. Research and clinical studies on the disorder have helped to improve survival, and currently, the median survival for a child with CF born in the 1990s is 40 years.^{5,6}

CF is inherited via an autosomal recessive pattern and is the most common fatal autosomal recessive genetic disorder affecting whites.¹ The distribution of CF is highest among white persons of northern European ancestry. It affects a significant number of individuals of southern European and Hispanic ancestry, as well.⁷ A significantly lower incidence rate for the disease exists among blacks of African descent, native Americans, and Asian Americans.⁷

The gene associated with CF was first identified in 1989.¹ It is located on chromosome 7 and involves approximately 250,000 DNA base pairs, coding for a 6.5 kilobase mRNA molecule.⁸ This mRNA molecule in turn codes for the CF transmembrane conductance regulator (CFTR)—a transmembranous protein found in a wide variety of epithelial cells in the pancreas, salivary glands, intestine, sinuses, bronchial mucosa, and reproductive tract. The CFTR protein is an anion channel; its dysfunction leads to faulty ion transport in the exocrine glands, a characteristic of patients with CF.⁹ More than 700 mutations of this protein, which have been linked to various pathologic phenotypic expressions of CF, have been found in patients with clinical manifestations of the disease.

Faulty sodium and chloride ion transport across the dysfunctional CFTR proteins results in the production

of thick, highly concentrated secretions that affect exocrine gland function. The hallmark of CF is manifestations of this dysfunction in the respiratory system, which typically results in secondary clinical disease, including chronic lung infections.⁷ Although CF's effects on the respiratory system are generally understood to be the primary source of morbidity and mortality, other organ systems are also affected, including the pancreas, gastrointestinal system, hepatobiliary system, and reproductive system.

CF can manifest itself in various severity patterns. Some patients have significant disease in the first years of life that results in early death. Other patients, however, such as the patient in this case study, may live a nearly normal life span with minimal or mild respiratory disease manifestations.⁷ Classically, patients present with chronic lung infections and pancreatic insufficiency; the latter leads to nutrient malabsorption, particularly of fats and proteins.⁷

A sweat test is the primary tool used in the diagnosis of CF; a chloride level greater than 60 mEq/L is considered a positive test result. In combination with the patient having typical pulmonary disease, pancreatic malabsorption, or a family history of CF, the test is considered diagnostic.² It should be noted, however, that some patients with clinical signs or genetic evidence of CF may have normal sweat test results, and further evaluation of these patients is necessary.¹⁰

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For adults such as the patient in this case study, longer life may be associated with a variety of complications. Hepatic disease occurs in adult patients with CF, with the most common abnormality being steatosis, occurring in 30% to 64% of patients.¹¹ Advanced liver disease may develop, including ascites, recurrent variceal bleeding, and encephalopathy.⁷ Ninety-five percent of men with CF are sterile; this has been elucidated to be the result of abnormal development of the mesonephric portion of the male reproductive tract, resulting in obstructive azoospermia and/or congenital bilateral absence of the vas deferens.¹²⁻¹⁴ The fertility rate of women with CF is approximately 20%¹⁵; this may be a result of the thick mucus secretions associated with the disease. However, the existence of specific reproductive sequelae for women with CF has not been determined.^{16,17}

In general, curative treatment for CF is highly intensive; supportive treatment is the mainstay, with lung transplantation and, in the future, gene therapy representing areas being investigated to provide more fundamental solutions to address the clinical manifestations of CF.¹⁸⁻²¹ Treatment of this condition is made more difficult by the fact that patients with CF often have increased clearance for most drugs, including aminoglycosides and other antibiotics.²²

A specialized interdisciplinary team is important for effective treatment of CF, as was accessed by the treating physicians in this case study. Often, the team includes a primary care physician (PCP), pulmonologist, clinical nurse or nurse practitioner, dietitian, respiratory therapist, and social worker; the focus is on both the patient as well as his or her family.⁷ Specialized care centers appear to be more effective in treating patients with CF than a traditional approach. Several studies around the world have documented improved results for patients with CF who were treated at specialized centers.²³⁻²⁵ However, it should be noted that these teams may or may not be effective in communicating other health issues to patients, particularly reproductive and sexual health concerns to adolescents.^{17,26,27}

There is tremendous debate as to whether CF screening is an appropriate response to identify children with the disease. Prenatal screening under limited conditions has been considered acceptable by an expert National Institutes of Health review panel in the United States and also by similar institutions in other countries.²⁸⁻³² However, there is some question as to the cost-effectiveness of such an intervention because of the varying rates of the CF gene's roughly 700 mutations across the broad range of racial groups and potential provider-training issues with regard to performing and interpreting test results.³³⁻³⁵ Furthermore, a patient's

carrier state and the effect it could have regarding the children he or she may have in the future may not be well remembered or understood by patients,³⁶ and such tests may cause significant psychological trauma.³⁷

Overall, CF is a common hereditary disease that warrants significant attention by the primary care practitioner. Much progress has been made in the treatment of patients with the disease. A focused effort by using multidisciplinary teams appears most effective. Primary care practitioners should integrate their efforts with these teams so that the maximum benefit associated with treating this disease can be obtained. Patients with CF have significant health barriers to overcome; however, with appropriate support, direction, and education, these patients can live substantive and extended lives that were impossible only several decades ago.

