Cystic Fibrosis Adult Care: Consensus Conference Report

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James R. Yankaskas, MD;† Bruce C. Marshall, MD;† Beth Sufian, JD; Richard H. Simon, MD; and David Rodman, MD

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Abbreviations: ADA = Americans with Disabilities Act; BMD = bone mineral density; BMI = body mass index; CBAVD = congenital bilateral absence of the vas deferens; CF = cystic fibrosis; CFF = Cystic Fibrosis Foundation; CFRD = cystic fibrosis-related diabetes; CFTR = cystic fibrosis transmembrane conductance regulator; COBRA = Comprehensive Omnibus Budget Reconciliation Act; CPT = chest physiotherapy; DEXA = dual-energy x-ray absorptiometry; DIOS = distal intestinal obstruction syndrome; DM = diabetes mellitus; ERCP = endoscopic retrograde cholangiopancreatography; FBG = fasting blood glucose; GGT = gamma-glutamyl transferase; HPOA =hypertrophic pulmonary osteoarthropathy; IBW = ideal body weight; LFT = liver function test; OGTT = oral glucose tolerance test; 25-OHD = 25-hydroxyvitamin D; PD = potential difference; PEG = polyethylene glycol; PEP = positive expiratory pressure; PFT = pulmonary function test; SSDI = Social Security Disability Insurance; SSI = Social Security Income; TOBI = aerosolized tobramycin; UDCA = ursodeoxycholic acid

No achievement highlights the striking developments of the past few decades in cystic fibrosis (CF) care more clearly than the tremendous growth of the adult CF population. This demographic shift has created the need for adult-specific CF care programs and protocols. In June 1999, the Cystic Fibrosis Foundation (CFF) convened a consensus conference to discuss the state of adult CF care. This document summarizes the findings of that meeting and incorporates information gathered since the conference convened. The recommendations embodied herein are intended to serve as a template for US adult CF programs and a resource for those wishing to find information specific to adult CF care. In cases in which prior publications sufficiently treat the subject, references are provided. In cases in which insufficient evidence was available to reach consensus, the best consensus opinions are provided. This document is not intended to replace the *Clinical Practice Guidelines for Cystic Fibrosis*[1] but rather to act as an adult-specific complement.

*From the University of North Carolina (Dr. Yankaskas), Chapel Hill, NC; the Cystic Fibrosis Foundation (Dr. Marshall), Bethesda, MD; Sufian & Passamano (Ms. Sufian), Houston, TX; University of Michigan (Dr. Simon), Ann Arbor, MI; and University of Colorado (Dr. Rodman), Boulder, CO.
†Co-first authors.
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Correspondence to: James R. Yankaskas, MD, Pulmonary and Critical Care Medicine, 7011 Thurston Bowles Bldg, CB No. 7248, The University of North Carolina, Chapel Hill, NC 27599-7248; e-mail: pwsjry@med.unc.edu

Epidemiology and Survival

Of the 22,301 patients with CF in the 2000 *Cystic Fibrosis Foundation Patient Registry Annual Data Report*, 8,637 (38.7%) were ≥ 18 years of age.[2] This represents a dramatic increase in the number of adults over the past 3 decades, up from about 700 (10% of all CF patients) in 1970 (Fig 1).

These changes are attributable in large part to the significant improvement in survival over the past 30 years. The median predicted survival of only 16 years in 1970 is now up to approximately 32 years. For patients born in the 1990s, the median survival is predicted to be > 40 years.[3] The average age for all patients in the Cystic Fibrosis Foundation Registry is now > 16 years. Among adults with CF, 64% are between the ages of 18 and 29 years, 25% are between 30 and 39 years, 10% are between 40 and 49 years, and 2% are > 50 years of age.[2] The oldest living patient in the 2000 CFF Patient Registry was 78 years old.[2]

Data collection techniques and patient definition are two factors that lead some to speculate that there may be an additional 2,000 to 7,000 patients with CF in the United States who are not included in the CFF Patient Registry. Many of these patients are thought to be adults. Patients reported in the CFF Registry primarily fulfill the classic criteria for CF with both phenotypic manifestations and laboratory abnormalities consistent with CF transmembrane conductance regulator (CFTR) dysfunction (see "Diagnosis" section). If patients with CFTR dysfunction manifesting as pancreatitis,[4,5] chronic sinusitis,[6] or congenital bilateral absence of the vas deferens (CBAVD)[7–9] were included, the number of adults with CF would be considerably higher.

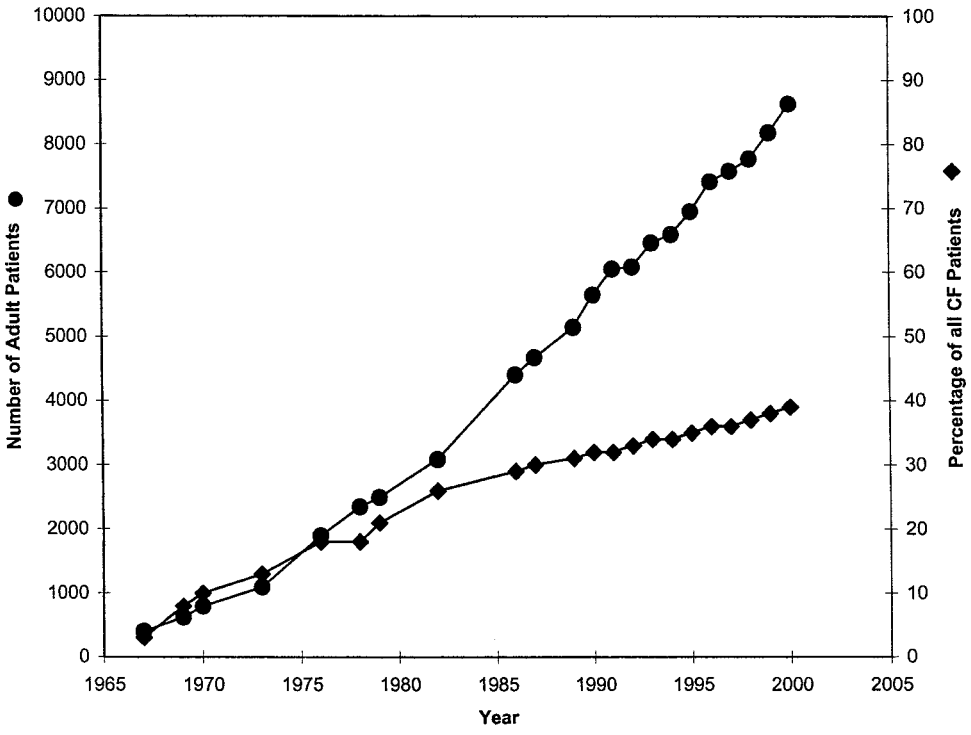

FIGURE 1. Adult CF patients, 1965 to 2000.

The growth of the adult CF population is predicted to continue in the foreseeable future. Even without further improvements in survival over the next 5 years, the number of adults with CF in the United States in the year 2005 will likely exceed 10,000 and represent > 40% of the total CF population.

Among adults with CF, 53.9% are men, and 46.1% are women.[2] This may reflect the reported survival advantage in men.[10] The ethnic breakdown is 93.7% white, 3.2% Hispanic, 2.7% African American, and 0.4% of other ethnicity. Nearly 90% of the adults have completed high school, and more than one quarter of them have completed college. About half of the adults with CF are working full-time or part-time, and one quarter are students. Approximately one third of adults with CF are married. There were 97 live births to women with CF in 2000, representing a significant increase in births to CF patients over the past decade.

The lung function of adults with CF is highly variable.[2] Using FEV_1 as a measure, about 36% of adult patients have normal or mild lung dysfunction (*ie*, FEV_1, > 70% of predicted), 39% have moderate dysfunction (*ie*, FEV_1, 40 to 69% of predicted), and the remainder have severe dysfunction (FEV_1 < 40% predicted). The mean FEV_1 percent predicted for all adults with CF is 60.8%. As a group, adults have more severe pulmonary disease than children and are at increased risk for serious complications (Table 1).

The health-care needs of adults with CF are considerable.[2] Each year, they make an average of 4.7 CF clinic visits, experience 1.5 acute exacerbations, and are admitted to the hospital 1.0 times. In response to the increasing numbers of adults with CF, the number of adult CF programs has grown from < 10 in 1992 to > 79 in 2002.

DIAGNOSIS

Although CF is usually discovered early in life (70% by the age of 1 year), the diagnosis is being

Table 1—*Complication Rates in Adults and Children

Complication	Adults, %	Children, %
P aeruginosa colonization	79	47
Ciprofloxacin resistance	22	4
Tobramycin resistance	15	6
B cepacia colonization	6	2
Massive hemoptysis†	1.8	0.1
Pneumothorax‡	1.4	0.2
On supplemental oxygen continuously	6	1
CFRD requiring insulin	16.2	2.5

*2000 CFF Registry data.
†Bleeding volume of > 240 mL in 24 h or requiring transfusion.
‡Requiring chest tube.

made in adults with increased frequency. Among 22,301 patients in the 2000 CFF Patient Registry, the diagnosis was established at or after the age of 18 in 831 (3.7%).[2] Patients diagnosed as adults usually present with chronic respiratory problems. As a group, they have milder lung disease, less pseudomonal infection, and are more likely to be pancreatic-sufficient than patients in whom CF is diagnosed at an earlier age.[2,11,12] Physicians unfamiliar with the spectrum of CF phenotypic manifestations may not consider a diagnosis of CF, thus delaying the diagnosis. Also contributing to a delay in diagnosis is the finding that some adult patients have normal or borderline sweat test results.[13–15]

Despite these differences, the criteria for establishing a CF diagnosis are the same for adults and children.[16] CF is usually suspected because of the presence of one or more typical CF phenotypic features (Table 2). The diagnosis is confirmed by the documentation of CFTR dysfunction. When performed by an experienced laboratory in accordance with National Committee for Clinical Laboratory Standards,[17] the quantitative pilocarpine iontophoresis sweat test remains the single most useful diagnostic test for CF in adults. It should be the initial test performed in a suspected case. Although there is a spectrum of sweat chloride levels ranging from normal (< 40 mM), to borderline (40 to 60 mM), to abnormal (> 60 mM) among patients in whom CF is diagnosed during adulthood, the sweat chloride concentration will be abnormal in $> 90\%$ of those diagnosed patients.[2] However, as noted, a normal sweat chloride value cannot be used as the sole criterion for ruling out the diagnosis of CF.

In patients suspected of having CF who have a normal or borderline sweat chloride value, CFTR mutation analysis should be performed. The sensitivity of such testing is limited because current commercial panels screen for only a minority of the $> 1{,}000$ identified CF mutations, and patients who receive diagnoses after the age of 18 years are more likely to carry infrequent or unidentified mutations.[2,11,12] Genotype analysis was performed for 673 of the 831 patients in the 2000 CFF Patient Registry who received diagnoses at or after 18 years of age. Of these patients, two of the common ΔF508 mutations were identified in 142 patients (21.1%), one ΔF508 mutation was identified in 348 patients (51.7%), and no ΔF508 mutations were identified in 183 patients (27.2%).[2] For patients suspected of having CF in whom a diagnosis cannot be made on the basis of the identification of two CFTR mutations, the measurement of nasal potential difference (PD) may be used to confirm the diagnosis.[16,18,19] However, this technique is not available at all medical centers. More comprehensive genotype analysis by DNA sequencing is available for patients with unusual clinical and/or CFTR function tests (*ie*, sweat chloride or nasal PD measurements) through the CFF-sponsored Mutation Analysis Resource Center at Johns Hopkins University (Baltimore, MD; Garry Cutting, MD, Director).

Adult patients also may come to medical attention with atypical presentations such as chronic/recurrent pancreatitis,[4,5] chronic sinusitis,[6] or CBAVD.[7–9] Men presenting with obstructive azoospermia secondary to CBAVD present a particularly challenging diagnostic problem. The majority have no other phenotypic features of CF, but 50 to 60% of those men carry one identified CF mutation, and 15 to 20% are compound heterozygotes. A diagnosis of CF should be assigned to such patients only if there is documentation of elevated sweat chloride values, two CF mutations, or an abnormal nasal PD measurement.[16] It is important to consider alternative diagnoses (*eg*,

Table 2—*Phenotypic Features Consistent With a Diagnosis of Cystic Fibrosis*

Chronic sinopulmonary disease manifested by:
Persistent colonization/infection with typical CF pathogens including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, mucoid and nonmucoid *P aeruginosa*, and *B cepacia*
Chronic cough and sputum production
Persistent chest radiograph abnormalities (*eg*, bronchiectasis, atelectasis, infiltrates, and hyperinflation)
Airway obstruction manifested by wheezing and air trapping
Nasal polyps, and radiograph or CT scan abnormalities of the paranasal sinuses
Digital clubbing
GI and nutritional abnormalities, including:
Intestinal: DIOS and rectal prolapse
Pancreatic: pancreatic insufficiency and 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, and complications secondary to fat-soluble vitamin deficiency
Salt loss syndromes: acute salt depletion and chronic metabolic alkalosis
Male urogenital abnormalities resulting in obstructive azoospermia

immunodeficiency, ciliary dyskinesia, and Young syndrome) in patients with atypical presentations.

People who receive diagnoses of CF as adults may be overwhelmed by the implications of a disease that leads to premature death for many children and young adults. It is important for the CF care team to educate such patients about the disease. In particular, they should be informed that patients who receive diagnoses in adulthood often have much better prognoses than patients who receive diagnoses during early childhood.

Standard Care

Overview

Data comparing the relative effectiveness of various approaches to adult CF care (*ie*, multidisciplinary vs subspecialty vs primary care-based) are lacking. However, based on the strong association between the establishment of comprehensive CF Care Centers and improved patient outcomes, the committee strongly recommends a multidisciplinary approach modeled on the highly successful pediatric CF care system. The health-care team should include at least a part-time commitment from a physician, nurse, respiratory therapist, dietitian, and social worker. Ideally, all members of the team should have specific training in adult CF care. Back-up personnel should be available in the event that a team member is unable to perform his or her duties. The pulmonary and GI/nutritional manifestations of the disease predominate in adults as in children, but several other issues also emerge.

Comprehensive Care

The primary objectives of the adult health-care team are to: (1) ensure optimum care; (2) facilitate access to pertinent medical resources; (3) coordinate care among specialists and primary care practitioners; and (4) support quality of life and independence for each patient. Frequent patient contact with the Center is necessary to accomplish these objectives. In general, quarterly visits are sufficient, although some patients with special needs or advanced disease may require more frequent attention. The Adult CF Care Team may function in a primary care capacity or in concert with an independent primary care practitioner. Coordination and communication with other medical professionals involved in the patient's care are essential.

The optimal management of CF requires input from all members of the health-care team. Evaluation and intervention by team members should be individualized to suit each patient's circumstances. However, a minimum of one comprehensive evaluation per year by each team member (*ie*, nurse, respiratory therapist, dietitian, and social worker) is recommended. These evaluations should encompass an assessment of adherence with therapies and the identification of relevant psychosocial issues as well as specific medical issues. When the center is serving in a primary care capacity, health maintenance (*eg*, vaccinations and cancer screening) should be provided according to national guidelines for age and gender. Ideally, the center should have a case management conference or other mechanism in place for a periodic review of the status of each patient and the formulation of a treatment plan. These assessments should be documented in the medical record and communicated with other health-care professionals involved in the care of the patient.

