Concise Clinical Review

Managing Cystic Fibrosis

Strategies That Increase Life Expectancy and Improve Quality of Life

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The survival of patients with cystic fibrosis (CF) continues to improve. The discovery and cloning of the CFTR gene more than 21 years ago led to the identification of the structure and function of the CFTR chloride channel. New therapies based on the understanding of the function of CFTR are currently under development. The better clinical status and improved survival of patients with CF is not only a result of understanding of the molecular mechanisms of CF but also a result of the development of therapeutic strategies that are based on insights into the natural course of the disease. Current CF treatments that target respiratory infections, inflammation, mucociliary clearance, and nutritional status are associated with improved pulmonary function and reduced exacerbations. Patients benefit from treatment at a specialized CF center by a multidisciplinary dedicated team with emphasis being placed on frequent visits, periodic testing, and monitoring adherence to therapy. The purpose of this review is to survey recent developments in CF care that are responsible for the improved survival and quality of life of patients with CF.

Keywords: cystic fibrosis; treatment; survival; prognosis; lung function

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disorder among whites, with a rate of 1 case per 2,500 births. There are an estimated 80,000 children and young adults with CF worldwide. In 1989 the CF Transmembrane Conductance Regulator (CFTR) gene was cloned (1–3). Mutations in the CFTR gene result in absence or dysfunction of the protein that regulates ion transport across the apical membrane at the surface of certain epithelia. Although CFTR functions mainly as a chloride channel, it has many other roles, including inhibition of sodium transport through the epithelial sodium channel, regulation of the outwardly rectifying chloride channel, ATP channels, intracellular vesicle transport, and inhibition of endogenous calcium-activated chloride channels (4, 5). CFTR is also involved in bicarbonate–chloride exchange. A deficiency in bicarbonate secretion leads to poor solubility and aggregation of luminal mucins (6). Obstruction of intrapancreatic ducts with thickened secretions causes autolysis of pancreatic tissue with replacement of the body of the pancreas with fat, leading to pancreatic insufficiency with subsequent malnutrition. In the lungs, CFTR dysfunction leads to airway surface liquid (ASL) depletion and thickened and viscous mucus that adheres to airway surfaces (7). The result is decreased mucociliary clearance (MCC) and impaired host defenses. Dehydrated, thickened secretions lead to endobronchial infection with a limited spectrum of distinctive bacteria, mainly *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airways disease. Pulmonary insufficiency is responsible for most CF-related deaths.

When CF was first recognized by Dorothy Andersen in 1938 as a specific entity (8), most patients died shortly after diagnosis. However, data from a number of patient registries (9–12) show that over the last 4 decades the survival of patients with CF has progressively improved. According to the U.S. Cystic Fibrosis Foundation Patient Registry Annual Data Report, the median predicted survival age for patients has increased from 25 years in 1985 to 37 years in 2008 (10). The length of survival is directly correlated to the decade the patient was born (10), and patients born today are expected to have a median survival into their sixth decade (9). The observed increased survival of the patients with CF is due to better insights into the natural course of the disease leading to treatments that target respiratory infections, inflammation, MCC, and nutritional status. The purpose of this article is to review the strategies that increased the survival and quality of life in patients with CF.

ENHANCEMENT OF MUCOCILIARY CLEARANCE

CF is characterized by retained dry thick mucus that serves as a nidus for chronic infection. Airway clearance is considered an integral component of the management of CF. Several mechanical devices and airway clearance techniques, specifically tailored to the needs of patients with CF, were developed to promote airway clearance (13). These include the active cycle of breathing techniques, autogenic drainage, positive expiratory pressure (PEP) masks, Flutter, and Acapella (13). In the United States, high-frequency chest wall oscillation devices are widely used. Short-term studies have shown a benefit for airway clearance maneuvers compared with no intervention; however, long-term well-controlled studies are lacking (14). There are no airway clearance techniques (ACTs) that were demonstrated to be superior to others (15), so the prescription of ACTs should be individualized. It is also unclear if during the early phase of CF lung disease, while the patient is asymptomatic and with no signs of lung involvement, practicing physiotherapy for airway clearance is beneficial. Recent CF pulmonary guidelines recommended that daily airway clearance should be provided to all patients with CF (16). Aerobic exercise is recommended as an adjunctive therapy for airway clearance and for its additional benefits to overall health (16).