CASE STUDY

Initial Presentation

A 30-year-old woman with a history of chronic respiratory infections and gastrointestinal (GI) symptoms presents to a new primary care practice group for evaluation of a 4-month history of daily cough and mucus production. After a focused history and physical examination, the physician refers the patient to a CF care center for evaluation and follow-up.

QUESTIONS

- **What is the epidemiology of CF in adults?**
- **What are clinical features of CF?**

DISCUSSION

As increasing numbers of CF patients survive into adulthood, PCPs should expect to encounter adult CF patients in their practices. According to a recent Cystic Fibrosis Foundation (CFF) report, the number of CF patients 18 years of age and older increased 66% between 1987 and 1997.³⁸ Approximately one third of the 30,000 CF patients currently living in North America are over age 18, and it is estimated that a majority of the CF population will be adults by the year 2010.³⁹

Each year, 6% to 8% of the nearly 1000 new CF diagnoses occur in adults. In such patients, the organ system dysfunctions typical of CF (eg, pancreatic insufficiency, pulmonary disease) may be less severe or absent. Late diagnosis of CF may require testing beyond sweat chloride determinations to identify known mutations in the CF gene or actual measurements of in vivo function of the CF gene product (ie, nasal potential difference) (**Table 1**). When the diagnosis is made in infancy, it is most often suggested by acute or persistent respiratory

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Table 1. Criteria for the Diagnosis of Cystic Fibrosis

One or more characteristic phenotypic features, or a history of cystic fibrosis in a sibling, or a positive newborn screening test result

and

An increased sweat chloride concentration (≥ 60 mEq/L) by pilocarpine iontophoresis on 2 or more occasions, or identification of 2 cystic fibrosis mutations, or demonstration of abnormal nasal epithelial ion transport

Adapted with permission from Rosenstein BJ, Cutting GR: The diagnosis of cystic fibrosis: a consensus statement. *J Pediatr* 1998;132:594.

symptoms, failure to thrive or malnutrition, fatty or abnormal stools, or a combination of factors. Older patients typically come to medical attention because of infertility problems, digestive complaints, unexplained bronchiectasis, or frequent respiratory infections. **Table 2** lists the clinical features consistent with a diagnosis of CF.

QUESTION

- **What is a CF care center?**

DISCUSSION

A network of 115 CFF-accredited care centers supervise treatment and provide preventive management services for 91% of the estimated 23,000 patients who have been diagnosed and are receiving care in the United States. Partially funded by grants from the CFF, the centers adhere to standards of care established in the CFF's *Clinical Practice Guidelines for Cystic Fibrosis*.^{40,41}

Providing optimal care to the CF patient population requires specific expertise and protocols. For example, sputum samples processed in a CF center's microbiology laboratories allow for identification of pathogens and sensitivities specific to the CF patient community that might be overlooked in a routine microbiology laboratory, resulting in delays in initiation of antibiotic therapy, inappropriate treatment, and less effective management of a pulmonary exacerbation. CF care centers offer guidance to patients about therapies and scientific advancements, assist with recognition and prevention of CF complications, and provide age-appropriate CF education and counseling. Additionally, through ongoing research and participation in CF patient registries, the regional CF care centers contribute to the expanding base of knowledge about CF, its genetic basis, and the safety and efficacy of new life-extending therapies.

History

The patient, who gave birth to a full-term, healthy baby boy 4 months ago, developed a cough during the

Table 2. Clinical Features Consistent with a Cystic Fibrosis Diagnosis

Chronic sinopulmonary disease manifested by:

Persistent colonization/infection with typical cystic fibrosis pathogens

Chronic cough and sputum production

Persistent abnormalities on chest radiograph (eg, bronchiectasis, atelectasis, infiltrates, hyperinflation)

Airway obstruction manifested by wheezing and air trapping

Nasal polyps, radiographic or computed tomographic abnormalities of paranasal sinuses

Digital clubbing

Gastrointestinal and nutritional abnormalities, including:

Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse

Pancreatic: pancreatic insufficiency, recurrent pancreatitis

Hepatic: 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 deficiency

Salt loss syndromes (eg, acute salt depletion, chronic metabolic alkalosis)

Male urogenital abnormalities resulting in obstructive azoospermia

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

third trimester of pregnancy. Her pregnancy was complicated by gestational diabetes that was effectively managed with dietary modifications. She experienced no other significant problems and took prenatal vitamins routinely throughout her pregnancy.

While the patient was hospitalized for delivery of her baby, a chest radiograph showed hyperinflation with increased interstitial markings in the right upper lobe. A 14-day course of a cephalosporin was prescribed, and the patient was routinely discharged following the delivery. At a follow-up visit 3 months later, a second course of therapy with ciprofloxacin was prescribed for the unremitting infection, and breast feeding of her infant was prematurely terminated. Since completing the second course of antibiotics for her respiratory infection, the patient has been using over-the-counter remedies for her persistent cough. She reports that the cough disturbs her sleep and makes it difficult to hold a sustained conversation. The

patient denies shortness of breath but complains that her excessive mucus has become intolerable.

In addition to the cough and mucus, the patient complains of fatigue and persistent abdominal discomfort since parturition. She has difficulty with bloating, flatulence, and intermittent diarrhea and is frequently constipated and uncomfortable despite the use of laxatives and enemas.