Pulmonary Disease

Assessment: The pulmonary status of patients should be regularly monitored by an assessment of symptoms, a physical examination, and, on most visits, spirometry. FEV_1, expressed as the percent predicted of a healthy nonsmoking reference population, is accepted as the single most useful objective measure of pulmonary status.[20] Oxygen saturation should be measured routinely in patients with moderate-to-severe pulmonary disease to assess the need for supplemental oxygen. The measurement of oxygen saturation during exercise and/or sleep may be indicated in some situations.

A complete microbiological assessment of expectorated sputum, including antibiotic susceptibility testing, should be performed at least on an annual basis, and preferably on a quarterly basis. Oropharyngeal swab cultures,[21,22] which are commonly obtained from children who do not produce sputum, have not been fully studied in adults. The microbiology laboratory should follow published guidelines[23] for the processing of CF sputum in order to isolate the wide range of organisms found in these specimens. Multiply-resistant Gram-negative organisms, such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*, are found in up to one third of adults with CF.[24] This has significant implications for disease management and infection control. The microbiology laboratory must be capable of distinguishing among these organisms and performing extended antimicrobial susceptibility panels if necessary. Antibiotic synergy testing may be helpful in some situations and is available at the CFF-sponsored reference laboratory at Columbia University for patients who have received follow-up at accredited CF care centers.[25] Confirmed or suspected *B cepacia* isolates should be sent to the

CFF-sponsored reference laboratory at the University of Michigan[26] for the confirmation of identity and further characterization.

The role of chest imaging in the monitoring of adults with CF has not been extensively studied. Standardized chest radiograph scoring may be useful in documenting the progression of disease or response to therapeutic intervention.[27,28] The committee did not support the use of annual surveillance chest radiographs but reached a consensus opinion that posterior/anterior and lateral chest films should be obtained every 2 to 4 years in patients with stable clinical status. Imaging also should be considered for patients with signs or symptoms consistent with a significant acute pulmonary exacerbation, pneumothorax, lobar atelectasis, or hemoptysis. Chest CT scans may be appropriate in certain clinical situations but cannot be recommended on a routine basis.

Additional diagnoses such as asthma, nontuberculous mycobacterial infection, allergic bronchopulmonary aspergillosis, sinus disease, and gastroesophageal reflux, should be considered in patients whose symptoms, clinical course, or response to treatment are atypical for CF.

Treatment: The cornerstones of treatment for those with CF are antibiotic therapy, airway clearance, and nutritional support; which are similar for children and adults. The reader is referred to several reviews[29–32] for a more detailed discussion of the specific components of a standard treatment regimen, which include antibiotic therapy for pulmonary exacerbations, and chronic suppressive therapy, airway clearance and exercise, therapy with mucolytic agents, bronchodilators, and anti-inflammatory agents, supplemental oxygen, and nutritional support. Because of the potential complexity, all aspects of the medical regimen should be reviewed on a regular basis with an assessment of adherence and potential side effects from medications.

Basic principles in the treatment of pulmonary exacerbations will be covered first, followed by a discussion of the various components of maintenance therapy for the treatment of pulmonary disease. Nutrition will be covered later in the article.

Pulmonary Exacerbations: Pulmonary exacerbations are common in adults with CF. The approach to treatment of an exacerbation described in *Clinical Practice Guidelines for Cystic Fibrosis*[1] of the CFF is applicable to the adult population. Specific antibiotics are selected on the basis of a recent sputum culture. *Pseudomonas aeruginosa* is by far the most common pathogen found in adults with CF. Therapy with fluoroquinolones is often used for mild-to-moderate exacerbations. Two antipseudomonal antibiotics are used in combination (*eg*, a β-lactam and an aminoglycoside) for the treatment of moderate-to-severe pulmonary exacerbations. Clinicians must be aware that for many antibiotics, differences in the volume of distribution and the rate of elimination in CF patients require higher doses and shorter dosing intervals.[33]

As noted above, adults are more likely to be infected with multidrug-resistant organisms such as *B cepacia*. Antibiotic combinations are typically used for the treatment of exacerbations related to these organisms. Some centers treat empirically and others use synergy testing to select a treatment regimen. Inhaled antibiotics are at times used in combination with parenteral agents. The optimal approach has not been validated in clinical trials. In order to prevent person-to-person spread of these organisms,[34] the center must have rigorous infection control practices in place in the outpatient clinics and the inpatient units.

Chronic Suppressive Antibiotic Therapy: Chronic suppressive antibiotic therapy often is employed because the treatment of pulmonary exacerbations will not eradicate the lung infection. Aerosolized tobramycin (TOBI) has been the most thoroughly studied chronic suppressive therapy. In two large, multicenter, double-blind, placebo-controlled trials conducted over a 24-week period, treatment with TOBI was found to produce significant improvement in pulmonary function, to decrease the density of *P aeruginosa* in sputum, and to decrease the number of days that subjects were hospitalized.[35] These studies included patients with moderate-to-severe pulmonary disease, which was defined as an FEV_1 between 25% and 75% of predicted. Subset analyses demonstrated that adolescents had the greatest response, although all age groups and disease severity categories showed significant improvement from the therapy. A 24-month open-label follow-up[36] of these trials demonstrated sustained improvement in FEV_1 compared to the group that had initially received placebo.

A significant long-term concern in using chronic suppressive therapy of any type is the emergence of antimicrobial resistance. The TOBI trials showed no increase in the prevalence of *B cepacia* or other resistant organisms in the TOBI-treated group. There was a modest but detectable shift in the minimum inhibitory concentrations of the *P aeruginosa* strains infecting the TOBI-treated subjects. The sustained improvement in pulmonary function appears to outweigh the risk of tobramycin resistance that may develop over time, but this must be carefully considered for each individual.

Who should be considered for this therapy? Any

adult patient chronically infected with *P aeruginosa* is a potential candidate. Certainly, any patient who falls within the patient selection criteria for the phase III clinical trial[35] (*ie*, those with FEV_1 between 25% and 75% of predicted) deserves serious consideration for inclusion in a therapeutic trial of this drug. More severely affected patients also may benefit, but they should be carefully monitored during the initiation of therapy. The more difficult issue is the case of the mildly affected patient with an FEV_1 of $> 75\%$ predicted. Interventions at this point in the disease course may have a profound impact on the subsequent course of disease. The current trend is toward more aggressive therapy and earlier intervention. TOBI should be considered for this mildly affected group, particularly for those in whom the pulmonary disease is more active. Indications of more active disease may include increased symptoms, declining pulmonary function, or increased frequency of pulmonary exacerbations. An ongoing clinical trial of TOBI in this mildly affected patient population hopefully will shed additional light on this issue.

One caveat with this therapy relates to the delivery of the antibiotic to the airways. Particle size is critical to antibiotic deposition. Too small a particle will tend to deposit in the distal air spaces and alveoli where significant systemic absorption may occur. Too large a particle will tend to deposit in the central airways. TOBI should be administered with the nebulizer systems that were validated in the clinical trials.[35]

The data presented above specifically refer to the TOBI preparation of tobramycin. A number of smaller, less rigorous clinical trials of other formulations of tobramycin and gentamicin using a variety of dosing regimens ranging from 80 to 600 mg, two to three times a day have been reported.[37–42] Because of methodological concerns with these trials, the efficacy and safety of preparations other than TOBI have not been established.

Inhaled colistin (Coly-Mycin; Monarch Pharmaceuticals; Bristol, TN) has been reported to be of benefit in case series and uncontrolled clinical trials.[43,44] The rarity of antimicrobial resistance has been touted as an advantage with this drug; however, the transmission of colistin-resistant *P aeruginosa* recently has been reported.[45] Bioavailability from the aerosolized route of administration has not been studied adequately. Safety is also a concern due to the fact that bronchospasm occurs in a substantial proportion of patients after the nebulization of this medication.[45,46] In a recent short-term comparison trial[47] in the United Kingdom, pulmonary function improved in the TOBI-treated group, but there was no significant change in the colistin group. Thus, the efficacy and safety of aerosolized colistin has not been established.

Scheduled parenteral antipseudomonal therapy is an alternative suppressive strategy that has been popular in Denmark. Retrospective and uncontrolled reports have suggested improved survival in patients treated with 2-week courses of therapy, four times per year irrespective of symptoms.[48] However, a randomized trial[49] comparing suppressive IV antibiotic therapy administered four times per year vs standard treatment for symptoms of an exacerbation showed no difference in outcomes between the two groups. This approach cannot be recommended at this time.

There are few data and no convincing evidence to support the use of chronic oral antibiotic therapy in the adult CF population. However, therapy with macrolide antibiotics have garnered attention based on their effectiveness in the treatment of diffuse panbronchiolitis.[50] Promising preliminary observations suggested a clinical benefit in CF[51–53] and led to several randomized, controlled clinical trials. A double-blind, placebo-controlled azithromycin trial in the United Kingdom[54] included 41 children, 20 of whom did not have persistent *P aeruginosa* infection. The crossover study design included two 6-month treatment phases and an intervening 2-month washout period. The median relative improvement in FEV_1 in the azithromycin phase was 5.4%. Oral antibiotic use was reduced, but the number of pulmonary exacerbations and courses of IV antibiotics did not differ in the azithromycin and placebo phases. A 3-month randomized, placebo-controlled, double-blind trial of azithromycin enrolled 60 stable adults in Australia who were chronically infected with *P aeruginosa*.[55] By chance, the treatment assignments resulted in significant differences between the azithromycin and placebo groups. At baseline, the placebo group contained more men, and on average the patients were taller, heavier, and had better lung function than those in the azithromycin group, requiring adjustments in their statistical analyses. Nevertheless, the azithromycin group had a 3.6% relative improvement in FEV_1, had undergone fewer courses of IV antibiotic therapy, and had fewer hospital days. A 24-week, multicenter, randomized, placebo-controlled, double-blind trial of azithromycin[56] in the United States enrolled 185 patients who were ≥ 6 years of age and were chronically infected with *P aeruginosa.* The azithromycin group experienced a 6.2% treatment benefit in relative FEV_1 percent predicted change from baseline, decreased pulmonary exacerbations, decreased hospitalizations, and a 0.7-kg weight gain compared to the placebo group. The drug was well tolerated in all

three trials. In summary, despite differences in patient populations, study design, and treatment regimens, all three trials demonstrated clinical improvement with azithromycin therapy. The mechanism of action remains to be elucidated. Based on this evidence, we believe that azithromycin should be considered for CF patients who are ≥ 6 years of age who are chronically infected with *P aeruginosa.* The US trial regimen was 500 mg thrice weekly for patients weighing ≥ 40 kg, and 250 mg thrice weekly for patients weighing 25 to 40 kg. A sputum smear and culture for acid-fast bacilli should be obtained prior to initiating chronic macrolide therapy because of the slight risk of having an undiagnosed nontuberculous mycobacterial infection developing macrolide resistance. For patients receiving chronic macrolide therapy, a smear and culture for acid-fast bacilli should be obtained every 6 months.

AIRWAY CLEARANCE AND EXERCISE: There are a variety of airway clearance techniques available. Conventional chest physiotherapy (CPT) is the technique of percussion and postural drainage. Despite the absence of randomized, controlled clinical trials, the available evidence and clinical experience supporting conventional CPT appears to be convincing.[57,58] Potential problems with this modality include hypoxia, particularly in patients with severe lung disease,[59] and gastroesophageal reflux.[60] Furthermore, CPT is physically demanding and time-consuming for both the patient and his or her support person(s). Poor adherence is common.[61]

As patients become older and more independent, they frequently seek airway clearance methods that can be performed without assistance. Several alternative modalities have been developed, including active cycle breathing, forced expiratory technique, positive expiratory pressure (PEP) devices, autogenic drainage, and high-frequency chest wall oscillation systems (*ie*, The Vest, formerly called ThAIRapy Vest [Advanced Respiratory; St. Paul, MN]; the Flutter device [Axcan Scandipharm; Birmingham, AL]; and the intrapulmonary percussive device). A detailed description of each of these methods can be found in a review.[62] Meta-analysis suggests that CPT resulted in greater sputum production than no treatment, and that the addition of exercise improved FEV_1. No other differences between modalities were found.[63]

Expiratory resistance or PEP devices may promote mucus clearance by preventing airway closure and increasing collateral ventilation. They are used via a mask or a mouthpiece and can be adapted for the concomitant delivery of bronchodilators. These devices have been extensively studied in Europe, with most trials demonstrating equivalence to conventional CPT.[64] A long-term (*ie*, 1 year) trial showed that PEP therapy was superior to conventional CPT with respect to maintaining pulmonary function.[65] A report[66] demonstrated that PEP was also more effective than the Flutter device in maintaining pulmonary function over the course of a 1-year trial. The devices are relatively inexpensive, portable, and well-tolerated, although some patients find them fatiguing. Theoretical concern that they might increase the risk of pneumothorax has not been borne out in practice.

The Vest is a chest wall compression and oscillation system composed of a fitted vest coupled to a pneumatic compressor. Therapy is delivered to the entire chest at the same time with the patient in a seated position. This allows the administration of nebulized medications during the therapy session, minimizing the patient's time commitment; but the major advantage over conventional CPT is the degree of independence afforded to the patient. A prospective study[67] demonstrated that use of The Vest is equivalent to conventional CPT in patients hospitalized for a pulmonary exacerbation. The major disadvantages with this system are the expense and lack of portability. Some severely affected patients complain that it is harder to breathe during the treatment. Others, particularly those with indwelling venous access devices (*eg*, the Port-a-Cath; Deltec, Inc; St. Paul, MN), may find The Vest uncomfortable.

Additional clinical trials are needed to define the optimal airway clearance regimens. To provide meaningful results, such studies must involve an adequate number of patients observed over a time frame of at least several months. Sputum production has been the primary outcome variable in many of the published trials to date, but it may prove to be an unreliable marker of efficacy. The preservation of pulmonary function provides more convincing evidence of efficacy.

Physical activity augments airway clearance[68–70] and should be viewed as an important adjunct to the airway clearance techniques described above. A randomized clinical trial[71] demonstrated that regular aerobic exercise attenuates the decline in pulmonary function over a 3-year period compared to a control group. In addition, appropriate vigorous physical exercise enhances cardiovascular fitness, increases functional capacity, and improves quality of life. The level of physical fitness, as measured by maximal oxygen uptake, correlates with survival in CF.[72] For these reasons, with the exception of those patients whose clinical condition prevents it, all adults with CF should be encouraged to exercise.

Ideally, patients should learn exercise techniques under the supervision of a qualified physical therapist. In patients with moderate-to-severe pulmonary disease, it is important to ensure adequate oxygenation during exercise.[73] Aerobic activities, such as swimming, jogging, and cycling, are the most commonly recommended forms of exercise. Patients should be encouraged to exercise several times per week. Pulmonary rehabilitation regimens previously targeted for adults with emphysema and chronic bronchitis will likely prove to be effective in the CF population.