Because the primary initiating event for airway obstruction in CF is the dry and thick mucus, mucolytics are a logical first-line therapy. The viscid nature of CF sputum is largely due to DNA from the vast numbers of degenerating neutrophils

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present in the airways. Clinical studies showed that inhalation of recombinant human DNase (dornase alfa, or Pulmozyme) was associated with improved lung function (17, 18), improved high-resolution chest CT scores (19–21), better overall well-being, and a reduction of exacerbations (17). The recommended dose is 2.5 mg in a one-time use ampoule inhaled once daily; some individuals may benefit from twice-daily inhalation. Several studies suggested that dornase alfa prevents the progression of airway inflammation in patients with near-normal lung function (18, 22–24). This has led to recently published guidelines for chronic therapies in CF suggesting that there may be a role for dornase alfa even in young patients in whom CF lung disease may not be apparent (18, 21, 25).

CFTR dysfunction is associated with ASL depletion and thickened viscous mucus that adheres to airway surfaces resulting in decreased MCC. Rehydrating agents, which reestablish the hydration state of the ASL by drawing water from the interstitium into the ASL via imposed transepithelial osmotic gradients, can improve MCC rates. Osmotic agents also may stimulate mucus clearance by increasing ciliary beat frequency and cough clearance (26). Inhaled hyperosmolar agents such as hypertonic saline induce osmotic flow of water into the mucus layer, thereby rehydrating secretions and improving mucus rheology and transportability of sputum (27, 28) and increasing hydration of the airway surface (29, 30). Inhalations of hypertonic saline (4 ml twice daily after pretreatment with bronchodilators) improved MCC and lung function and reduced exacerbation rates in patients with CF (31–34). This improvement in mucociliary function may reduce bacterial load and chronic inflammation within the airways with a concomitant stabilization of lung function. Although the question whether hypertonic saline improves MCC *in vivo* remains open, the reduction in pulmonary exacerbations is sufficient to recommend the therapy as a second line to rhDNase (35). Hypertonic saline is inexpensive, safe, and well tolerated in young children (34).

The variation in response seen in individuals to both rhDNase and hypertonic saline raises the possibility that certain individuals will respond better to one agent compared with the other (36). Although both treatments are recommended as single agents to improve MCC, the potential additive or synergistic effect of using them together has not been established.

PREVENTION OF INFECTION WITH *P. AERUGINOSA*

Respiratory infection with *P. aeruginosa* is well recognized as a leading cause of morbidity and mortality in patients with CF (37–41). The presence of *P. aeruginosa* in the lower airways is associated with a more rapid decline in pulmonary function, worsening nutritional status, more hospital admissions, and a shorter life expectancy (37, 38). One of the keys to successful management of CF is to prevent infection with *P. aeruginosa*.

The mechanism of acquisition and maintenance of *P. aeruginosa* infection in the CF lungs is unclear. *P. aeruginosa* is found in many natural and domestic environments, including plants, soils, and surface water, especially warm moist environments containing organic material or contaminated human or animal waste. Laboratory studies have shown that *P. aeruginosa* can survive within droplet nuclei and can potentially remain suspended within aerosols for prolonged periods (42). A number of clinical studies have demonstrated that patients with CF can produce aerosols containing *P. aeruginosa* that can be transmitted to other patients with CF (42). Cross-infection between patients was shown to occur among siblings (43) or during social/communal events such as summer and winter camps (44, 45). The route of cross-infection between people with CF is not clear, but there is evidence the airborne route is important. During coughing, patients with CF produce viable aerosols of *P. aeruginosa* and other gram-negative bacteria of respirable size range (46). Several methods are used to reduce the risk of cross-infection, including avoiding close social or intimate contact between patients (47). In the absence of appropriate infection-control measures, transmissible strains pose a threat to *P. aeruginosa*–negative patients by creating an increased acquisition risk for infection (48–50). Clinical experience also suggests that early infection by transmissible multiresistant strains may be more difficult to eradicate than infection by sporadic strains (49).