The patient's medical records confirm a history of frequent, sporadic chest infections and complaints of constipation and/or diarrhea. She states that she "nearly always" had or was recuperating from bronchitis or a respiratory infection and that her GI problems (ie, excessive gas, foul-smelling stools) were a source of embarrassment to her as a child and adolescent. Approximately 4 years ago, the patient developed pneumonia (that may have been associated with flu) and required hospitalization. At the time, she had an 8 pack-year smoking history and smoked 1 pack of cigarettes daily. The patient recalled coughing up "a lot of thick green mucus and some blood" and reports that she stopped smoking immediately thereafter. Further information on the hospitalization was not included with her medical records; the CF physician makes a notation to request this information.

The patient and her husband of 1 year live with their son in Madison, Wisconsin. The patient currently works part-time at a new job in the public relations department of a national health food store chain.

Physical Examination

Physical examination reveals a height of 62 in and a weight of 130 lb. Temperature is 98.8°F, pulse is 96 bpm, blood pressure is 112/66 mm Hg, and respiratory rate is 24 breaths/min. On head and neck examination, the nasal mucosa and pharynx are normal, and the trachea is midline. No lymphadenopathy is noted. Chest examination reveals symmetrical expansion with no dullness. Auscultation reveals coarse crackles anteriorly over the right upper lobe; otherwise, the lungs are clear. Abdominal examination reveals slight distention; bowel sounds are present and normal, and palpation reveals no organomegaly or tenderness. Digital clubbing is present.

Diagnostic Testing

Results of studies are as follows:

Laboratory Studies

Leukocyte count: $6.7 \times 10^3/\text{mm}^3$
Hemoglobin: 14.3 g/dL
Hematocrit: 42%

Glycosylated hemoglobin: 5%
Random glucose: 90 mg/dL
Blood urea nitrogen: 10 mg/dL
Creatinine: 0.8 mg/dL
Albumin: 4.3 g/dL
Alkaline phosphatase: 90 U/L
Lactate dehydrogenase: 102 U/L
Cholesterol: 114 mg/dL
Aspartate aminotransferase: 20 U/L
Sputum: culture-positive for *Pseudomonas aeruginosa* sensitive to tobramycin, ceftazidime, ciprofloxacin, imipenem, ticarcillin, and mezlocillin
Urine: no growth
Sweat chloride: 96 mEq/L

Radiographic Studies

Chest radiography reveals normal cardiac and bony structures, hyperinflated lungs with generalized increase in lung markings, loss of volume in the right upper lobe with prominence of bronchial markings, and no acute infiltrates.

Pulmonary Function Studies

Forced vital capacity (FVC): 3.06 (85%)
Forced expiratory volume in 1 second (FEV_1): 2.04 (67%)
 FEV_1/FVC : 67%

Genotype

Heterozygous ΔF508 , unknown mutation

QUESTION

- **What are the pathophysiologic effects of CF?**

DISCUSSION

Pathophysiologic Effects of CF

In CF patients, absence or malfunction of the so-called CFTR results in defective chloride and water transport, leading to a lack of water in the external secretions of several organs (ie, lungs, liver, pancreas, small intestine, skin, and reproductive tract). CFTR may also play a role in infection. In the lung, normal CFTR is involved in clearing *P. aeruginosa*, whereas in the gut certain organisms may enter epithelial cells through CFTR. Alteration of ion concentrations appears to interfere with the function of naturally occurring antibiotic peptides in the lung. It is unclear how the absence or malfunction of CFTR produces the injuries that result in progressive pulmonary dysfunction with recurrent infection. In some organs (eg, pancreas, male genital tract), dysfunction may be the result of plugging by tenacious secretions.

Virtually all adult CF patients have elements of pulmonary disease, with colonization by *P. aeruginosa* being the most common. Pulmonary complications of CF—recurrent respiratory tract infection (pneumonia), pneumothorax, and hemoptysis—occur more frequently among adult patients and reflect pathologic changes in the airways and lung parenchyma resulting from repeated infection. It is noteworthy that CF pulmonary disease is progressive and the primary cause of mortality among CF patients.

Exocrine pancreatic insufficiency is common in CF and typically causes malabsorption and failure to thrive, which lead to the recognition of CF during childhood. It is now understood that pancreatic insufficiency can be acquired in CF patients (eg, as a result of recurrent pancreatitis leading to destruction of pancreatic tissue). Endocrine pancreatic insufficiency manifesting as diabetes mellitus also occurs in CF and is more common among adults.

Cells throughout the GI tract express CFTR. CF patients often have gallbladder disease and a range of GI problems including gastroesophageal reflux disease (GERD), constipation, and intestinal obstruction by mucofeculent material. CF-related liver disease can cause cirrhosis and portosystemic hypertension. In some instances, GI disorders may result directly from the abnormal CFTR function. In other cases, the problems may reflect inadequate therapy due to limitations of available treatments or poor patient adherence.

Organ Involvement in This Patient

This patient's clinical history is consistent with malabsorption due to pancreatic insufficiency and a heterozygous $\Delta F508$ genotype with unknown mutation. Although her lung disease is mild by pulmonary function criteria, CF pulmonary disease has been shown to have a less constant relation to genotype and appears to be modified by environmental factors and other genes.⁴² In addition, the patient demonstrates features that are common in adult CF patients: colonization by *P. aeruginosa*, abnormal mucus, recurrent respiratory tract infection, and GI symptoms.

QUESTION

- What are immediate management goals for this patient?