The health-care team must assist the patient and family in tailoring an airway clearance regimen that provides the best fit to the patient's lifestyle and activities. Typically, this consists of conventional CPT and/or a suitable alternative airway clearance technique, combined with an aerobic exercise program. The frequency and duration of each treatment should be individualized. Patients with minimal-to-mild symptoms may only require one session a day, whereas others with a greater volume of thick secretions may need three or more sessions per day. Developing an individualized regimen that is acceptable to the patient and the physician is a trial-and-error process that requires staff who are well-versed in airway clearance techniques and exercise physiology. Care providers must consistently encourage and monitor adherence, a major issue with this aspect of care, and modify the regimen as necessary.

MUCOLYTIC AGENTS: Recombinant human DNase (also known as α-dornase or Pulmozyme; Genentech; South San Francisco, CA) decreases the viscosity of CF sputum by catalyzing extracellular DNA into smaller fragments.[74] A large phase III randomized, double-blind, placebo-controlled trial showed a modest improvement in pulmonary function in the DNase-treated groups (5.8% and 5.6% relative improvement in FEV_1 from baseline, respectively, in the groups treated once and twice a day compared to the placebo group), decreased pulmonary exacerbation rate (28% and 37% reductions, respectively, in the age-adjusted risk of pulmonary exacerbations in patients treated once and twice a day compared to the placebo group), and some improvement in CF-related symptoms.[75] The decrease in respiratory tract infections resulted in fewer days in the hospital and fewer days receiving parenteral antibiotics for the DNase-treated groups.

It is not clear whether the differences in pulmonary function and respiratory tract infection rate observed in this clinical study will impact mortality. The majority of participants in the phase III trial continued receiving DNase for up to 2 years in an open-label extension of the study. Age-adjusted and height-adjusted pulmonary function at the 2-year point was declining at the same rate as in the placebo-treated group during the randomized portion of the trial.[76] This would suggest that DNase had perhaps delayed but not prevented progression of the disease. However, it should be kept in mind that this trial consisted of a patient population that was not representative of the CF population as a whole. Specifically, this was an older group of patients with more significant obstructive airways disease. Another randomized trial[77] in even more severely affected patients with FVC values of $< 40\%$ also showed improvement in FEV_1 from baseline (DNase-treated group, 9.4%; control group, 2.1%) over the 12-week study period.

More recently, the results of the Pulmozyme Early Intervention Trial have been published.[78] This phase III, double-blind, placebo-controlled trial in children with mild disease showed modest improvement in pulmonary function and a reduction in pulmonary exacerbations over a 2-year period. The long-term impact of treating a mildly affected population of patients is not known at present.

Postmarketing clinical experience has confirmed the relative safety of DNase. Hoarseness, voice alteration, and pharyngitis are the major adverse events related to DNase, and, in most cases, these symptoms are self-limited and do not require the cessation of drug therapy.[75] In addition, concerns that DNase might release neutrophil elastase bound to DNA and thereby exacerbate the inflammatory state have been resolved. Shah et al[79] found a decline in neutrophil elastase activity and interleukin-8 levels in the sputum of CF patients treated with DNase over a 6-month time period.

Should DNase be prescribed to all CF patients? Patients with chronic productive cough, particularly those with moderate-to-severe obstructive airways disease, should be considered for a therapeutic trial of once-per-day DNase for a period of several months. The drug can be started safely during an acute pulmonary exacerbation[80] as well as during a stable period. Patients should be monitored by symptoms, pulmonary function tests (PFTs), and pattern of exacerbations. Unfortunately, there are no clear-cut criteria to judge clinical response. In the phase III trial, subjects who did not show an improvement in spirometry still had a reduction in pulmonary exacerbation rate.[75] Often the patient's subjective response to the drug is a major factor in the decision to continue therapy for the long term. This is certainly reasonable; however, patients should be encouraged to give the drug a fair trial of at least several months. Some severely affected patients

seem to benefit symptomatically from a twice-a-day regimen.

Mildly affected patients also should be made aware of this drug and its potential benefits. The relatively high cost of DNase may factor into a decision about whether to prescribe this therapy for a mildly affected adult, but a therapeutic trial in an individual patient is justifiable and should be considered with currently available information.

There are no well-validated alternative mucolytic agents available at this time. N-acetylcysteine reduces viscosity of sputum *in vitro*, presumably by breaking disulfide bonds. The nebulized form of the drug has been used in CF patients but has not been carefully studied. Trials[81,82] in patients with COPD have not demonstrated a significant beneficial effect. Furthermore, the drug can be very irritating to the upper airway and can cause bronchoconstriction.[83] Some European studies have suggested a modest benefit from oral N-acetylcysteine, particularly in patients with moderate-to-severe disease,[84] but others have not confirmed these findings.[85] It is not even clear that adequate amounts of orally administered drug penetrate into the airways to have a mucolytic effect.[86] For these reasons, the efficacy and safety of N-acetylcysteine has not been established.

There has been renewed interest in the use of nebulized hypertonic saline solution to facilitate airway clearance. It improves mucociliary clearance,[87] likely by its effects on sputum viscoelasticity.[88,89] A short-term (*ie*, 2-week) clinical trial[90] demonstrated that nebulization of a 6% saline solution twice a day resulted in an improvement in PFTs compared to a control group that nebulized an isotonic saline solution (15.0% vs 2.8% improvement, respectively, in FEV_1 from baseline; $p = 0.004$). Hypertonic saline solution has the potential to cause bronchospasm in patients with CF,[91] but this may be preventable by pretreatment with a bronchodilator. The preliminary data are promising, but it is premature to recommend the widespread use of hypertonic saline solution at this time.

BRONCHODILATORS: The majority of patients with CF demonstrate bronchial hyperreactivity at least some of the time.[92] Bronchodilators have therefore become a standard component of the therapeutic regimen. Nebulized β-adrenergic agonists are the most commonly prescribed agents. They are often used to provide symptomatic relief and, prior to CPT, to facilitate clearance of the airways. Konig and colleagues[93] reported that maintenance albuterol treatment reverses the progressive downhill course in lung function in CF patients. A longer term, placebo-controlled, double-blind study[94] also showed sustained improvement in PFT scores in a group of patients treated with albuterol, but the difference from the control group was not statistically significant, likely because of an insufficient number of study subjects.

These agents are, in general, well-tolerated in the CF population. Most patients demonstrate improved pulmonary function with bronchodilators,[95,96] but the occasional patient may actually worsen with bronchodilator therapy.[97] Airflow may decrease paradoxically, or hyperinflation may worsen because of smooth muscle relaxation and decreased airway elasticity. Periodic pulmonary function testing and careful attention to symptoms will identify those few patients in whom bronchodilator therapy is counterproductive.

In summary, the potential benefits of inhaled β-agonist agents outweigh the risks. They should be considered for all adults with CF. Long-acting aerosolized β-adrenergic agonists also may have a role in this disease. Salmeterol has been associated with better preservation of pulmonary function and oxygenation through the night.[98,99] In addition, a 24-week randomized, double-blind, placebo-controlled crossover study[100] involving 23 patients with mild-to-moderate pulmonary disease showed that high-dose salmeterol (100 μg/d) was equally safe, and was associated with better pulmonary function, fewer antibiotic interventions, and fewer respiratory symptoms compared to twice daily therapy with nebulized albuterol. Oral preparations have no advantage over the inhaled medications in reversing bronchospasm,[101] so they are not commonly used.

Anticholinergic bronchodilators may be helpful for some patients with CF. Atropine has been associated with unacceptable systemic side effects, but ipratropium bromide is very poorly absorbed and much better tolerated. It has been shown to have some benefit in asthma[102] and may be of use in CF patients as well. Weintraub and Eschenbacher[103] observed that ipratropium may be more effective than β-adrenergic agonists in adults with CF. Adults may have less bronchospasm but more secretions than children. The airway of the adult CF patient may more closely mimic that of the adult with chronic bronchitis, and therefore may be more responsive to the effects of a parasympathomimetic agent. Some patients appear to benefit from combination therapy with a β-adrenergic agonist and an anticholinergic agent.[104] A therapeutic trial of combination therapy is indicated for patients with bronchospasm that is not well-controlled by β-agonist therapy alone.

Theophylline increases mucociliary clearance, diaphragmatic contractility, and CNS respiratory drive.[105] Unfortunately, it has a narrow therapeutic range that requires the monitoring of plasma concentrations. In

addition, a variety of adverse effects occur with this drug, including nausea, vomiting, and gastroesophageal reflux, which limits its utility in patients with CF.

ANTI-INFLAMMATORY THERAPIES: Some patients with CF have asthma or asthma-like symptoms that require more than therapy with bronchodilators alone. The full asthma armamentarium can be used to treat their bronchospasm. Inhaled or oral glucocorticoids seem to be generally more efficacious than cromolyn or nedocromil, but both classes of drugs are widely used in the treatment of CF patients. Other patients with CF require glucocorticoids for the treatment of allergic bronchopulmonary aspergillosis. We will not focus on these issues but rather will address the role of anti-inflammatory agents for the nonasthmatic patient with CF with chronic airways infection and inflammation.

Short-term therapy (3 weeks) with daily corticosteroids in stable patients with severe obstruction showed no benefit.[106] A population with less severe disease treated with 2 weeks of daily therapy with corticosteroids (2 mg/kg/d), followed by alternate-day steroid therapy for an additional 10 weeks (1 mg/kg every other day), showed improvement in pulmonary function, and a decrease in serum cytokine and IgG levels.[107] A longer study[108] (4 years) of therapy with alternate-day steroids (2 mg/kg every other day) also suggested a benefit from steroids with respect to pulmonary and nutritional parameters. This promising result led to a larger multicenter randomized trial comparing alternate-day therapy with prednisone at 2 mg/kg and 1 mg/kg to placebo. This trial enrolled only children and adolescents with CF, but the results are of interest to adult care providers. The higher dose group was discontinued because of an unexpectedly high incidence of cataracts, glucose intolerance, and growth retardation.[109] The 1 mg/kg and placebo groups continued to the end of the 4-year trial. The steroid-treated group showed benefit with respect to pulmonary function, particularly the subset of patients colonized with *P aeruginosa*.[110] However, that benefit was at the expense of growth. A subsequent analysis[111] showed that steroid-treated men had persistent growth impairment after steroid therapy was discontinued, as indicated by reduced adult height in comparison with the placebo group. Bone density was not an end point in this trial but is another significant concern with this therapy. In summary, the data suggest that corticosteroids may have a beneficial effect but at significant cost. For this reason, long-term oral corticosteroid therapy, even in an alternate-day regimen, probably should be avoided if possible. These studies do, however, suggest that an anti-inflammatory approach has promise.

Therapy with inhaled steroids is a potential way to reduce inflammation without significant systemic adverse effects. Relatively low doses of inhaled beclomethasone (400 μg/d) showed no effect on various markers of airways inflammation.[112] Higher doses of inhaled steroids have shown some promise in preliminary studies,[113,114] but larger trials with longer term data are needed before this therapy can be recommended.

High-dose ibuprofen therapy (20 to 30 mg/kg, up to 1600 mg, bid) slowed the progression of pulmonary disease in mildly affected patients (*ie*, $FEV_1 > 60\%$ of predicted), particularly in children 5 to 12 years of age.[115] It is important to emphasize that a pharmacokinetic study should be done to verify that therapeutic blood levels of the drug have been achieved. Close monitoring for adverse events is also important, including a semiannual check on renal function. The potential risks of ibuprofen (GI and renal) should be carefully weighed in deciding whether to treat mildly affected adults. There are no data to support this therapy in patients with moderate-to-severe obstructive airways disease (*ie*, $FEV_1 < 60\%$ of predicted). Because of concern about an increased risk of hemoptysis, high-dose ibuprofen therapy should be avoided in this subset of patients.

The use of leukotriene modifiers in the CF population deserves careful study. These drugs have some attractive features, but, given the scarcity of data in CF patients, they cannot be recommended at this time.

OXYGEN: Clinically apparent cor pulmonale is a poor prognostic indicator.[116] The goals should be to prevent the development and/or progression of pulmonary hypertension. Data from Toronto[117] demonstrate that subclinical pulmonary hypertension develops in a significant proportion of patients with CF and is strongly correlated with hypoxemia, independent of pulmonary function. Furthermore, subclinical pulmonary hypertension appeared to be associated with increased mortality compared to a group with a similar degree of spirometric impairment without pulmonary hypertension.

The most important therapy for the prevention of pulmonary hypertension is supplemental oxygen, but there are limited data available on its use in treating CF. Zinman et al[118] were unable to demonstrate a beneficial effect of nocturnal oxygen therapy in patients with CF. However, there were several weaknesses in this study. A relatively small number of patients were enrolled, and some of them did not meet the usual criteria for receiving supplemental oxygen therapy. In addition, oxygen was used only at night for an average of 7.0 ± 1.9 h. In the absence of persuasive data in CF patients, we must turn to the

literature on oxygen administration in COPD patients.

Supplemental oxygen has been shown to improve exercise tolerance and survival in COPD patients. The Nocturnal Oxygen Therapy Trial Group[119] and the Medical Research Council Working Party[120] both demonstrated that oxygen administration improved survival in severely affected, hypoxic COPD patients. The criteria for supplemental oxygen therapy in these studies (*ie*, $Pa_{O_2} < 55$ mm Hg during the daytime while breathing room air or < 59 mm Hg in the presence of pedal edema, polycythemia, or ECG evidence of impairment of the right side of the heart) have been widely adopted by the medical community. Continuous oxygen therapy is indicated for such patients.

Patients are more likely initially to develop hypoxemia with exercise or during sleep.[121–123] Clinicians must be aware of this and must intermittently screen patients with moderate-to-severe pulmonary disease accordingly. Oxygen is indicated during exercise if the exercise oxygen saturation level falls below 88 to 90%. Nocturnal oxygen therapy is indicated if oxygen saturation is $< 88\%$ to 90% for $\geq 10\%$ of the total sleep time.

Complications: In general, adults with CF have more severe pulmonary disease than children. This puts them at higher risk for serious complications such as pneumothorax and massive hemoptysis (Table 1). The adult care team must have expertise in dealing with these medical emergencies in a timely and proficient fashion. The CFF consensus statement on pulmonary complications[124] details an approach to these problems.

The majority of CF patients die in adulthood of respiratory failure. The health-care team must be prepared to deal with the complex medical and psychosocial end-of-life issues (see "End-of-Life Options" section). The issue of advanced care directives should be addressed in the clinic with all patients, particularly in severely affected patients, when their conditions are stable. An individual patient's decisions about end-of-life issues and lung transplantation may impact the health-care team's treatment approach, including decisions about ICU admission, ventilatory support, and management of pneumothorax.