There is increasing evidence that antibiotic therapy initiated early after the onset of *P. aeruginosa* infection is an effective strategy to eradicate the organism in the majority of cases and thereby postpone chronic colonization (51, 52). Because *P. aeruginosa* strains infecting CF airways at early stages are sensitive to antibiotics, their eradication is often achieved without the development of antibiotic resistance (53). Although several protocols for eradication of *P. aeruginosa* after the first isolation are in use (50–52, 54–56), no consensus exists regarding the optimal antibiotic protocol. Eradication therapy with either a colistin/ciprofloxacin regimen or with nebulized tobramycin is being attempted. The recent EarLy Inhaled Tobramycin for Eradication (ELITE) study has provided the first randomized comparison of eradication regimens of different durations. It demonstrated that a 28-day regimen of inhaled tobramycin (300 mg b.i.d.) is effective in treating early *P. aeruginosa* infection (57). No therapy was shown to be effective in preventing *P. aeruginosa* colonization. Three-monthly cycles of intravenous anti–*P. aeruginosa* prophylaxis in *P. aeruginosa*–negative children did not prevent initial or chronic infection (58). Based on these and similar studies, the current strategies to reduce *Pseudomonas* colonization in CF are by adherence to infection control measures and early and aggressive eradication of new *P. aeruginosa* colonization (54–56, 59).

Although *P. aeruginosa* is found in airway secretions in a high proportion of patients with CF, other less common microorganisms, such as *B. cepacia* or nontuberculous mycobacteria, are also likely to play a role in the pathogenesis of CF airway disease. Methicillin-resistant *S. aureus* (MRSA) is an important emerging pathogen in CF. The prevalence of MRSA in the respiratory tract of individuals with CF has increased substantially, and according to one study it is now more than 20% (60). MRSA is associated with worse survival, and aggressive treatment aimed to eradicate MRSA should be considered (60).

SUPPRESSION OF CHRONIC *PSEUDOMONAS* COLONIZATION

Chronic colonization of the airways with *P. aeruginosa* bacterium is associated with a more rapid decline in lung function (37). Although multiple factors can potentially explain the susceptibility of CF airways to this organism, their individual relevance is still largely unclear. The persistence of chronic *P. aeruginosa* lung infection in patients with CF is mainly due to biofilm-growing mucoid (alginate-producing) strains. Bacterial biofilms cause chronic infections because they show increased tolerance to antibiotics, resist phagocytosis, and are relatively impervious to other components of the innate and the adaptive immune system (61, 62). The inability to eradicate chronic *P. aeruginosa* infections in patients with CF, even with high-dose antibiotics, necessitates multiple courses of antibiotics to control the bacterial load in the airways and improve lung function (63). The Copenhagen CF center has advocated intensive intravenous antibiotic therapy (2 wk of intravenous antibiotic

therapy every 3–4 mo) for chronic *P. aeruginosa* infections, which seemed to restrain but not eradicate the bacteria (12, 64). However, other studies do not support this approach (58). The efficacy of inhaled tobramycin has been investigated in patients with mild-to-moderate CF and established chronic *P. aeruginosa* infection in a series of short- and long-term randomized controlled studies (65). Inhaled tobramycin was shown to produce sustained improvements in lung function in patients with CF and confirmed *P. aeruginosa* infection (66). This intervention is associated with other indirect benefits, such as improved patient nutritional status, hospitalization time, and the requirement for intravenous antipseudomonal antibiotics. The Cystic Fibrosis Foundation (CFF) recommends the chronic use of inhaled tobramycin for patients with CF with persistent colonization of *P. aeruginosa* of the airways (25). The recommendation is directed to patients with severe disease to improve their lung function and also to asymptomatic patients with mild lung disease to reduce the rate of exacerbations (25). Recently, tobramycin inhalation powder was developed to enhance airway delivery efficiency, shorten delivery time, and increase patient adherence (67).

The intermittent inhalations strategy (every other month) has been challenged lately. Many centers have moved to a continuous treatment strategy, whether with one drug or alternating drugs. A recent study suggested that inhalations of colistin-tobramycin combination were more efficient than respective single antibiotics for killing *P. aeruginosa* in biofilms *in vitro*, and demonstrated significantly reduced *P. aeruginosa* cell counts in a rat lung infection model and in patients with CF (68).

Other inhaled antibiotics are being used in some centers, although insufficient scientific evidence of efficacy has yet to be obtained (69). Recently, repeated intermittent 28-day courses of inhaled Cayston (aztreonam for inhalation solution) were shown to improve lung function and health-related quality of life in patients with CF infected with *P. aeruginosa* (70). This drug is now available in the United States. Other new inhaled antibiotics are at different stages of clinical trials and are expected to be available in the near future (71, 72).