DISCUSSION

This patient's health problems stem from her inadequate knowledge of CF and the lack of a programmatic approach to CF management. Although her condition does not meet the criteria for a pulmonary exacerbation

Table 3. Criteria for Pulmonary Exacerbation in Cystic Fibrosis

Increased cough
Increased sputum production and/or change in appearance of expectorated sputum
Fever ($\geq 38^{\circ}\text{C}$ for at least 4 hours in a 24-hour period) on more than 1 occasion in the previous week
Weight loss ≥ 1 kg or 5% of body weight associated with anorexia and decreased dietary intake
School or work absenteeism due to illness in the previous week
Increased respiratory rate and/or work of breathing
New findings on chest examination (eg, rales, wheezing, crackles) or radiograph
Decreased exercise tolerance
Decrease in FEV ₁ of $\geq 10\%$ from previous baseline study within past 3 months
Decrease in hemoglobin saturation (as measured by oximetry) of $\geq 10\%$ from baseline value within past 3 months

Pulmonary exacerbations are identified by the presence of at least 3 of the 10 listed new findings or changes in clinical status when compared with the most recent baseline visit. If the patient has not been seen within the previous 3 months, baseline pulmonary status must be judged from the patient's own perception of well-being.

FEV₁ = forced expiratory volume in 1 second.

Adapted with permission from Cystic Fibrosis Foundation: *Clinical practice guidelines for cystic fibrosis*. Bethesda, MD: The Foundation, 1997.

tion of CF (**Table 3**), for which hospitalization and parenteral antibiotics would be warranted, her persistent respiratory and GI symptoms require an organized approach to CF management. In addition to being educated about CF, the patient should be started on a daily mucus clearance regimen, pancreatic enzyme replacement and vitamin supplementation, and a therapeutic regimen to reduce the frequency of pulmonary infections. Daily techniques can help to stabilize and maintain respiratory health in CF patients and reduce the rate of decline in pulmonary function. Declining lung function is directly correlated with increased hospitalizations and office visits (**Table 4**). Therapies that decrease exacerbations and improve nutritional status and pulmonary function would be expected to lead to decreases in health care resource utilization.

Mucus Clearance

Mechanical measures to clear abnormal mucus are important to virtually all patients with CF and should be a routine component of CF management. In the typical case, chest physiotherapy is initiated in infancy

Table 4. Clinical Characteristics of Cystic Fibrosis Stratified by Pulmonary Severity

FEV ₁ % Predicted* (N = 15,172) [†]	% of Total Patients	Patients Below 5% NCHS Weight (%)	Mean Office Visits	Mean Acute Exacerbations [‡]	Mean Hospital Stay (days)	% Total Patients Cultured Positive for		Death Rate, per 100 patients
						<i>P. aeruginosa</i>	<i>B. cepacia</i>	
Normal (≥ 90%)	30.5	9.3	4.0	0.3	7.5	47.5	1.5	0.1
Mild (70% to 89%)	26.6	15.2	4.6	0.6	8.5	64.4	3.0	0.2
Moderate (40% to 69%)	28.2	31.0	5.6	1.6	9.2	80.5	6.0	0.9
Severe (< 40%)	14.7	59.5	6.4	2.9	11.4	88.0	8.0	7.4
Total	100	24.4	5.0	1.1	9.4	67.5	4.2	1.4

B. cepacia = *Burkholderia cepacia*; FEV₁ = forced expiratory volume in 1 second; NCHS = National Center for Health Statistics; *P. aeruginosa* = *Pseudomonas aeruginosa*. Adapted with permission from Cystic Fibrosis Foundation: *Report of the 1997 patient registry*. Bethesda, MD: The Foundation, 1997.

*Knudson equation and the average FEV₁ of up to 4 pulmonary function tests were measured.

[†]Total number of patients includes only cystic fibrosis patients age 6 years or older whose pulmonary function tests were measured.

[‡]Acute exacerbations include total hospitalizations for respiratory tract infection and total home intravenous episodes.

or childhood as an adjunct to antibiotics in the treatment of infections. As a patient matures, alternate approaches to airway clearance are often introduced to accommodate the patient's need for independence or to avoid complications (eg, GERD). These approaches include special breathing techniques (eg, autogenic drainage, active cycle breathing) and the use of mechanically applied pressure devices (eg, Flutter valve). A recent meta-analysis suggests that several of these alternative approaches to mucus clearance may compare favorably with conventional chest physiotherapy.⁴³ Vigorous physical exercise also improves airway clearance and should be encouraged, both as an adjunct to mechanical mucus clearance techniques and as a means of promoting aerobic conditioning.

Treating Pancreatic Insufficiency

Pancreatic enzyme replacement. Over time, most CF patients require pancreatic enzyme replacement, which enables CF patients to digest fat, absorb critical nutrients from the diet, and be free of the bulky, malodorous stools that characterize pancreatic malabsorption. According to the CFF, 93% of patients seen at CF care centers in 1997 reported taking pancreatic enzyme supplements.³⁸ The CFF guidelines recommend a lipase dose of 1000 to 2500 U/kg body weight per meal, not to exceed 2500 U/kg body weight per meal; patients who are on higher doses should be closely monitored for colonic stricture.^{44,45}

Vitamin Supplementation

Adult CF patients should take fat-soluble vitamins (A, D, E, and K) to prevent secondary complications of pancreatic enzyme deficiency. Supplementation is important, because malabsorption of fat-soluble vitamins may be a problem even with pancreatic enzyme treatment. Specialized vitamin preparations are available for CF patients, although many centers advocate the use of a high-quality multivitamin preparation (2 tablets/daily).