Exocrine Pancreas

Diagnosis of Pancreatic Insufficiency: Eighty-five to 90% of patients with CF have exocrine pancreatic insufficiency, which is defined as elevated fecal fat excretion.[125] The majority of adults with CF have exocrine pancreatic insufficiency, although those with mild mutations of CFTR may have residual pancreatic function and may not require supplemental pancreatic enzymes. These patients are, however, at increased risk for acute or recurrent episodes of pancreatitis.[4,5] The decision to treat a patient with enzyme supplements rests on demonstrating the presence of steatorrhea. This generally correlates with symptoms of diarrhea, foul-smelling greasy stools, weight loss or poor weight gain, flatus and abdominal discomfort, and fat-soluble vitamin deficiency. For young adults who received diagnoses during childhood, enzyme supplementation should be continued. For newly diagnosed adults, a 72-h fecal fat collection should be performed while the patient is on a fixed oral fat intake or with dietary records. Fecal fat excretion ([grams of fat excreted/grams of fat ingested] $\times$ 100%) can be calculated from these data. Fecal fat excretion of $> 7\%$ indicates steatorrhea in an adult and mandates the initiation of pancreatic enzyme and vitamin supplementation (see "Nutrition" subsection). In specialized CF centers, the quantitative assessment of pancreatic excretory function may be performed to better define the stimulated output of pancreatic enzymes into the duodenum,[126] but this is not necessary on a routine clinical basis. Levels of fecal chymotrypsin,[127] serum pancreatic trypsinogen,[128] and fecal pancreatic elastase-1[129] may be low in patients with pancreatic insufficiency, however, these tests have not been fully evaluated for use in adults with CF. Recent evidence[130] has suggested that the fecal pancreatic elastase 1 immunoassay may prove to be a noninvasive, simple, and reproducible method of assessing pancreatic function.

Pancreatic Enzyme Supplements: Most modern pancreatic enzyme products are capsules that contain enteric-coated microencapsulated enzymes, either as microspheres or microtablets. The enteric coating prevents inactivation of the enzymes in the acidic gastric environment. The dissolution of generic microspheres or microtablets may not be equivalent to that of proprietary brands.[131] The substitution of one brand for another by the pharmacist may result in vastly different clinical responses despite equal enzyme doses and should not be allowed. The ratio of proteases to lipases differs in various brands of enzymes; however, it is uncertain whether this is clinically relevant. The US Pharmacopoeia requirements state that enzyme products may contain not $< 90\%$ of the amount stated on the label but do not set an upper limit for the content. The manufacturers usually overfill the capsules to compensate for enzyme degradation during storage.[132]

Enzyme supplements should be given with meals and snacks, with the number of capsules divided between the beginning and the end of the meal. Some patients may be able to take all of the capsules at the beginning of the meal without problems. Enzyme dosing can be calculated on the basis of the amount of fat ingested with each meal.[133] In general, patients need 500 to 4000 U lipase per gram of fat ingested per day. This method of dosing mimics the body's response to adjusting pancreatic enzyme excretion but may be tedious to calculate. Although less physiologic, it is frequently more practical and convenient to determine the enzyme dose based on body weight.[134] Adults should start with approximately 500 U lipase per kg body weight per meal, and half of that with snacks. If this dose quickly corrects the fat malabsorption, then attempts should be made to reduce the dose to the minimum effective dose. If symptoms of steatorrhea continue (or if the results of 72-h fecal fat collection tests are still abnormal), then the dose should be increased in increments of approximately 150 to 250 U lipase per kilogram per meal until symptoms improve, up to a maximum of 2500 U lipase per kilogram per meal (or 4000 U lipase per gram of fat per day). Doses higher than this level should be used with caution because of the risk of the occurrence of fibrosing colonopathy with higher doses.[134–136] Patients receiving doses $>$ 2500 U lipase per kilogram per meal should be reevaluated, and attempts should be made to reduce the dose of enzyme supplements.

Poorly Responding Patients: Some patients may continue to have symptoms of steatorrhea despite taking appropriate doses of enzyme supplements. Adherence to the enzyme therapy should be assessed in this situation. Giving some of the enzyme capsules at midmeal may be of some benefit. The hyperacidity of the upper GI tract in CF patients is one of the most common reasons for suboptimal response to enzyme therapy. Gastric acid output may not be neutralized because of inadequate bicarbonate secreted by the pancreas. This retards the dissolution of the enteric-coated microspheres or microtablets.[137] Drugs that reduce gastric acid production (*eg*, H_2-blockers and proton-pump inhibitors) may help to improve the dissolution of these products and reduce steatorrhea.[138,139] Other therapeutic considerations include the addition of non-enteric-coated, powdered preparations (*eg*, Viokase; Axcan Scandipharm), or a trial of an alternate brand of microencapsulated product with a different dissolution profile.

Short bowel syndrome, previous intestinal resections, and rapid GI transit are other conditions in which the microencapsulated enzyme preparations may not dissolve well. The addition of small amounts of pancreatic enzyme non-enteric-coated, powdered preparations with or without gastric acid suppression may improve fat digestion in the more proximal intestine and may improve steatorrhea. In patients who have continued symptoms despite adequate enzyme supplementation and acid suppression, other diagnoses should be considered, including infectious gastroenteritis, parasitic infestation (*eg*, giardiasis), lactose intolerance, bacterial overgrowth of the small intestine, cholestasis, *Clostridium difficile* disease, celiac disease, short bowel syndrome, Crohn disease, food allergies, or intestinal tumors. Appropriate evaluation and treatment for these disorders should be conducted when indicated.[140]

Nutrition

General Principles: The importance of nutritional status in the long-term survival of patients with CF is well-documented.[141–144] The prevention of malnutrition should be a primary goal of the health-care team. A standard North American diet with 35 to 40% of calories from fat is recommended.[133] The tendency to restrict fat consumption in these patients should be discouraged since dietary fat is the highest density source of calories, improves the palatability of foods, and is needed to maintain normal essential fatty acid status. In general, CF patients with pancreatic insufficiency are not at risk for developing hyperlipidemia.[145] However, patients with pancreatic sufficiency may be at risk and should be screened according to national guidelines for the general population.[146]

Individuals with CF should be encouraged to follow a normal dietary pattern with no specific restrictions. The dietitian can assist patients in selecting more energy-dense foods with additional snacks to improve energy intake. Snacks such as nuts, muffins, cheese, and milkshakes may be helpful. Commercial oral supplements also may be used, but one must ensure that these costly supplements are an addition to, rather than a replacement for, calories from food.

Careful monitoring of patient nutritional status is aimed at the early detection and correction of unfavorable trends. Patients should be made aware of their ideal body weight (IBW) range, as estimated by using the Metropolitan Life Insurance Company height and weight tables for individuals of small frame.[147] Instructions can be provided for patients to monitor their weight at home and to report promptly significant weight loss. Weight should be measured on each clinic visit and compared to IBW based on height. The *Clinical Practice Guidelines for Cystic*

Fibrosis[1] of the CFF suggests that patients be categorized as adequately nourished (> 90% IBW), underweight (85 to 89% IBW), mildly malnourished (80 to 84% IBW), moderately malnourished (75 to 79% IBW), or severely malnourished (< 75% IBW). Some centers track body mass index (BMI); BMI is calculated as follows: weight (kg)/height (m^2) with a normal range of 20 to 25. A BMI of < 19 indicates significant malnutrition and a need for aggressive nutritional intervention. Some centers also find it helpful to measure triceps skinfold and midarm circumference as indicators of body fat and lean body mass.[133]

Approach to the Malnourished Patient: Patients who are malnourished or are losing weight should be evaluated in more detail and observed more closely. A dietitian should assist in the evaluation. Caloric need and actual intake should be assessed. Energy needs are based on individual requirements and can be calculated based on basal metabolic rate using the World Health Organization equations.[133] It is also important to assess malabsorptive symptoms. The approach to patients who continue to have steatorrhea despite taking appropriate doses of enzymes has been reviewed above. For patients with weight loss unrelated to caloric intake or malabsorption, alternative GI diagnoses and diabetes mellitus (DM) should be considered in the differential diagnosis.

Patients with moderate or severe malnutrition are candidates for more aggressive nutritional interventions. There are data suggesting that nutritional repletion has a positive impact on the course of the disease for such patients.[148–151] The placement of a nasogastric tube each night for supplemental feedings during sleep is an option for some patients, but this is inconvenient and poorly tolerated by some patients, particularly those with severe pulmonary disease. The insertion of a gastrostomy or jejunostomy tube is an acceptable method for increasing caloric intake in selected patients. Placement is generally well tolerated; however, the risk/benefit ratio must be carefully considered in patients with severe pulmonary disease because of the potential for respiratory compromise following the procedure. Choice of an enteral supplement must be individualized. Semi-elemental formulas do not require pancreatic enzymes, but complete formulas are generally well tolerated when given with enzyme therapy.[152] Parenteral nutrition may be appropriate for short-term nutritional repletion in a severely malnourished patient,[153] but the enteral route is more appropriate and safer for long-term support.

Vitamin Supplementation: Patients with pancreatic insufficiency are prone to malabsorption of the fat-soluble vitamins (*ie*, A, D, E, and K). Clinicians must be aware that patients may manifest clinically important vitamin deficiency states (*eg*, night blindness in vitamin A deficiency, spinocerebellar degeneration or hemolytic anemia in vitamin E deficiency, metabolic bone disease in vitamin D deficiency, and bleeding diathesis in vitamin K deficiency). Vitamin supplementation is recommended, including the following: vitamin A, 10,000 IU/d; vitamin E, 200 to 400 IU/d; vitamin D, 400 to 800 IU/d and adequate sunlight exposure; and vitamin K, 2.5 to 5 mg/wk.[133] The vitamins containing vitamins A, D, E, and K that are specially formulated for CF patients are sufficient for most adult patients when taken at a dosage of two tablets per day. Some patients require additional supplementation. To ensure adequate amounts of vitamin K, patients receiving frequent courses of antibiotics or those with a history of hemoptysis should be given an additional 2.5 to 5 mg vitamin K each week.[154] Serum levels of retinol, vitamin E, and 25-hydroxyvitamin D (25-OHD) should be checked annually, and vitamin doses should be adjusted accordingly. Clinicians should be aware that other nutrient deficiency states (*eg*, zinc, essential fatty acids, and antioxidants) have been reported in CF patients, but routine monitoring or supplementation is not recommended at this time. As in the general population, menstruating women often need supplemental iron to prevent iron-deficiency anemia. Other patients with CF are also at risk of developing iron-deficiency anemia. In some cases, iron-deficiency anemia must be distinguished from anemia resulting from chronic disease.

CF-Related DM

A CFF consensus conference[155] addressed the diagnosis, screening, and management of CF-related DM (CFRD). This section will briefly highlight the salient points of that report. Glucose intolerance and CFRD are age-related complications of CF. The CFF patient registry of > 22,000 individuals indicates that the incidence of insulin-requiring DM in CF-affected children < 10 years of age is similar to that of unaffected children (*ie*, < 1%). However, from adolescence into adulthood there is a progressive increase in the incidence of CFRD. More than 15% of patients > 35 years of age have CFRD and are receiving insulin therapy.[2,156] An even larger percentage may have undiagnosed CFRD. Using oral glucose tolerance tests (OGTT) to screen a large patient population, one US CF center has reported[155,156] a prevalence of 43% in patients > 30 years of age (Fig 2). The pathogenesis of CFRD is complex, but largely is related to fibrosis and the destruction of the pancreas. Therefore, CFRD is

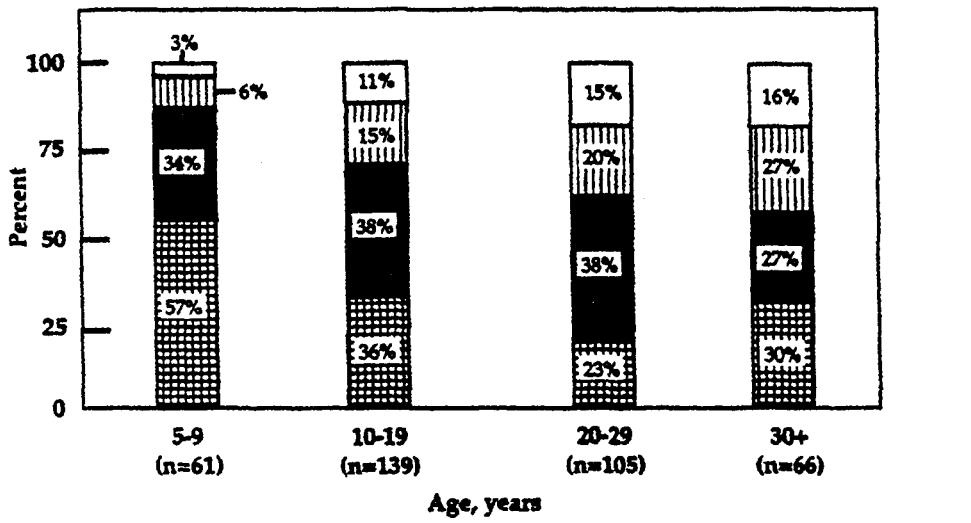

FIGURE 2. Glucose tolerance categories in CF patients, expressed as the percentage of prevalence within age groups.

seen most commonly in individuals who have exocrine pancreatic insufficiency.

CFRD is associated with increased morbidity and mortality.[144,157,158] Several studies[155] have shown deterioration in pulmonary function and BMI in the 2 to 4 years preceding the diagnosis of CFRD. In an analysis of 3,227 adults who were observed in the CFF patient registry from 1991 to 1996, the presence of CFRD requiring insulin was associated with more than a 2.5-fold increase in the relative risk of mortality during the observation period. A cause-and-effect relationship between CFRD and excess morbidity and mortality cannot be definitively established. CFRD simply may be a marker of advanced disease and concomitant metabolic stress. However, one study[159] showed that the initiation of insulin therapy reversed the deterioration in body mass and pulmonary function in patients with CFRD. This lends weight to the hypothesis that untreated CFRD is an independent risk factor for poor outcomes. Also in favor of this hypothesis are the recent data showing that patients with relatively mild lung disease and impaired glucose tolerance appear to be at risk for a more rapid decline in pulmonary function compared to patients with normal glucose tolerance.[160]

Microvascular complications occur in patients with CFRD, with a reported incidence of 5 to 16% for retinopathy, 3 to 16% for nephropathy, and 5 to 21% for neuropathy.[161–163] However, the occurrence of macrovascular complications (*eg*, atherosclerosis, myocardial infarction, and stroke) appears to be rare.[164]

Several clinical situations that are more common in the adult patient appear to be associated with CFRD. Women with CF who become pregnant may be at increased risk of gestational diabetes. Of note, women with CFRD who become pregnant appear to be at increased risk of deterioration in pulmonary function and excess mortality in the 2 years following parturition compared to nonpregnant CF women with CFRD.[165] CFRD frequently develops in those patients with end-stage lung disease and has been associated with frequent pulmonary exacerbations,

the use of corticosteroids, and supplemental (enteral or IV) feedings. The posttransplantation immunosuppressive regimen is frequently associated with onset and/or exacerbation of CFRD.