EARLY AND AGGRESSIVE TREATMENT OF PULMONARY EXACERBATIONS

The natural history of CF lung disease is one of chronic progression with intermittent episodes of acute worsening of symptoms termed pulmonary exacerbations (73, 74). Although a generally accepted definition of a pulmonary exacerbation has not been developed, clinical features of an exacerbation include increased cough and sputum production, shortness of breath, chest pain, hemoptysis, loss of appetite, loss of weight, and a decline in lung function (74–76). Pulmonary exacerbations can cause abrupt decline in lung function that may not be fully reversible (75) and therefore should be prevented or treated without delay. Early recognition and vigorous management of pulmonary exacerbations is crucial to the maintenance of lung function, good quality of life, and survival. The current guidelines for treatments of exacerbations recommend increased airway clearance therapy and the addition of antibiotic therapy that is based on the results of the most recent sputum culture (73, 77). However, it remains to be determined whether the optimal treatment should be with oral, inhaled, or intravenous antibiotics, and whether this treatment should be provided in a hospital setting or at home (78). Also unresolved is the issue of the number of antibiotics to be used and the duration of therapy (73). Therapeutic strategies that have been shown to reduce exacerbations are strongly recommended, and include the chronic use of inhaled tobramycin in patients infected with *P. aeruginosa*, daily inhalations with Pulmozyme, inhalations of hypertonic saline twice daily, and prolonged oral azithromycin administration (25, 79). Furthermore, during an exacerbation patients may become catabolic and appetite may be diminished, and therefore nutritional support should be considered.

TREATMENT OF AIRWAY INFLAMMATION

Airway inflammation in patients with CF begins early in life and results in increased airway obstruction and progressive damage. An exaggerated inflammatory response, relative to the burden of infection, is responsible for much of the pathology found in the CF lungs (80–82). The respiratory system in CF is characterized by high concentrations of neutrophils and proinflammatory cytokines with reduced concentrations of antiinflammatory factors (83, 84). Monitoring airway inflammation continues to be a challenge as the currently available sputum markers show considerable variability in expression, and systemic markers are frequently negative despite significant airway inflammation. The role of antiinflammatory agents in CF has been the subject of intense investigation, and the antiinflammatory therapies described below have been shown to significantly reduce the rate of respiratory exacerbations and cause slight improvement in pulmonary function (85–88).

Macrolides**,** mainly azithromycin, are being used to reduce inflammation in patients with CF colonized with *P. aeruginosa.* Azithromycin given orally 3 times a week, 250 mg (below 36 kg of weight) or 500 mg (more than 36 kg of weight) was shown to significantly reduce the number of respiratory exacerbations and the rate in decline of lung function as well as improving quality of life (85, 89, 90). It can also reduce sputum viscosity and airway adhesion of *P. aeruginosa* and disrupt the ability of the bacteria to produce alginate (91). Recently, azithromycin was also associated with a significant reduction in pulmonary exacerbations and a significant increase in weight gain in patients not infected with *P. aeruginosa* (92). The pharmacological mechanism that causes the beneficial effect in CF is unclear. Most of the data concerning CF have been extrapolated from other disease models, such as diffuse panbronchiolitis (93). Side effects of azithromycin are mild, with no increased *P. aeruginosa* resistance (85).

High-dose ibuprofen (25 mg/kg/dose) given orally twice a day was shown in randomized controlled studies to significantly slow the rate of decline in FEV_1 when compared with placebo (94). The effect was most dramatic for patients who were less than 13 years of age at the time of enrollment and with milder lung disease (94, 95). Despite its apparent benefit, ibuprofen is infrequently administered due to the need to measure plasma levels and because of potential gastrointestinal and renal side effects that are more common when administered together with aminoglycosides.