Reducing the Frequency of Respiratory Tract Infections

Although regular, effective mucus clearance is an important first step in preventing respiratory tract infection, airway clearance alone will not interrupt the cycle of clinical infection once the lungs are colonized by *P. aeruginosa*. Patients with *P. aeruginosa* in their mucus are at risk for progressive decline in pulmonary function (at a rate of approximately 2% to 4% per year). Thus, a goal of CF-related research is to develop treatment strategies to reduce the potential for development of acute exacerbations and to help patients maintain pulmonary function.

Mucolytic Agents

Extracellular DNA that is released from degenerating neutrophils accumulates in the airways of CF patients and contributes to the viscosity of airway secretions. Dornase alfa, a purified recombinant human

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DNase that can digest extracellular DNA, has been shown to reduce the viscoelasticity of sputum from CF patients in vitro.⁴⁶ In a large randomized, double-blind, placebo-controlled study, CF patients with mild-to-moderate lung function (FVC > 40% predicted) who received a daily 2.5-mg dose of aerosolized dornase alfa demonstrated a mean increase in FEV₁ of 5.8% within 2 weeks, which was sustained through the duration of the 24-week study.⁴⁷ In addition, treated patients had fewer pulmonary exacerbations requiring intravenous antibiotics than untreated patients during the study period.

Antibiotics

Several antibiotic approaches have been explored in the maintenance therapy of CF lung disease. Among the most aggressive is that espoused by Danish CF physicians who treated patients colonized by *P. aeruginosa* with parenteral antibiotics at 3-month intervals.⁴⁸ Although these physicians assert that this treatment approach improves survival when compared with historical controls, the strategy has not been adopted outside of Scandinavia. Emergence of antibiotic-resistant *Pseudomonas* is a potential concern. Use of chronic oral antibiotics to suppress other CF-related pathogens, specifically *Staphylococcus aureus*, has been tried but discontinued as a result of demonstrated higher rates of pseudomonal infection.⁴⁹

The use of inhaled aminoglycosides is an increasingly attractive approach to suppression of pulmonary infection in CF and has been advanced by recent clinical trials. In studies of CF, inhaled aminoglycoside concentrations demonstrated in respiratory tract secretions after nebulization therapy exceeded those that can be safely achieved with parenteral administration.⁵⁰⁻⁵² Also, the concentrations of aminoglycosides achieved by inhalation are associated with a lower occurrence of renal toxicities and ototoxicities.⁵¹⁻⁵³

An aerosol form of tobramycin solution for inhalation was approved by the US Food and Drug Administration in 1997 and is increasingly used in maintenance regimens for CF patients. Based on the 1997 CFF patient registry, 28% of CF patients received some form of nebulized tobramycin in the preceding year. Two recent randomized, multicenter, double-blind, placebo-controlled trials demonstrated that chronic intermittent administration of aerosolized tobramycin in CF patients was well tolerated and associated with improved lung function, decreased density of *P. aeruginosa* in expectorated sputum, and decreased risk of hospitalization.^{52,53}

Bronchodilators

Anticholinergic and β_2 -agonist bronchodilators are used in CF patients as part of the therapeutic regimen. Bronchial reactivity can be demonstrated in virtually all CF patients at some time during the clinical course of their disease.⁵⁴ Although bronchodilators may enhance the effectiveness of mucus clearance and alleviate some symptoms, their benefits to maintenance therapy for CF are best determined by the response of individual CF patients.

Initiation of CF-Specific Therapy and CF Education

Two weeks later, the patient meets with members of the CF care team to review her test results and discuss a treatment regimen. In light of the favorable findings on lung function studies and chest radiography and the range of drug sensitivities determined by sputum culture, the adult CF specialist initially reassures the patient. However, the patient is cautioned that her persistent respiratory and GI symptoms are indicators that she would benefit greatly from a routine treatment regimen.

In recognition of the demands of the patient's recent marriage, new baby, and career change, the CF care team develops an immediate, short-term treatment regimen that is time-efficient and can be learned and implemented easily. The goals of therapy are to improve mucus clearance, treat the exocrine pancreatic insufficiency, and reduce the frequency of respiratory infections.

To give the patient a sense of control over decisions about her therapy, the team reviews strategies to help her accomplish effective daily mucus clearance. The patient chooses to learn autogenic drainage as her primary mucus clearance technique and indicates her willingness to purchase a Flutter device to use as her back-up method.

To ease the patient's symptoms, decrease her risk of pulmonary infections, and improve her lung function, the team recommends a trial of inhaled dornase alfa therapy. She meets with members of the home care staff who train her to self-administer the medication by nebulizer and to clean and maintain the device. Her pulmonary status will be monitored over the next several clinic visits to assess the effectiveness of this combined maintenance regimen.

Consultation with CF Nutritionist

The team nutritionist meets with the patient to review her dietary habits and to provide education about the physiologic mechanisms of pancreatic insufficiency and its potential effects on overall health status. The patient is told she needs to liberalize her intake of

dietary fats and to take pancreatic enzyme supplements.