Screening and Diagnosis: A casual or random glucose determination should be performed annually in all adults with CF. A value < 126 mg/dL (7 mmol/L) is considered to be normal. A value of ≥ 126 mg/dL is considered to be abnormal and warrants measurement of fasting blood glucose (FBG) level. A casual glucose value of > 200 mg/dL (11.1 mmol/L) on two or more occasions is diagnostic of CFRD, as are either an FBG level of ≥ 126 mg/dL on two or more occasions or an FBG level of ≥ 126 mg/dL in association with a casual glucose level of > 200 mg/dL.[155] In ambiguous cases, an OGTT (using 1.75 g/kg up to a maximum of 75 g) should be performed. A 2-h postprandial glucose value of > 200 mg/dL is considered to be diagnostic of CFRD. An OGTT also should be performed in all women with CF who are contemplating pregnancy. It should be repeated soon after conception, and early in the second and third trimesters.[166] Certain clinical situations such as unexplained weight loss or failure to gain weight, delayed onset of puberty, and unexplained deterioration in pulmonary function suggest the possibility of undiagnosed CFRD. Glucose tolerance should be assessed in these situations.

Treatment of CFRD: The consensus of the committee was to treat CFRD aggressively in patients with fasting hyperglycemia. The principles of insulin and nutritional therapy in CFRD differ from those in either type 1 or type 2 DM. Therefore, the optimal management of CFRD is by the multidisciplinary CF team in conjunction with an endocrinologist or diabetologist. The goals of therapy are as follows:

- Maintain optimal nutritional status;
- Control hyperglycemia to reduce acute and chronic diabetes complications;
- Avoid severe hypoglycemia;
- Promote psychological, social, and emotional adaptation to living with CFRD; and
- Be as flexible as possible within the framework of the patient's lifestyle.

Patients with CFRD and fasting hyperglycemia should be treated with insulin. The use of oral hypoglycemic agents cannot be recommended at this time. The nutritional management of CFRD is similar to the general approach for all patients with CF except that more attention is paid to the timing of meals and the avoidance of concentrated carbohydrates. The pattern of hyperglycemia in CFRD differs from that in type 1 DM. Some basal insulin secretion is usually preserved, making fasting hyperglycemia less severe and ketosis extremely uncommon. In contrast, postprandial hyperglycemia is often a prominent feature of CFRD. Therefore, a typical regimen often includes the use of very short-acting insulin (*eg*, lispro) prior to each meal. Appropriate dosing requires that patients either eat a predictable meal or use a carbohydrate counting system to estimate insulin requirements. A small amount of long-acting insulin may be required as well. Regular home glucose monitoring is essential in making the necessary adjustments in the insulin regimen.

Monitoring of therapy also should include the quarterly measurement of hemoglobin A_{1c}. Hemoglobin A_{1c} values are often a less useful guide than in type 1 DM, but similar target values of $< 7\%$ for adults and $< 8\%$ for adolescents should be the goal. However, even a "good" glycohemoglobin value may be associated with an unacceptable degree of postprandial hyperglycemia in some individuals. Goals for glycemic control in pregnant women are more stringent than those for men and nonpregnant women.[167]

All patients with CFRD should be screened annually for microvascular complications with a dilated eye evaluation and a urinalysis for microalbumin measurement. The presence of proteinuria should be taken particularly seriously in patients with CFRD, as it may indicate the onset of diabetic nephropathy. The concomitant use of nephrotoxic drugs (*eg*, aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, and posttransplant immunosuppressive agents) may increase the susceptibility to nephropathy. As with all people with diabetes, hypertension should be aggressively treated, usually with a regimen that includes an angiotensin-converting enzyme inhibitor.

The natural history of the abnormalities in glucose metabolism in CF patients is not fully understood. At this point in time, the treatment for impaired glucose tolerance and CFRD without fasting hyperglycemia is not recommended except in the context of clinical trials or in the clinical situations detailed above (*eg*, unexplained weight loss).[155]

The diagnosis of diabetes is difficult for some adults who see it as yet another burdensome imposition or as a sign of end-stage disease. Monitoring and treatment of CFRD are relatively labor-intensive and add to an already complex regimen. The support and understanding of the CF team will help the patients to incorporate this additional challenge into their daily regimen.

Hepatobiliary Disease

A CFF consensus conference[168] addressed the clinical features, diagnostic evaluation, and management of liver and biliary disease. The salient features of that document are highlighted here. The involvement of the liver and biliary tree in CF may lead to a gradually progressive biliary fibrosis and cirrhosis. It is estimated that up to 17% of children have clinically significant liver disease.[169,170] Data about the prevalence in adults are incomplete, but in one retrospective review[170] of 233 adults (> 15 years of age), 24% were found to have hepatomegaly or persistently abnormal liver blood test results. As the median survival time for CF patients increases, clinically significant liver disease and its complications will likely become a more important consideration.

Screening for Liver Disease: Examination and measurement of the liver and spleen by palpation and percussion should be performed at each clinic visit. A panel of liver function tests (LFTs) including serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase (GGT), and bilirubin should be obtained yearly. None of these tests correlates with the degree of hepatic fibrosis. Nevertheless, if any of these values is > 1.5 times the upper limit of normal, repeat testing should be performed within 3 to 6 months. Patients with persistent elevations (*ie*, occurring for > 6 months) or high elevations (*ie*, more than three to five times the upper limit of normal) of LFT results should be investigated more completely.

Diagnostic Evaluation: A workup for liver disease should begin with a focused history and physical examination. Other causes of elevated aspartate aminotransferase and alanine aminotransferase levels (*eg*, hepatitis A, B, or C virus; cytomegalovirus; Epstein-Barr virus; alcohol; drugs; or toxins) and/or elevated GGT or alkaline phosphatase levels (*eg*, gallstones, cholecystitis, biliary obstruction, or bone disease) should be considered in the differential diagnosis. In addition to the routinely measured LFTs, biochemical evaluation should include total and direct bilirubin levels, total protein level, albumin level, prothrombin time, blood ammonia level (if significant portal hypertension is suspected clinically), cholesterol and glucose levels, and a CBC count to check for hematologic consequences of hypersplenism.

An ultrasound evaluation of the right upper quadrant of the abdomen should be obtained to detect the presence of gallstones, common bile duct stones, nodularity of the liver suggesting cirrhosis, findings suggesting steatosis, and bile duct or hepatic vein dilatation. This test provides very useful information but cannot detect or quantify the degree of fibrosis of the liver. Hepatic scintigraphy has limited clinical utility in the evaluation of suspected liver disease.

Endoscopic retrograde cholangiopancreatography (ERCP) can reveal strictures, dilatation, stones, and other abnormalities of the biliary tree. Although changes in intrahepatic bile ducts are relatively common in CF liver disease,[171] common bile duct stenosis is much less common (*ie*, < 10% of patients with advanced liver disease)[171] than initially reported.[170] Because of the risks associated with this procedure, ERCP should be used only when there are clear-cut clinical indications. MRI cholangiography is a noninvasive technique that is used to visualize the biliary tree. It may be useful in examining the extrahepatic biliary tree, gallbladder, and major intrahepatic ducts.[172] This imaging modality should be considered prior to the use of ERCP.

Upper GI endoscopy is the most sensitive way to detect esophageal varices, gastric varices, portal hypertensive gastropathy, or gastric and duodenal ulcers. Endoscopy should be considered in adults with portal hypertension to determine whether varices are present since this information has prognostic and therapeutic implications.

Liver biopsy may be useful in making a specific diagnosis, and in determining the presence and extent of portal fibrosis or cirrhosis. However, not all clinicians believe that liver biopsy is indicated in investigating liver disease in CF because of the patchy nature of CF-related biliary cirrhosis and the lack of definitive therapy. Careful consideration of the risks of a liver biopsy should be made on an individual basis in conjunction with an experienced gastroenterologist.

Management of Liver Disease: A multidisciplinary approach is recommended for the management of liver disease in CF. The team should include the CF center staff, a gastroenterologist/hepatologist, a surgeon experienced in hepatobiliary surgery, and a radiologist. The reader is referred to the 1999 CFF consensus document[168] for a detailed description of each of the following three major CF-related causes of liver disease: (1) cholestasis/biliary cirrhosis/multilobular cirrhosis; (2) hepatic steatosis; and (3) hepatic congestion from cor pulmonale. It is important to establish a definitive diagnosis since each is managed differently and is associated with its own set of complications. For the purposes of this document, we will focus on the most common CF-related liver lesion, cirrhosis. Cholestasis, focal biliary cirrhosis, and multilobular cirrhosis are part of

a sequential progression that occurs over a variable period of time, therefore, certain aspects of treatment are similar for these three lesions. The therapeutic approach includes medical therapy, nutritional therapy, management of complications (*eg*, portal hypertension and liver failure), and prophylactic therapy.

MEDICAL THERAPY: There is convincing evidence of the benefit from therapy with ursodeoxycholic acid (UDCA) in non-CF patients with a similar liver lesion (*ie*, primary biliary cirrhosis).[173,174] UDCA therapy significantly retards the progression of this cholestatic liver disease, as evidenced by improved survival times free of liver transplantation. UDCA therapy improves bile flow in CF patients,[175] may displace toxic hydrophobic bile acids that accumulate in the cholestatic liver,[176] may have a cytoprotective effect,[176,177] and may stimulate bicarbonate secretion into bile.[178] Several, but not all, clinical trials[179–185] have demonstrated improvement in LFT results with UDCA therapy. A randomized, double-blinded, placebo-controlled trial[186] demonstrated significant clinical, nutritional, and biochemical improvement in the group treated with UDCA. Liver histology improved in another prospective 2-year trial of UDCA treatment.[187]

Conclusive evidence that UDCA alters mortality or the progression to cirrhosis is lacking. Nonetheless, clinicians should strongly consider treating CF patients who have cholestasis/fibrosis/cirrhosis. The appropriate dose is 20 mg/kg/d UDCA administered in two daily doses.[188,189] Adverse effects and toxicity from UDCA are uncommon. When they occur, they are usually not clinically significant and rarely lead to the discontinuation of treatment. Monitoring during therapy should include LFTs 3 months after initiating therapy and each 6 to 12 months thereafter. Repeat liver biopsy is generally not recommended because the focal nature of the liver lesion may make the assessment of histologic change over time difficult in an individual patient. There is no scientific justification for using UDCA in patients with CF who have little or no documented liver dysfunction or portal fibrosis.

Taurine has been suggested as an adjunctive therapy in liver disease because CF patients are commonly deficient in taurine.[185] However, in a randomized, double-blind trial, Colombo et al[186] showed no significant effect of taurine supplementation (17 to 33 mg/kg/d) on liver blood test results or fecal fat excretion measurements in patients with CF liver disease who were treated with UDCA or placebo.

NUTRITIONAL THERAPY: Monitoring fat-soluble vitamin status is even more important in the presence of liver disease[190] than in the presence of pancreatic insufficiency alone. All vitamin doses should be given with a meal and with pancreatic enzyme supplements. Supplementation with the water-soluble form of vitamin E (d-α-tocopherol polyethylene glycol [PEG]-1000 succinate) at a dose of 400 to 1200 IU/d will correct or prevent vitamin E deficiency in this setting. Patients also may need large doses of vitamin D_2 or D_3 (800 to 1,600 IU/d) or 25-OHD (calcifediol; 2 to 4 mg/kg/d) to normalize serum 25-OHD concentrations. The optimal dose of vitamin A supplementation has not been determined; however, patients with low serum retinol levels (*ie*, < 15 to 20 μg/dL) should be supplemented with 10,000 to 20,000 IU per day. Serum retinol and retinol-binding protein should be monitored to ensure the adequacy of therapy, as well as serum retinyl ester concentration to assess for toxicity (elevated serum retinyl esters). Prothrombin time should be monitored to assess vitamin K status. Significant prolongation of the prothrombin time should be treated with 5 to 10 mg vitamin K given once per week to daily, depending on the response to therapy. Following any change in vitamin dosing, repeat biochemical testing to ensure nutritional adequacy should be performed in 1 to 2 months.

PORTAL HYPERTENSION AND LIVER FAILURE: A detailed description of the management of these complications can be found in the CFF Consensus Statement.[168] If esophageal varices are documented by endoscopy, prophylactic β-blocker therapy should be considered. There is no direct evidence of efficacy in CF, but β-blockers reduce the risk of a first episode of variceal bleeding[191–193] in adults with other forms of liver disease. Adverse effects of β-blockers, such as bronchospasm and depression, need to be taken into consideration. Endoscopic variceal ligation can be considered for patients who have large varices or who do not tolerate β-blocker therapy.[194,195] Patients who are at high risk of bleeding from varices or have recurrent variceal bleeding may be candidates for a portosystemic shunt.[196,197] Liver transplantation is a viable consideration for a patient with decompensated cirrhosis, particularly if pulmonary function is relatively well-preserved. Liver transplantation in CF patients results in a 1-year survival rate of approximately 75 to 80%.[198,199]

PROPHYLACTIC THERAPY: All patients with CF liver disease should receive a complete immunization series for both the hepatitis A and hepatitis B virus vaccines, unless prior infection with these viruses has been documented. Patients should be counseled about the risks of ethanol use and encouraged to avoid ethanol. Potentially, hepatotoxic med-

ications and herbal therapies also should be avoided, if possible.

Other Hepatobiliary Manifestations: Micro-gallbladder occurs in about 30% of patients, and cholelithiasis or cholecystitis occurs in 1 to 12% of patients.[200] Cholelithiasis in CF is not responsive to UDCA therapy.[201] Hepatic scintigraphy may be helpful in evaluating a patient for suspected cholecystitis. If, in the presence of gallstones, clinical symptoms of gallbladder dysfunction or pain are present or if LFT results remain abnormal, a laparoscopic or surgical cholecystectomy should be performed, unless end-stage liver disease is present. The health-care team should be aware of the potential impact of any abdominal surgery on pulmonary function, particularly in patients with moderate-to-severe pulmonary dysfunction. A liver biopsy and intraoperative cholangiogram always should be obtained during any cholecystectomy procedure in a patient with CF.

Common bile duct stenosis occurs occasionally in patients, possibly because of compression of the bile duct by the fibrotic pancreas.[170,171] Primary sclerosing cholangitis may occasionally occur; however, cholangiographic findings consistent with primary sclerosing cholangitis may be caused by CF. Finally, cholangiocarcinoma also has been reported.[202]

GI Complications

Abdominal Pain: Abdominal pain is a frequent complaint in patients with CF.[203] Of the many causes of abdominal pain, only distal intestinal obstruction syndrome (DIOS) and fibrosing colonopathy are unique to CF. All other causes of abdominal pain that occur in the general population also occur in patients with CF, and do so with the same presenting signs and symptoms. However, some causes of abdominal pain that are unusual in the general population occur at an appreciably higher frequency in CF. Hence, the list of likely diagnoses that need to be considered when evaluating a patient with CF and abdominal pain is longer than it otherwise would be.

A practical approach to abdominal pain in a patient with CF is to build a differential diagnosis based on the primary location of the pain (*ie*, epigastric, periumbilical, or hypogastric). The relatively frequent causes of epigastric pain in CF are gastroesophageal reflux, biliary tract disease, pancreatitis, and gastritis/peptic ulcer disease. Periumbilical pain can be caused by DIOS, appendicitis, and intussusception. Hypogastric pain in CF can arise from DIOS, *C difficile* colitis, and, much less commonly, from fibrosing colonopathy or colon cancer.