The patient informs the nutritionist that she tries to eat only organically grown food and avoids fatty and processed foods. She also states that she does not like taking prescription medications, especially on a regular basis. The nutritionist counsels the patient about the benefits of enzyme supplementation and provides her with educational materials about the GI tract. In addition to expected effects, regular use of pancreatic enzyme supplements enhances absorption of calcium, thus potentially reducing the patient's risk of osteoporosis, and reduces the frequency of unpleasant and embarrassing GI symptoms. The patient agrees to a 3-month trial of enzyme supplements and works with the nutritionist to identify acceptable dietary sources of fat to support her unique nutritional needs.

Consultation with CF Nurse

Before departing the clinic, the patient meets with the CF nurse who provides practical suggestions for maintaining her new daily treatment regimen. The patient is informed that members of the CF team may telephone periodically to check on her progress. The signs and symptoms of respiratory exacerbation are reviewed to ensure that the patient understands when it may be important to contact the CF center. The nurse gives the patient a handbook on adult CF and suggests that she share it with her husband, because spouses often want to participate in clinic visits, learn about CF, and understand how they can contribute to care. Finally, the CF nurse reinforces that new mothers are often fatigued and that persistence of this symptom should not be interpreted as a failure of her CF treatment plan.

QUESTION

- **How should adult CF patients be monitored?**

DISCUSSION

Outpatient Monitoring in CF

The clinical practice guidelines developed by the CFF⁴⁰ recommend that all patients with a confirmed diagnosis of CF receive preventive and maintenance care on a regular outpatient basis to monitor for nutritional, GI, and pulmonary manifestations of CF and to provide patient education and case management. Each visit to a CF center should include a historical assessment, a CF-focused physical examination, a functional psychosocial assessment, laboratory and imaging procedures, and therapeutic interventions.

In the absence of published evidence regarding the optimal interval for monitoring CF patients, a consensus panel of the CFF⁴⁰ has recommended evaluation

every 3 months. The panel contends that the primary outcome measures of nutritional status (height and weight) and pulmonary status (pulmonary function testing) provide more reliable and useful data when monitored 4 times per year. Although this schedule is quite appropriate for the growing child with CF, the optimal frequency of adult CF patient exams may vary. For the stable patient with mild-to-moderate disease who adheres to an effective treatment regimen, 2 to 3 clinic visits per year may be adequate. Conversely, a severely ill CF patient awaiting lung transplantation may require monthly assessment. The number of annual clinic visits required for a CF patient is best determined by that patient's adult CF specialist and other CF team members, who have intimate knowledge of each patient's health status, disease severity, therapeutic adherence, and lifestyle.

A complete physical examination and routine monitoring should also be performed to detect any decline in percentage of ideal weight for height. At regular clinic visits, patients should be questioned regarding their diet, digestion, and stooling pattern, and physicians should be alert to signs and symptoms of GI problems (ie, GERD, obstructive bowel symptoms, constipation). Annual laboratory studies should include a complete blood count, liver function testing, and serum or plasma retinol and α -tocopherol. Physicians may choose to perform a stool guaiac and additional blood chemistries and diagnostic tests when physical evaluation merits further assessment. In addition, routine immunizations should be up to date, and an annual influenza immunization should be administered to CF patients, unless otherwise contraindicated.

Primary Care of Non-CF Problems

An important corollary of longer survival is the recognition of CF-related health problems and surveillance for non-CF health problems relevant to all adults as they grow older. These concerns are properly the domain of PCPs and include sexually transmitted diseases, drug and alcohol abuse, breast cancer screening in women, prostate cancer screening in men, colonoscopy, and risk reduction for coronary artery disease. Optimal health care management for adult CF patients relies on communication and coordination between the patient's PCP and CF specialists, especially for patients who are pregnant or have concomitant arthritis or diabetes mellitus.

QUESTION

- **What has this CF patient missed by not having specialized care until now?**

DISCUSSION

The case patient was fortunate to experience relatively mild disease and good health up to this time. However, her late diagnosis of CF and acceptance of routine health care over the years precluded her from benefiting from regular sputum cultures, mucus clearance, and pancreatic enzymes and vitamin supplementation. These techniques are important aspects of preventive health care, and their omission may have inadvertently increased the patient's risk for developing pulmonary exacerbations, chronic colonization by *P. aeruginosa*, or CF-related conditions (eg, distal ileal obstruction syndrome). The failure to diagnose and treat this patient's CF at an early age likely compromised her growth and skeletal development during childhood and puberty and perhaps increased her long-term risk for osteoporosis. In addition, this patient may have avoided years of emotional trauma related to recurrent diarrhea and foul-smelling stools.

Clinical Course Over the Next Year

During the 9 months following the patient's first clinic visit, the CF care team becomes satisfied with the patient's commitment to and proficiency in performing regular autogenic drainage. Her pulmonary function and her mucus secretions and cough improve. The patient reports exercising first thing in the morning, which appears to help loosen mucus and improve her energy level. On 2 occasions, the patient reports an increase in cough and mucus production and schedules an appointment at the CF center. When her sputum cultures are positive for *P. aeruginosa*, she is prescribed a 14-day course of ciprofloxacin. Fortunately, her pulmonary infections during the year are not severe enough to require hospitalization.

The patient initially is poorly consistent with her pancreatic enzyme replacement therapy and occasionally excludes fats from her diet rather than take the enzyme supplements. However, this practice produces persistent and familiar GI problems, and at one point she becomes so badly constipated that she comes to the emergency department for enema therapy. Eventually, she accepts the CF care team's advice and begins taking the supplements routinely with each meal. Her bowel habit regulates to approximately 2 to 3 times daily, and her pancreatic insufficiency appears to be well controlled by enzyme supplements and dietary modifications.

The patient's routine CF clinic visits throughout the year provide opportunities to discuss the incremental benefits of aerobic fitness and to reinforce the importance of diligent, aggressive mucus management techniques to optimize CF outcomes. The patient's husband

accompanies her on her third clinic visit, and the patient reports that he has begun assuming more responsibility for the baby and household chores. Consequently, she and her husband both have more free time to exercise, and she feels "less stressed and more healthy."

Second Annual CF Center Visit

Approximately 1 year after her first visit to the CF center, the patient schedules her routine annual examination. During the examination, she mentions that she has experienced an increase in thirst over the last several weeks but otherwise feels good. Her stooling patterns remain consistent at about 2 to 3 daily. She indicates that she routinely performs autogenic drainage, takes her dornase alfa, and regularly uses enzyme supplements.

Physical Examination

Physical examination reveals her weight to be 124 lb (a weight loss of 6 lb). Temperature is 98.6°F, pulse is 94 bpm, blood pressure is 110/70 mm Hg, and respiratory rate is 22 breaths/min. Bowel sounds are present and normal. Palpation reveals no organomegaly or tenderness.

Laboratory Studies

Chest radiography reveals normal cardiac and bony structures, hyperinflated lungs with generalized increase in lung markings, loss of volume in the right upper lobe with prominence of bronchial markings, and no acute infiltrates.

Her pulmonary function remains improved, and the patient's laboratory results are all within normal range, with the exception of an elevated random glucose level. A fasting blood glucose test is scheduled for the following morning.

The patient's fasting blood glucose level is 142 mg/dL, indicating that she has developed CF-related diabetes (CFRD).

QUESTION

- **What are diagnostic and management considerations in CFRD?**

DISCUSSION

Cystic Fibrosis–Related Diabetes

CFRD is caused by insulin deficiency and reflects changes in glucose metabolism that occur in CF, including undernutrition, chronic and acute infection, elevated energy expenditure, malabsorption, increased work of breathing, and glucagon deficiency. Because these factors are not static, glucose tolerance may vary

in CF patients. CFRD occurs with increasing frequency in the adult CF population,⁵⁵ but the prevalence may be underestimated in the United States and Europe. Although the oral glucose tolerance test (OGTT) is a commonly used marker for diabetes, Moran et al⁵⁶ found abnormal results in 43% of CF patients older than 30 years and in 26% of CF patients age 10 to 19 years. In addition, unpublished data from the CFF patient registry suggest that the mortality of patients with CFRD is 6 times greater than that of patients without this complication of CF and that patients with CFRD are more likely to be underweight and have severe CF pulmonary disease.³⁸

Diagnostic Criteria

Based on these and other findings, the CFF recently convened a consensus panel of experts in CF, diabetes, and nutrition to review the literature and develop recommendations on the diagnosis, screening, and management of CFRD.⁵⁷ As a result of that meeting, the following diagnostic criteria were proposed:

- 2-hour plasma level ≥ 200 mg/dL during a 75-g OGTT
- Fasting plasma glucose (FPG) ≥ 126 mg/dL on 2 or more occasions
- FPG ≥ 126 mg/dL plus casual glucose level ≥ 200 mg/day
- Casual glucose levels ≥ 200 mg/dL with symptoms of hyperglycemia on 2 or more occasions

In addition, CFRD should be identified as CFRD with fasting hyperglycemia (FPG ≥ 126 mg/dL) or CFRD without fasting hyperglycemia (FPG < 126 mg/dL), because of the American Diabetes Association recommendation that the terms type 1 diabetes and type 2 diabetes are inappropriate for the CF population.⁵⁵

Management Goals

Management goals for adults with CFRD include maintaining or achieving normal weight, controlling hyperglycemia (ie, maintaining near-normal blood glucose levels) and thereby reducing acute and chronic diabetic complications, and avoiding hypoglycemia.⁴⁰ Compared with patients with non-CF diabetes, patients with CFRD need not restrict their intake of calories, fat, protein, and salt.^{40,58} In addition, the patient with CFRD will likely need to learn “carbohydrate counting” to accurately account for the carbohydrate content of a dietary item within the carbohydrate allotment for a meal or snack.⁴⁰ Although CF patients who develop diabetes are insulin deficient,

there is little data to support the use of oral diabetes agents in CFRD.⁵⁷

Initiation of Treatment for CFRD

The CF team physician prescribes multiple daily injections of short-acting insulin and explains that the dosage must be calculated based on the carbohydrate content of the patient’s meals. The physician recommends beginning with a 4-times-daily injection schedule (before meals and at bedtime) and instructs the patient to monitor her glucose levels frequently throughout the day. They agree to reassess this plan in 3 months during her next clinic visit.

The CF nurse discusses insulin treatment and administration options, and the patient decides to begin with syringes. The nurse notes that an insulin pump may offer greater flexibility and better glycemic control, but the patient asks to revisit this option later. The patient is educated about the warning symptoms of hypoglycemia and the importance of appropriate treatment. She is also told how to recognize and treat vaginal candidiasis, which can be a problem for women with CFRD. After the nurse demonstrates how to calculate, draw up, and self-administer an insulin dose, she gives the patient a booklet about CFRD and directs her to the staff nutritionist.