EPIGASTRIC PAIN: In a survey of 50 adults with CF, a majority had symptoms of gastroesophageal reflux. Eighty percent had a history of heartburn, and 56% had a history of dyspepsia.[204] The evaluation and management of reflux in CF patients does not differ from that of the non-CF population, other than possibly avoiding postural drainage positions during CPT that exacerbate reflux. Cholelithiasis is another source of epigastric pain occurring in up to 12% of patients with CF. Alkaline phosphatase and GGT are often elevated in patients with CF because of intrinsic liver disease, with the result that these tests are less specific for cholelithiasis in this group. Diagnostic evaluation and treatment of cholelithiasis in CF can be found in a recent review by a CFF hepatobiliary disease consensus group.[168] Because of the relatively high frequency of biliary tract disease in CF, an abdominal ultrasound is often helpful in evaluating epigastric or right-upper-quadrant abdominal pain in CF patients.

Pancreatitis is a cause of epigastric pain that occurs almost exclusively in the subgroup of patients with CF who are pancreatic sufficient.[205] The recognition that mutations in CFTR are found in a large subgroup of patients with chronic pancreatitis who lack other evidence of CF has complicated the perception of what constitutes a CF diagnosis. Pancreatitis in CF usually presents with acute recurrent episodes, but chronic abdominal pain also is seen. The approach to diagnosing and treating pancreatitis in CF patients is similar to that for the general population. Although the incidences of gastritis and peptic ulcer disease have not been reported to be increased in CF patients over the general population, they are still common causes of epigastric pain in CF patients. Their evaluation and treatment are also similar for the CF and the non-CF populations.

PERIUMBILICAL PAIN: Periumbilical pain in adults with CF is most often caused by DIOS, which is discussed elsewhere in this article (see "DIOS" section). Appendicitis, presenting with the classic symptoms of periumbilical pain that migrates to the right lower quadrant, occurs in patients with CF, although probably at no greater frequency than in the non-CF population.[206,207] The diagnosis of appendicitis often may be delayed in CF patients because its early symptoms are mistakenly attributed to DIOS. Older studies in the literature[208] reported that intussusception in the region of the iliocecal valve was relatively frequent in adults with CF. However, common experience suggests that clinically significant intussusception is rare.

HYPOGASTRIC PAIN: Hypogastric pain and abdominal bloating are frequent complaints in patients

with CF. The most frequent cause is malabsorption that allows ingested nutrients to reach the colon where bacteria metabolize them to gaseous products. An indication that malabsorption is the cause of the abdominal pain is the coexisting symptom of steatorrhea. The therapeutic approach is to optimize pancreatic enzyme supplementation, as reviewed above.

The other major cause of hypogastric pain in patients with CF is DIOS. The likelihood that DIOS is the source of the abdominal pain is increased if the patient has intermittent constipation and abdominal distension (see "DIOS" section).

A less common cause of hypogastric pain in CF is *C difficile*-associated colitis.[208,209] The diagnosis should be considered particularly if the patient recently has received antibiotics or if the pain is accompanied by fever, leukocytosis, and/or blood in the stools. However, positive test results for *C difficile* also have been described in individuals with CF with abdominal pain who lack these other signs and symptoms.[210] Positive stool culture findings and/or toxin can sometimes be found in asymptomatic patients with CF, confusing the issue further. When the diagnosis of abdominal pain remains uncertain, colonoscopy showing pseudomembranes and/or inflamed mucosa, or an abdominal CT scan showing colonic thickening will support the diagnosis of *C difficile* colitis.

OTHER CAUSES: Other causes of abdominal pain in adults with CF deserve comment, although their incidence is quite low.[211] Fibrosing colonopathy, which is associated with the ingestion of very high doses of pancreatic enzymes, is manifested by inflammation and strictures in the right colon. Although it has been reported to occur in adults with CF,[212,213] it is a syndrome restricted mostly to the pediatric age group. An association between Crohn disease and CF has been suggested in the older literature.[214] However, some of these cases may have been caused by fibrosing colonopathy, which was just being described at that time. Colon cancer also has been reported[202] to occur at increased frequency in CF, although its incidence is still quite low. Consideration of the diagnosis is often delayed because its signs and symptoms are initially attributed to more frequent conditions that have similar clinical manifestations.[215] Colon cancer screening recommendations for adults with CF have not been established.

DIOS: Recurrent episodes of intestinal obstruction occur in 3.5% of patients with CF.[2,216,217] The obstruction is caused by excessively viscid intestinal contents as a result of CFTR mutations leading to abnormal digestive fluid secretion. The previous name, *meconium ileus equivalent*, has been replaced by DIOS in recognition that the site of obstruction can occur within the right colon as well as in the terminal ileum.[218] DIOS occurs almost exclusively in patients with pancreatic insufficiency. A number of precipitating factors have been suggested to be responsible for triggering episodes of DIOS, including dehydration, use of medications that suppress intestinal motility such as narcotics, and noncompliance with pancreatic enzyme replacement. However, in the majority of patients presenting with DIOS, no precipitating factor can be identified.[219]

The diagnosis of DIOS is based heavily on eliciting the symptoms of distal small bowel/right colon obstruction. Depending on the degree of obstruction, typical symptoms are decreased stool output, colicky periumbilical and/or right-lower-quadrant pain, abdominal distension, nausea, and vomiting. A physical examination may uncover high-pitched bowel sounds with rushes that can progress to silence if peritoneal irritation and secondary ileus occur. Occasionally, a mass in the right lower quadrant can be palpated, representing a distended cecum and right colon. If blood tests show a WBC count that is elevated above baseline, this suggests that bowel viability is jeopardized. Alternative diagnoses such as appendicitis and *C difficile* colitis also should be considered in this circumstance. Supine and upright radiographs of the abdomen usually reveal a right colon distended with bubbly-appearing intestinal contents and dilated loops of small bowel containing air-fluid levels. Although DIOS is the most common cause of these signs and symptoms, other less frequent diagnoses must be considered (see "GI Complications" section).

The goal of DIOS management is to recognize the condition promptly and to institute treatment early so as to avoid the need for surgical intervention, if at all possible. One of the greatest dangers is if DIOS is mistakenly diagnosed as irritable bowel syndrome. Unlike this latter benign condition, DIOS can rapidly progress to life-threatening total bowel obstruction. Treatment includes the correction of systemic dehydration that occurs secondary to vomiting and/or decreased oral intake because of abdominal pain. If the patient is not vomiting and bowel sounds are present, a cautious attempt at relieving the obstruction by an oral or nasogastric tube route can be made. Although a variety of agents used to thin bowel contents has been recommended, such as diatrizoate (a radiographic contrast solution)[220] or N-acetylcysteine,[221] PEG electrolyte solutions are now frequently employed.[222,223] If the severity of bowel obstruction is too great to safely administer treatment by mouth, enemas can be used in an attempt to relieve the blockage. Large volumes of

lavage fluid are sometimes required to clear the bowel. The success of clearing the right colon by enemas may be improved if radiocontrast dye is added to the solution and the procedure is monitored fluoroscopically.[224] At the first signs that the obstruction is lessening and that bowel motility is returning, a PEG solution can be administered by the oral or nasogastric route. However, if signs and symptoms warn that the integrity of the bowel wall is in imminent danger, prompt laparotomy is needed to resect a questionably viable bowel and to relieve the intraluminal obstruction by irrigation.

A small number of patients with CF experience recurrent episodes of DIOS and require preventive therapy. Chronic oral administration of N-acetylcysteine, mineral oil, prokinetic agents,[225] and, more recently, PEG solutions have been recommended. If the episodes occur infrequently, the institution of aggressive treatment at the first sign of blockage may be sufficient. In the rare circumstance in which DIOS recurs frequently, a daily PEG solution can be prescribed with the dose titrated to relieve symptoms.

Cancer Risks and Screening

Cancer risk becomes a concern as the population of individuals with CF ages. Although patients with CF appear to be at greater risk for some specific cancers, overall there appears to be little excess risk (if any) for cancer. The largest study conducted to date,[202] a retrospective cohort study of $>25{,}000$ patients with CF in the United States and Canada, showed no increase or decrease in overall cancer risk. There was, however, a clear increase in the risk of cancers of the digestive tract, where 13 cancers were observed and only 2 had been expected (observed/expected ratio, 6.5; 95% confidence interval, 3.5 to 11.1). These cancers were distributed throughout the GI tract, with primary sites in the esophagus, stomach, small bowel, and large bowel, as well as the liver and pancreas. An analysis from the United Kingdom[226] involving 412 patients demonstrated a similar increased risk of pancreatic and intestinal cancer. The pathophysiology underlying the increased risk of GI cancers is unknown, but may be another manifestation of the CF disease process. Increased risks of cancer have been seen in other disorders affecting the GI tract, including Crohn disease and celiac disease.[227] A possible decreased risk of melanoma and breast cancer has been postulated for patients with CF and CF carriers, but research to date has not been supportive of this hypothesis.[228,229]

The application of primary and secondary preventive measures to the CF population should be a priority of physicians caring for these persons. Primary preventive measures, including smoking prevention/cessation and healthy diets that include antioxidants, such as vitamin E and selenium, are possibly more important for individuals with CF than for nonaffected persons. Secondary preventive measures that are designed for early cancer detection also should be applied within the CF population. It has been suggested that the early detection of colon cancer through fecal occult blood screening may reduce colon cancer mortality by up to 30%.[230,231] The sensitivity and specificity of occult blood screening in the CF population is unknown, and the test may be less specific in CF patients than in the general population. Nevertheless, endoscopy should be considered in an individual with CF and a positive occult blood test finding. Other recommendations, including annual mammography in women after age 40 years, breast and testicular self-examination, and prostate cancer screening should be followed by patients with CF, similar to their use in the general population.

Adolescence

Adolescence is a challenging period, both physically and emotionally, for children and families, even in the absence of chronic illness. The additional challenges of CF may affect normal adolescent development. Similarly, the challenges of adolescence may impact the health of the young person with CF. The pediatric CF team needs to be aware of these challenges, to assess their impact on individual development, and to plan effective interventions that will facilitate the movement of the adolescent with CF into adulthood and an adult care setting. A summary of adolescent physical and emotional challenges and the potential complicating features of CF is listed in Table 3.

Site of Care

Care for teenagers and adults with CF should be provided by personnel who are sensitive and responsive to their medical, developmental, and psychosocial needs. The model of a multidisciplinary team providing care for CF patients has been successful and should be incorporated into the care of adults with CF. Adults generally have more severe pulmonary disease, a higher prevalence of DM, and more complex financial and psychosocial issues. Therefore, a relatively higher intensity of pulmonary, respiratory therapy, and endocrine, nutritional, and psychosocial services may be needed. In addition, adult patients

Table 3—*Adolescent Challenges and Their Potential Interactions with CF*

Challenges of Adolescence	Potential Impact of/on CF
Rapid physical growth	Delayed growth (height and weight gain)
	Decreased body fat (especially women)
	Prevalence of eating disorders may exceed that of the general population
Pubertal changes	Delay in genital development (male)
	Delay in menarche (female)
Sexual development	Delay in dating and sexual relationships
	Sexual dysfunction
	Misunderstanding of fertility
	Issues with reproduction
Development of personal identity	Poor body image
	Low self-esteem and self-concept
Autonomy and independence	Parental overprotection
	Dependency
Development of interpersonal relationships	Difficulty forming intimate relationships
	Social isolation
	Fear of rejection leading to secrecy about illness
Planning for the future	Increased uncertainty of future
	Decreased expectations for self
	Delay in planning for future
	Need for realistic planning
	Use of denial as coping strategy
Risk-taking behavior	Sexual and substance abuse may be less than in general population, but still present
	Poor adherence to medications and therapy

have unique needs, including vocational counseling, contraceptive and reproductive services, and obstetric care. There is consensus that a multidisciplinary team with training and experience in adult CF care should oversee the care of adults with CF. The multidisciplinary team typically consists of physicians with internal medicine training and additional expertise in CF, usually obtained as part of subspecialty training (*eg*, pulmonology), and nurses, dietitians, respiratory therapists, and social workers. Care is delivered in inpatient and outpatient facilities that are appropriate for adults, with laboratory services as outlined in the *Clinical Practice Guidelines for Cystic Fibrosis*.[1]

Transition From Pediatric to Adult Care

Definition and Rationale

Obtaining health care in the adult care setting encourages independence and increased self-reliance. Transition should be a planned process over time, as an abrupt transfer to adult care could be unsuccessful. Important meetings and position statements of pediatric and adolescent health professionals in the past decade have brought consensus to the need for both adult care and a smooth transition for young adults with chronic conditions.[232–236]

Models of Transition

National and institutional policies, available financial and professional resources, and geographic proximity of CF pediatric and adult care clinics and hospitals all influence transition modeling for young adults with CF. The greatest distinction in choice of transition model is whether to transfer directly to adult care or to overlap pediatric and adult care over a period of time prior to transfer. The danger of the direct transfer approach is an abrupt severing of important relationships in pediatric care, with no introduction to the new care environment. This could lead to negative feelings for the patient and family, and ambivalence for the pediatric care team in letting go of their long-time patient. The likelihood of follow-through to the adult care setting could be seriously compromised.[237]

Young adults with CF have reported in satisfaction surveys that meeting with the pediatric physician and the adult care physician together prior to transfer to adult care is useful.[238–241] The joint meetings can be accomplished in either the pediatric or adult setting, in one or several clinic visits, depending on the patient's specific need, until the patient is seen alone in the adult care setting.[238,240,242–244]

Criteria for Successful Transition

There must be commitment by the institution and by both pediatric and adult care teams to the importance of transition. There should be frequent formal and informal communication, and shared responsibility for developing coordinated and workable transition plans in order to ensure the continuity of the patient's care.[244]

Clinicians should introduce the concept of transi-

tion early, even as early as the time of diagnosis, when outlining the long-term care of CF. Children should be introduced to the concept of adult center care in an age-appropriate way. The adolescent can be given more responsibility for self-care and decision making, health education, and self-care training, and should be seen alone in clinic visits.[245] More intensive preparation can take place during the year before transfer to the adult clinic. This may include visits by adult care team members to the pediatric clinic, touring the adult care clinic, and discussions about doubts and anxieties.[246] Adult care physicians should be sensitive to the transition process and make an effort to know their new patient before transfer. Other strategies include inviting parents to the first visit in adult care (even though parents are not ordinarily involved in internal medicine clinics) and introducing any changes in medical treatment gradually, since abrupt changes can be perceived as disapproval of previous care. Transition materials, such as adult program pamphlets, education packets, and readiness questionnaires are used in some CF centers to prepare patients and their families for adult care.[246–248]

Appropriate timing for transfer should be evaluated beginning in the high school years. In most cases, transfer will coincide with graduation from high school. The pace and progress of transition is expected to vary for individuals, depending on developmental maturity, self-care skills, special characteristics of the family, availability of adult clinicians, and, in some cases, stage of illness. Those who are medically unstable, nearing death, or waiting for a lung transplant may defer transfer until stability is restored.

It is ideal to have a coordinator (*eg*, social worker or nurse) for the transition process. This person can ensure that a transition plan is created among the patient, family, and pediatric and adult care teams. The coordinator can schedule, facilitate, and track transition clinic and initial adult clinic appointments, and address any psychosocial issues of the patient, family, and clinicians throughout the transition process until the patient is adapted to adult care.