The nutritionist explains the importance of dietary therapy to achieve glycemic control and notes the differences between managing CFRD and non-CF diabetes (eg, dietary fat intake should remain at approximately 40% and should not be limited, as is recommended for non-CF diabetics). The nutritionist reviews the patient’s current diet plan and discusses how to monitor carbohydrate intake. He notes that although she must account for her total carbohydrate intake, the type and source of carbohydrates and the amount consumed can vary. He explains how to incorporate alternative meal planning strategies to effectively manage her diabetes and to prevent acute and chronic complications of CF. Likewise, although the patient need not restrict her dietary sugar intake, she is advised to account for all the carbohydrates she consumes to determine how much insulin should be self-administered.

Follow-up Visit to Assess CFRD Management

The patient returns to the CF center 3 months later for follow-up assessment of her CFRD. Her random glucose level is within the targeted range, and the records of her daily monitoring indicate that she is achieving good control. The adult CF specialist recommends that she continue with her present regimen.

During the visit, the patient states that she and her husband are considering having another baby but that they are concerned about the potential impact of pregnancy on her diabetes and long-term health. The physician responds by reviewing some of the issues of pregnancy for women with CF.

QUESTION

- **What is known about the impact of pregnancy on women with CF?**

DISCUSSION

Pregnancy and CF

As the number of CF patients of reproductive age has increased, the annual number of pregnancies recorded in the CFF patient registry has steadily increased. Among female patients age 16 to 40 years who were seen at CF centers in 1997, 3.7% reported a pregnancy.³⁸ In light of these changing demographics, it is particularly important that care providers keep abreast of current understanding of the potential risks posed by pregnancy to the woman with CF and her fetus. Observation throughout the gestational period has shown that pregnancy can stress the pulmonary, cardiovascular, and nutritional status even in healthy non-CF women. In the absence of any underlying lung disease, increases in resting minute ventilation occur and may approach 150% of normal values in patients near term. Additionally, mild changes in pulmonary gas exchange occur and may be accompanied by declines in functional residual lung volume. Although such changes are of little or no concern in normal women, in CF patients with compromised pulmonary function such changes can negatively affect the health of both the mother and fetus. Before 1992, it was generally believed that pregnancy placed CF patients at an increased risk because many early studies suggested that general health appeared to deteriorate.^{59–62}

Although CF experts generally support CF patients who wish to conceive, they discourage women who have experienced significant decreases in pulmonary function (eg, hypoxemia, marked restrictive or obstructive disease) or nutritional status.⁶⁰ Canny et al⁶¹ also found that CF patients with mild lung dysfunction and the absence of underlying pancreatic insufficiency tolerate pregnancy with little effect on their pulmonary status. In a case-controlled study of pregnancy and CF, Frangolias et al⁶² concluded that pregnancy has little adverse effect on patients with stable CF but that poor outcomes can result in patients with advanced disease.

Ongoing data collection and analysis suggests that

the overall outcome for CF patients who become pregnant has improved. In a study by FitzSimmons et al,⁶³ data were evaluated in a nonconcurrent, prospective manner to assess the effects of pregnancy in women with CF. Each woman in the study was matched 1 year prior to the year of pregnancy with up to 4 controls (ie, age, FEV₁, weight percentile according to the National Center for Health Statistics). Data were collected to assess the impact of pregnancy on mortality, pulmonary function, and pulmonary complications. Additionally, the study evaluated whether poor nutritional status, poor pulmonary function, multiple pregnancies, and diabetes (CFRD) requiring insulin—as factors measured alone or in combination—independently increased the patient's risk. In women who delivered live births, the decline in FEV₁ at 2 years postdelivery was not significantly greater for pregnant CF women than for the controls with whom they were matched.^{63,64} At 3 years, the survival rates did not differ. General survival was lower for all women with CF who had poor nutritional status or poor pulmonary function. The researchers concluded that pregnancy is not an independent risk factor, either acutely or long-term. They postulated that outcomes may reflect improvements in patient care during pregnancy relating to more frequent monitoring and the patients' increased concern for their personal health.⁶⁴ Optimizing the patient's lung function, maintaining control of any CF-related complications (eg, diabetes), and working closely with the patient to normalize her body weight will maximize her chance for a healthy and successful pregnancy.

EPILOGUE

Although this patient's diagnosis of CF was not confirmed until after she was 30 years of age and had given birth to her first child, she has been fortunate to experience relatively mild disease and good health up to this time. The recent diagnosis of CFRD has necessitated the addition of in-home glucose monitoring and insulin therapy to her daily regimen, and it has placed an increased emphasis on the importance of nutritional management.

At the advice of her CF team, the patient acquires a home glucose meter with a memory and establishes a routine of measuring her glucose levels 3 times daily. She also begins taking a daily multivitamin plus calcium and starts a daily dietary log to facilitate a more complete assessment should adjustments be needed in the future. These new routines are added to her previous daily regimen of autogenic drainage, use of pancreatic enzyme supplements, and nebulized dornase alfa therapy.

At a follow-up visit after beginning treatment for CFRD, the patient reports that her energy level has increased, her cough is well controlled, and she is feeling well. Her baby and husband are both doing very well, and her public relations job is stimulating and enjoyable. She and her husband have decided to delay their decision regarding a second pregnancy for at least another year. During this period, the patient wants to work with the CF team to gain optimal control of her diabetes and to maintain her pulmonary function through aerobic training and cycling activities. HP

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