Evaluation

The ongoing evaluation of transition should occur at individual CF program sites to ensure the effective transfer of patients to the adult care setting. In general, there is a need for further study of transition models to identify which approaches work best in specific settings for specific patients and to evaluate whether the transition process helps individuals with CF to be successful in other areas of adult life.

Education and Careers

Career Planning

Career planning is an important component of the ongoing care provided by the CF center. Ideally, at diagnosis parents should be informed that career planning will be necessary as their child grows older. The CF center team should initiate a discussion of careers with the adolescent patient and may need to assist the patient's school counselor regarding the implications of CF on career planning. The Meyers-Briggs type inventory, a career counseling tool, identifies jobs of interest that a person is capable of performing. Government-funded vocational rehabilitation programs are available in all states at no cost and provide job training, placement, and assistance with school tuition.

People with CF face few absolute restrictions on choice of employment. Education and career choices should be based on an individual's intellect, ability, interests, and life goals. The CF center team should tailor career counseling to the individual and should not make blanket exclusions of career choice. Present and future physical limitations should be considered.

Career Choice Considerations

In the United States, health insurance is primarily provided through employment. Employment decisions should take into account the benefits package offered by the employer. Employers who employ >20 employees and offer health insurance as a benefit must provide Comprehensive Omnibus Budget Reconciliation Act (COBRA) continuation of coverage. Other employee benefits such as disability insurance coverage and life insurance should be reviewed. An employer who employs >15 employees will be covered by the Americans With Disabilities Act (ADA).

Careers that allow for flexibility in work hours, reduced work hours, flexible use of vacation and sick leave, additional paid or unpaid sick time (including use of coworker-donated sick time), and the option of working from home are attractive. Self-employment often allows for maximum flexibility. Other considerations may include the levels of pulmonary irritants in a work environment, the particular stress of a job, and the potential exposure to upper respiratory viruses. Certain jobs, such as work with children, may pose a direct threat to the health of the individual with CF because of the increased risk of infection. Infection control issues may impact people with CF who choose careers in health care. The CF center team should educate such patients about the modes of transmission of infectious agents and the potential implications of employment in health care.

Postsecondary Education

Education itself can be a meaningful and life-enhancing experience. Those with the emotional, financial, and academic ability to handle college and postgraduate studies should be encouraged to pursue advanced education regardless of disease severity.

Determination of Financial Assistance Available: The CF center can assist the adult with information regarding the educational financial assistance that is available. Companies that manufacture and sell products to people with CF offer scholarships. In some cities, funds set up by families who have lost a loved one to CF also can be a source of financial assistance.

Selection of School: Students have a variety of choices when determining where and how to pursue a postsecondary education. Many new advances in technology have created the opportunity to take courses by teleconference or correspondence. Those interested in attending a school outside their home city should inquire about local CF care, state insurance assistance, and weather or environmental concerns.

Accommodations Needed by Student: Section 504 of the Rehabilitation Act of 1973 provides that no entity that receives federal funds can discriminate against a person on the basis of disability. Section 504 protects students at colleges from discrimination based on disability and requires accommodations needed by the student because of their disability. Many universities and colleges have an Office of Disabled Students that can assist the adult with CF. Typical accommodations for a student with CF may include the following: a private room; an air-conditioned room; a reduction in minimum hours required each semester; parking privileges on campus; and a plan for obtaining assignments or rescheduling exams because of absences. The CF center may need to provide documentation of the student's disability and the need for specific accommodations.

Employment

According to the 2000 National CF Registry, 2,684 adults with CF (31.0%) were working full time, 867 (10.0%) were working part-time; 1,675 (19.4%) were students, and 299 (3.5%) were homemakers.

Protection From Discrimination

The ADA, Title I, prohibits discrimination against a qualified individual with a disability in regard to all terms, conditions, and privileges of employment if the employer employs ≥ 15 employees. The ADA also prohibits discrimination based on a relationship or association with an individual with a disability.

Accommodations for Disability

Under the ADA, people with CF also may be entitled to a reasonable accommodation if needed to allow them to perform the essential functions of their job. The provision of a reasonable accommodation can allow an adult with CF to continue working even if his or her health needs increase. Possible accommodations include additional sick time, modification of a work schedule, ability to work from home, and modification in policies and procedures of the employer.

Informing an Employer of a CF Diagnosis

It is illegal for a prospective employer to ask whether the applicant has a disability during the interview or on an application. Employers are allowed to inquire about qualifications, knowledge, skills, and ability to perform the job. After a person is hired, a person only needs to disclose a disability if the person needs a reasonable accommodation. The decision about disclosing a medical diagnosis can best be evaluated by the individual as he or she has knowledge of the specific work environment. The CF center can provide information about CF to an employer. For some, the effort required to keep their health status a secret can be stressful, and disclosure may be best in such a situation.

Family Medical Leave Act

The Family Medical Leave Act provides that an eligible employee will be allowed 12 weeks unpaid leave per year if the employee has a serious health condition that makes the employee unable to perform the functions of his or her position. The time can be taken in a 12-week block or intermittently. A family member also may take leave to care for a child, parent, or spouse. The employee must work for an employer who has 50 or more employees, must have worked for 1 year for the employer, and must have worked 1,250 h in the prior year. The employer must continue health insurance coverage during the leave period.

Medical Insurance

Obtaining and keeping medical insurance are two of the most important things for the adult with CF. In the United States, 85% of the population obtain

heath insurance through their employer, their spouse, or a parent's employer. If possible, changes in employment should be carefully planned to avoid interruption or loss of medical insurance.

The Health Insurance Portability Accountability Act

The Health Insurance Portability Accountability Act guarantees health insurance coverage in specific situations with relation to group health insurance for people who change or leave their jobs by providing creditable coverage that can be used to avoid a preexisting condition clause contained in the new policy as long as there is not more than a 63-day break in coverage. The Health Insurance Portability Accountability Act also mandates that if an employer provides health insurance to employees and/or dependents, then all employees and/or dependents must be covered regardless of their medical condition.

COBRA

COBRA requires that continuing medical insurance be made available to qualified individuals. The act applies to employers with ≥ 20 employees who offer health insurance as a benefit. The maximum duration of continued insurance eligibility after employment termination depends on the circumstances (Table 4). In each situation, the employee must pay the premiums during the period of continuation of coverage.

State Law for Disabled Children

Most insurance policies contain limiting age language that ends insurance coverage for a dependent child when the child reaches a certain age. Most state insurance laws allow the child to continue as a covered dependent as long as the child demonstrates that he or she is incapable of self-support because of a physical or mental disability. The continuation of coverage will require that the treating physician sign a form indicating that the child meets the requirements of the law.

Table 4—*Duration of COBRA Insurance Eligibility Based on the Circumstances*

Qualifying Event	Length of Period of Continuation, mo
Termination from employment	18
Death of the covered employee	36
Divorce or separation from covered employee	36
Covered individual has left work and become eligible for SSDI benefits	29
Individual has reached a limiting age on his or her parents' policy	36

Denial of Coverage by an Insurer

It is becoming increasingly difficult for people with CF to receive approvals from their insurance companies for treatment needed. The adult with CF and the CF center team can be effective in advocating for the coverage of necessary treatment. Advocacy involves the appeal of a denial of coverage by the insurance company. Documentation of the medical necessity of the prescribed treatment will increase the likelihood of success of the appeal. If the appeal is denied, the CF center should not be discouraged but should appeal to the next level. In the event that Medicaid or Medicare denies treatment, the Medicare or Medicaid recipient also can appeal the denial of coverage.

Disability Insurance

Benefits for disabled adults with CF may be available under the Social Security Disability Insurance (SSDI), Supplemental Security Income (SSI), Medicaid, and/or Medicare programs.

SSDI Benefits

SSDI benefits are provided to adults who have worked enough to qualify for benefits but are no longer able to engage in substantial gainful activity because of a physical or mental impairment. Qualification for SSDI does not involve the income level of the person applying for benefits, or their spouse or parent. SSDI provides a monthly benefits check after a 5-month waiting period, and Medicare benefits after 24 months of receipt of benefits.

SSI Benefits

SSI benefits are provided to adults who have not worked enough to qualify for SSDI, meet certain low-income guidelines, and are no longer able to engage in substantial gainful activity because of a physical or mental impairment. SSI is also available to children who meet the income and disability requirements. SSI provides a monthly payment and Medicaid coverage effective immediately on approval of benefits.

Qualification for SSDI Benefits

Section 3.04 of the Social Security Listing provides that an adult with CF will qualify for SSDI benefits if the person has any of the following:

1. An FEV_1 equal to or less than the appropriate value specified in Table 5, corresponding to the individual's height without shoes;
2. Episodes of bronchitis, pneumonia, hemoptysis (more than blood-streaked sputum), or respiratory failure requiring a physician's intervention, occurring at least once every 2 months or at least 6 times a year. Each inpatient hospitalization for > 24 h for treatment counts as two episodes, and an evaluation period of at least 12 consecutive months must be used to determine the frequency of episodes;
3. Persistent pulmonary infection accompanied by superimposed, recurrent, symptomatic episodes of increased bacterial infection occurring at least once every 6 months and requiring IV or nebulization antimicrobial therapy; and
4. If the person's condition is as severe as one of the listing requirements.

The CF center can be instrumental in the approval of an application for Social Security benefits. A letter from the treating physician indicating which section of the listing the applicant meets with attachments, such as PFT results or discharge summaries from hospitalizations, will significantly increase the chances that the adult with CF will be approved for benefits on the initial application. The reviewer may not have a medical background. If the applicant is denied benefits, an appeal must be filed within 60 days.

Family Planning and Pregnancy

Fertility

Most men with CF are azoospermic because of anatomic abnormalities of the vas deferens and are functionally sterile, although 1 to 2% may be fertile.[249–251] Men in whom CF has been diagnosed in adulthood who have mild mutations are more likely to be fertile.[252]

In contrast, the woman with CF has a normal reproductive anatomy. It is often stated that women with CF are less fertile than healthy women[253,254]; however, > 100 women with CF become pregnant every year.[2] If fertility in women with CF is decreased, it is unclear whether this is related to their general health status or is related to abnormalities of the cervical mucus. The rheology of the cervical mucus is different in the woman with CF compared to the nonaffected woman. There is lower water content and no thinning at ovulation.[253,255]

Table 5—*FEV_1 Criteria for SSDI Eligibility*

Height Without Shoes		
cm	Inches	FEV_1, L
≤ 154	≤ 60	1.45
155–159	61–62	1.55
160–164	63–64	1.65
165–169	65–66	1.75
170–174	67–68	1.85
175–179	69–70	1.95
≥ 180	≥ 71	2.05

Contraception

Issues of female contraception are broadly similar for women with or without CF.[256] Men with CF should not assume that they are infertile. Semen analysis is recommended to determine fertility status. All persons with CF should exercise the same precautions as unaffected persons to prevent the spread of sexually transmitted diseases.

Reproductive Decision Making

Genetic counseling should be offered to individuals with CF who are contemplating starting a family, and CF carrier screening should be offered to their partners. The couple should be advised of the potential effects of parenting on the health of the CF patient. Childbirth imposes long-term responsibility on parents, with or without the presence of CF. No one is guaranteed the opportunity to witness the growth of their children, but parents with CF must face the possibility of their own early death with more than just vague concern. It is imperative for health-care providers to recognize that they should not impose their own views on an individual patient's reproductive decision making, but rather that they should present the patients with medical information to allow them to make an informed decision. These issues should be addressed prior to conception. The woman with severe lung disease also should be made aware that panel-reactive antibodies may be increased during pregnancy. Some transplant centers may consider elevated levels of panel-reactive antibodies to be a contraindication to lung transplantation.[257]

Alternatives to Normal Conception

Alternatives to normal conception are available and should be considered on an individual basis. For the partners of infertile men, artificial insemination with donor sperm is an option. Microsurgical epididymal aspiration of spermatozoa with intracytoplasmic sperm injection into the oocyte may allow men with CF to become biological fathers, but it is available only in larger fertility centers and has a success rate per cycle in the order of 12 to 45%.[258–260] It is also an expensive process.

Pregnancy

Some reports demonstrate good outcomes for women with CF during and after pregnancy,[165] but there are also reports of untoward outcomes.[261,262] There are normal changes that occur during pregnancy that may adversely affect the woman with CF. There are increases in minute ventilation[263] and oxygen uptake,[264] which may be problematic in the pregnant woman with severe lung disease. Blood volume and cardiac output can rise by as much as 50% toward the end of pregnancy as a result of the placental circulation and generalized vasodilatation.[264] These changes could precipitate right heart failure in the presence of severe lung disease. Thresholds of medical contraindication to pregnancy have not been established, although there are concerns about the patient with advanced disease, malnutrition, or diabetes.

Management of the Woman With CF During Pregnancy

Pregnancy in a woman with CF should be considered a high-risk pregnancy. It is important to provide continuity of comprehensive care by a coordinated team with knowledge and expertise in CF. In addition to the usual issues, such as monitoring of nutritional and pulmonary parameters, there are CF-specific issues that warrant careful attention, including altered drug pharmacokinetics. Screening for and treatment of DM during pregnancy is discussed below (see "CFRD" section).

An essential part of maternal care is the early recognition and prompt treatment of acute pulmonary exacerbations. If possible, medications with the least potential harm to the fetus should be chosen. There are several medications that are used for maintenance therapy, such as inhaled tobramycin and dornase-α, which have a class C designation. The use of these medications should be determined on an individual basis.

Breast-Feeding

Breast milk appears to be normal in women with CF, including normal ionic concentration levels and normal levels of available nutrients.[265] Breast-feeding requires an additional intake of up to 500 kcal per day for the healthy mother[266] and appears to be well-tolerated by the woman with CF as long as she is able to meet the increased caloric demands.

Bone and Joint Disease

Bone Disease

Many individuals with CF experience bone and joint disease, including low bone mineral density (BMD). A CFF Consensus Conference on these topics was convened in 2002. Bone disease (*ie*, osteopenia or osteoporosis) may lead to kyphosis and fractures. These problems occur more commonly in adults and those who have undergone lung transplantation.[267–271] The prevalence of bone disease in patients with CF depends on the health status of the individual (including severity of lung disease and nutritional status) and the definition of bone disease. Low BMD has been widely reported in children and adults with CF, and is associated most closely with low BMI and low lung function. The prevalence of osteoporosis in CF adults varies from 38 to 77%[268,272–276] and is higher than that reported in children (19 to 67%).[272,277–280]

The pathogenesis of low BMD in CF patients involves both decreased levels of osteoblasts (*ie*, bone-forming cells) and increased levels of osteoclasts (*ie*, bone-resorbing cells). These data are supported by bone metabolism studies demonstrating accelerated bone resorption (*ie*, increased urinary cross-linked N-telopeptides of type-I collagen) and diminished bone formation (*ie*, low serum osteocalcin levels),[281] but further studies need to be conducted before a clear understanding of bone metabolism in CF evolves. Low vitamin D levels, found commonly in CF children and adults,[275,279,282,283] may contribute to reduced bone formation, but osteomalacia or diminished bone mineralization has not been well-documented. GI absorption of calcium is impaired in persons with CF as well.[284] Vitamin-D insufficiency may result from diminished sunlight exposure, poor vitamin D absorption, or accelerated vitamin D catabolism. Hypogonadism and low growth factor levels also may exacerbate low BMD.[280] Other, unidentified factors also may affect bone formation in CF. Accelerated bone breakdown probably results from corticosteroid exposure, diminished physical activity, and chronic pulmonary inflammation, with the latter mediated potentially by inflammatory cytokines.[285] After lung transplantation, an accelerated decline in BMD may result from immunosuppressant therapies or chronic posttransplant problems (*eg*, obliterative bronchiolitis).

Screening and Diagnosis: Dual-energy radiograph absorptiometry (DEXA) is a safe, accurate, fast, and inexpensive method of measuring BMD at the spine, femur, and other sites. Lateral chest radiographs can detect kyphosis, vertebral compression fractures, and osteopenia, but are insensitive to low BMD when compared to DEXA. Nonetheless, since chest radiographs are available on all patients, the presence of osteopenia, kyphosis, or vertebral fractures should encourage a more quantitative measure of bone mass by DEXA. As a general rule,

children and adults with CF should be screened for bone disease by DEXA and, if BMD is normal (Z score [± SD] in children, 0 ± 1; and T score in adults, 0 ± 1), rescreening every 2 to 5 years may help to determine the rate of bone growth or loss. Z score, the number of SDs above or below age-matched control subjects, is used most often to define bone disease in children. T score, the number of SDs that a BMD measurement is above or below peak bone mass (which occurs between 25 and 30 years of age), is used most often to define bone disease in adults. For each SD below peak bone mass, the risk of fracture doubles.[286] Osteopenia is defined as a T score between − 1.0 and − 2.5, and osteoporosis as a T score < − 2.5.[287]

Treatment Recommendations: The treatment of established bone disease in CF patients has not been well-studied. Encouraging weight-bearing exercise, exposure to sunlight to promote vitamin D formation, maintaining a good nutritional status, and the proactive management of pulmonary infection are reasonable measures to maintain or increase BMD. Calcium and vitamin D supplementation is probably a useful intervention based on clinical studies in non-CF patients with low BMD. Calcium supplements in the form of calcium carbonate should be at least 1 g/d, an intervention that does not increase (and may decrease) the risk of nephrolithiasis. Predicting the optimum vitamin D supplement is not easy because of the variability in absorption of vitamin D.[288] Vitamin supplements that contain vitamins A, D, E, and K probably are not sufficient when used alone if vitamin D deficiency exists in adults.[282] For vitamin D deficiency (*ie*, serum 25-OHD level, < 18 to 20 ng/mL), vitamin D supplementation should be individualized to obtain a serum 25-OHD level of > 18 to 20 ng/mL and preferably > 30 ng/mL. If osteopenia is present in adults, as defined above (or in children as evidenced by a Z score between − 1 and − 2.5), one should supplement with vitamin D to keep 25-OHD levels at > 18 to 20 ng/mL. Advice from an endocrinology consultation may be helpful to exclude sex hormone deficiency and other predisposing conditions. If Z scores in children are < − 2.5 or T scores in adults are < − 2.5 (the definition of osteoporosis) and/or minor trauma fractures or kyphosis occur, a more aggressive stance toward therapy should be initiated. Preliminary data suggest that pamidronate, an IV bisphosphonate, is very useful to remineralize bone in patients with CF who have had osteopenia, osteoporosis, or both before,[289] and after lung transplantation.[290] Bone pain and fever may occur in the former group, but not the latter group, limiting the usefulness of this therapy. In adults, therapy with oral bisphosphonates (*eg*, alendronate) or calcitonin may be useful based on anecdotal reports in CF and well-controlled trials in non-CF patients. The evaluation and treatment of patients with CF who are lung transplant candidates is of particular importance given the anticipated exposure to immunosuppressants. Fractures should be managed conventionally with immobilization and short-term opioid analgesics. Calcitonin may be particularly helpful for vertebral fracture-associated pain. Currently, multiple trials are underway to study different therapies for CF bone disease.

Joint Disease

Joint disease affecting adults with CF may present as episodic arthritis and/or hypertrophic pulmonary osteoarthropathy (HPOA). Arthropathy occurs in up to 12% of patients with CF, is more common in adults, and appears to be caused by immunologic processes.[291] Acute episodes may affect all joints, are usually asymmetric, present with swollen, hot, red, and tender joints, often cause incapacitating pain, typically last 7 to 10 days, and usually are not erosive.[292] Serologic analysis to exclude other causes of arthritis should be considered. Joint fluid analysis is usually nonspecific and may be noninflammatory, but synovial tissue is often hyperemic and inflamed.[293,294] Short courses of nonsteroidal and steroidal anti-inflammatory medications are very useful in the management of CF arthritis. HPOA, which is similar to arthritis, is more common in adulthood (median age of onset, 20 years), affecting approximately 8% of patients, and is characterized by chronic, proliferative long-bone periostitis, causing symmetrical bone pain and painful oligosynovitis in the large joints.[295,296] Unlike arthritis, HPOA exacerbations tend to accompany pulmonary infectious exacerbations. The etiology of HPOA is unknown. Radiographic findings, which are specific but not highly sensitive, include periosteal new bone formation at the distal ends of long bones.[297] Therapy with nonsteroidal anti-inflammatory agents is usually successful, but some patients require more potent analgesia.

End-of-Life Options

Despite substantial therapeutic advances, CF remains uniformly fatal, and little has been written about end-of-life care for patients and their families.[298,299] Barriers to optimum end-of-life care for these patients include the following:

1. Difficulty predicting the timing of death. The most widely quoted predictive model[300] has been called into question.[144,301,302]

2. The influence of lung transplantation on decisions about end-of-life care.
3. Personal fears or lack of confidence have prompted many physicians to avoid dealing with the reality of dying with its requirements for communicating "bad news" and prognosis, negotiating clear goals of care, and advance care planning.[303]
4. Fears of opiate addiction and exaggerated risks of adverse effects result in undertreatment/inadequate control of symptoms in dying patients.[298,303]

Palliative Care

The amelioration of human suffering is an important goal for health-care providers. The attitudes, skills, and behaviors that physicians use to relieve suffering and improve quality of life for patients with life-threatening illnesses are termed *palliative care*. It may be combined with therapies aimed at restoring or prolonging life (*eg*, restorative care), or it may be the total focus of care.[303] An appropriate combination of restorative and palliative care is the hallmark of optimum management for patients with CF and their families. Palliative care includes, but is not limited to the following:

1. Interdisciplinary approach (involving the physician, nursing, social work, psychology, respiratory and physical therapy, pastoral care, and others).
2. Skilled management of symptoms that may cause suffering (*eg*, pain and dyspnea). This is the *sine qua non* of palliative care for patients with CF. Headaches and chest pain sharply increase in the 6 to 12 months prior to death in adults.[304] Opiates can be effective for pain and dyspnea without causing respiratory depression.[304–306] Issues such as anxiety, depression, and fatigue also require attention.
3. Efforts to maximize quality of life as defined by patient and family.
4. Family and care provider education, and training to improve patient care.
5. Assessment and treatment of psychological, social, and spiritual distress.
6. Respite care for family and care providers.
7. Assistance to plan for the last days of life, preparation of wills and other important documents, and planning for death, funeral, memorial service, burial, or cremation.
8. Loss, grief, and bereavement support for patient, family, and care providers.

Advance Care Planning

Planning is essential and should occur early in the course of the illness. The care team should be open, honest, and sensitive to family and cultural issues. Advance care planning is a process of structured discussion and documentation woven into the regular process of care. The goal is to ensure that a patient's wishes will be respected. It is a process that helps patients identify and clarify their personal values and goals about health, chronic illness, and medical treatment. The patient identifies the care they would like to receive in various situations. They also determine the person or persons whom they would like to make health-care decisions on their behalf in the event they cannot make decisions for themselves.[303] The sense of control and peace of mind that this process fosters in the patient and the family, and the anxiety reduction for proxy decision-makers are important benefits.[303] Most adults with CF have considered their wishes, often are aware of decisions made by others with CF, and are likely to be relieved when the physician discusses the issues with honesty and sensitivity. Finally, the physician and CF team should be flexible and should offer choices for the location of terminal care and dying (*ie*, critical care unit, private hospital room, hospice, or home with requisite support).

Assisted Ventilation

Assisted ventilation for respiratory failure was thought of as futile for patients with CF at one time.[307] However, that has changed dramatically with the advent of noninvasive modes of ventilatory support[308–310] and lung transplantation. One report[311] has suggested that even patients with respiratory failure may benefit from ventilatory support and that this form of therapy should be considered, particularly in patients awaiting lung transplantation. The issue of whether and when to use mechanical ventilation in CF patients may complicate end-of-life care. End-of-life care may be more difficult in a critical care setting. While offering some hope, the care team also must be realistic in presenting options to patients and their families. At most centers, only a minority of patients will survive an episode of respiratory failure long enough to have the opportunity for lung transplantation. The withdrawal of ventilatory support may become a common terminal event for patients with CF.

Lung Transplantation

Lung transplantation became a viable option for CF patients $>$ 10 years ago, but there is substantial morbidity and mortality associated with the proce-

dure.[312] The 5-year posttransplant survival rate is approximately 50%. In addition, the cadaveric organ donor supply has lagged behind the number of potential transplant recipients, resulting in longer and longer waiting times. The inadequate supply of donor lungs has led to the development of the living donor, bilateral lobar transplant procedure[313] as an alternative to the standard cadaveric procedure. This procedure raises unique questions because of the potential morbidity and mortality to the healthy donors. However, if suitable donors are available, the major advantage of this approach is that it can be performed on patients who are unlikely to survive long enough on the waiting list to receive cadaveric organs. The limited data available suggest that posttransplant survival following this procedure may be shorter than that following the standard cadaveric procedure.[314]

The adult care team regularly faces difficult decisions about candidacy for transplantation. The rationale underlying selection criteria for lung transplant candidates has remained constant since the procedure was first performed. Patients are considered who have limited survival and have exhausted conventional therapies. The hope is that the procedure will prolong survival and improve quality of life. The International Society of Heart and Lung Transplantation and the American College of Chest Physicians have published guidelines with specific selection criteria.[315,316]

Since 1992, the selection of CF patients for transplantation has been heavily influenced by a survival model based on percent predicted FEV_1. The model suggested that 2-year mortality rate approaches 50% for CF patients with an $FEV_1 < 30\%$ of predicted.[300] It was recommended that clinicians consider referral of such patients for transplant evaluation. The survival implications of an FEV_1 of $< 30\%$ of predicted have been revisited more recently.[143,301,302] It is clear that FEV_1 alone is inadequate in identifying appropriate candidates for transplantation. A more precise, validated survival model[144,317] that incorporates several additional parameters can identify a subset of CF patients who will more likely gain a survival advantage from the procedure. These parameters (*eg*, gender, nutritional status, diabetic status, sputum microbiology, and number of pulmonary exacerbations) are readily available in the clinical setting. The CF care team should consider including this tool in their assessment of potential lung transplant candidates. Close communication between the CF care team and the transplant center is very important in identifying appropriate candidates for transplant, and in the choice and timing of the procedure.

Appendix: Participants

This list reflects current positions held by participants as of October 2002.

Moira L. Aitken, MD
Director, Adult CF Clinic
Associate Professor
Pulmonary & Critical Care Division
University of Washington
Seattle, WA

Robert Aris, MD
Associate Professor
University of North Carolina at Chapel Hill
Chapel Hill, NC

John D. Armstrong II, MD
Professor and Associate Director
Health Care Ethics, Humanities & Law Program
University of Colorado Health Sciences Center
Denver, CO

Robert J. Beall, PhD
President and CEO
Cystic Fibrosis Foundation
Bethesda, MD

Michael P. Boyle, MD
CF Adult Program Director
The Johns Hopkins Hospital
Baltimore, MD

Preston W. Campbell III, MD
Executive Vice President For Medical Affairs
Cystic Fibrosis Foundation
Bethesda, MD

Cam Cooper
Chairman of the Board of Trustees
Cystic Fibrosis Foundation
Atlanta, GA

Joan Finnegan Brooks
President, MA/Rhode Island Chapter
Cystic Fibrosis Foundation
Natick, MA

Patrick A. Flume, MD
Associate Professor
Adult CF Program Director
Medical University of South Carolina
Charleston, SC

Daina E. Kalnins, BSc, RD, CNSD
Nutritionist/Dietitian
Respiratory Medicine
The Hospital For Sick Children
Toronto, ON, Canada

Michael R. Knowles, MD
Professor of Medicine
CF Adult Program Director
University of North Carolina at Chapel Hill
Chapel Hill, NC

Bruce C. Marshall, MD
Director of Clinical Affairs
Cystic Fibrosis Foundation/Cystic Fibrosis Foundation Therapeutics
Bethesda, MD

Susanna A. McColley, MD
CF Center Director
Northwestern University Medical School
Children's Memorial Hospital
Chicago, IL

Mary Jo McCracken, RN, MA, CPNP
Pediatric Pulmonary Nurse
University of Minnesota
Minneapolis, MN

Gwendolyn J. McDonald, RN, MS
Coordinator, Adult CF Clinic
University of Washington Medical Center
Seattle, WA

Sheila Morrison-Henderson, MSW, LCSW
Social Work Department
University of North Carolina at Chapel Hill
Chapel Hill, NC

Joseph P. Neglia, MD, MPH
Associate Professor
Department of Pediatrics and Epidemiology
University of Minnesota
Minneapolis, MN

Barbara L. Palys
Advisor
Cystic Fibrosis Worldwide
Harvard, MA

H. Worth Parker, MD
CF Adult Program Director
Northern New England CF Group
Dartmouth-Hitchcock Medical Center
Lebanon, NH

Suzanne Pattee, JD
Vice President For Public Policy & Patient Affairs
Cystic Fibrosis Foundation
Bethesda, MD

Walter M. Robinson, MD, MPH
Pulmonary Division
The Children's Hospital
Boston, MA

David Rodman, MD
CF Adult Program Director
Professor, University of Colorado Health Sciences Center
Denver, CO

Beryl J. Rosenstein, MD
CF Center Director
Professor, Department of Pediatrics
Vice President For Medical Affairs
The Johns Hopkins Hospital
Baltimore, MD

Richard H. Simon, MD, PhD
Professor, Internal Medicine
University of Michigan Health Science Center
Ann Arbor, MI

Ronald J. Sokol, MD
Associate Professor of Pediatrics
The Children's Hospital
University of Colorado Health Sciences Center
Denver, CO

Beth Sufian, JD
Attorney and Counselor at Law
Sufian and Passamano
Houston, TX

Elizabeth Tullis, MD, FRCP (C)
Adult CF Clinic Director
St. Michael's Hospital
Toronto, ON, Canada

Carol Campbell Welsch, MSW
Senior Clinical Social Worker
Pediatric Pulmonary Department
University of Michigan Health System
Ann Arbor, MI

James R. Yankaskas, MD
CF Adult Program Director
Professor of Medicine
CF/Pulmonary Research & Treatment Center
University of North Carolina at Chapel Hill
Chapel Hill, NC

Jonathan B. Zuckerman, MD
CF Adult Program Director
Maine Medical Center
Portland, ME

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