An exuberant inflammatory response to chronic infection characterized by recruitment of massive numbers of neutrophils to the airways is an important contributor to the tissue destruction that characterizes CF lung disease. However, distinct cytokine production by lung and blood neutrophils was demonstrated in children with CF (96). Several studies reported beneficial effects of systemic corticosteroids, especially in children who have mild lung disease. However, the improvement was transient and was associated with significant adverse effects, such as diabetes and cataracts (97). Therefore, systemic corticosteroids are not recommended as a routine therapy. The use of inhaled corticosteroids (ICS) in patients with CF is controversial. Controlled studies have not demonstrated a statistically

significant improvement in lung function, nor has discontinuing ICS in patients receiving long-term ICS therapy led to decline in lung function (98). A Cochrane review concluded that evidence is "insufficient to establish if ICS have a beneficial or harmful effect in people with CF" (99). Similarly, an expert committee assembled by the CFF recently advised against the use of ICS as antiinflammatory agents in adults and children 6 years of age or older who do not have asthma (25). ICS may be considered for patients with CF who have asthma or allergic bronchopulmonary aspergillosis (ABPA). Diagnosing asthma in patients with CF can be problematic; wheezing is a common physical finding (100), and this may be the result of the underlying CF lung disease rather than classic asthma. Asthma should be considered as a diagnostic possibility if a child has episodic airway obstruction that is relieved by bronchodilators, a strong family history of asthma, evidence of atopy (such as eczema or hay fever), and/or laboratory evidence of allergy such as eosinophilia or elevated IgE (101). Although the use of ICS has not been specifically studied for CF-associated asthma, it makes sense to initiate a trial for patients with recurrent episodes of bronchospasm and continue therapy if there is a clinical response.

EARLY DIAGNOSIS AND PREVENTION OF NONAPPARENT LUNG DAMAGE

It is conceivable that early intervention, before lung disease is established, will provide the most significant long-term benefits for patients with CF. In young children and patients with mild disease, lung pathology is frequently underestimated (19, 102, 103). A recent report from Australia demonstrated that a substantial number of asymptomatic infants, diagnosed by newborn screening (NBS), already had active pulmonary inflammation and infection with evidence of structural lung damage at 3 months of age (102). A study from the United States showed that children diagnosed before developing symptoms had better pulmonary function throughout early childhood compared with those who were symptomatic at diagnosis (104). Therapies that were shown to be beneficial in terms of delaying the development and progression of pulmonary disease when given early were physiotherapy, inhalations of hypertonic saline, Pulmozyme, and antibiotics and antiinflammatory drugs (21, 105, 106).

Early diagnosis is critical to intervene without delay in patients with CF. Despite the wide availability of the sweat test, CF diagnosis can be missed in early childhood. Therefore, NBS offers the opportunity for early intervention that may lead to improved outcomes (107). Lung function, measured by forced expiration, is usually normal in infants diagnosed by NBS at the time of diagnosis (108). Furthermore, children who were diagnosed by NBS were in a better nutritional state compared with their peers who were diagnosed based on clinical manifestations (109–115). Because nutrition and lung function are interrelated, it can be expected that early identification of patients by NBS will improve survival. Immediate referral to a CF center, as recommended by the guidelines for follow-up of infants diagnosed by NBS, will facilitate assessment of pancreatic function and the introduction of pancreatic enzymes, fat-soluble vitamins, and enhanced energy intake that will allow children with CF to achieve near-normal growth (116–118).

CORRECTION OF ENERGY IMBALANCE AND MAINTENANCE OF GOOD NUTRITION

In most patients with CF, the earliest manifestations of the disease are related to its associated gastrointestinal and nutritional derangements. Destruction of acinar pancreatic tissue, pancreatic ductular obstruction, and lack of enzymatic activity lead to malabsorption (particularly of fats), diarrhea, and failure to thrive. Progressive lung disease further increases calorie requirements by increasing the work of breathing. In addition, chronic pulmonary infection and inflammation are associated with reduced appetite. Without intervention, many patients develop malnutrition. Longitudinal studies demonstrate that undernutrition is closely related to the decline of lung function and early infection with *P. aeruginosa* (119–122). Wasting was shown to be a significant predictor of survival independent of lung function, arterial blood oxygen, and carbon dioxide tensions (115). In the 1970s the Toronto CF Clinic showed that a high-fat, high-calorie diet promoted a normal growth pattern that was associated with improved survival (123). Since then proactive and aggressive approaches have been adopted to prevent and correct malnutrition. This includes the use of pancreatic enzyme replacement therapy with emphasis on high-calorie, high-protein, unrestricted diet and prevention of fat-soluble vitamin deficiency (123–125). Nutritional status should be monitored closely during routine visits to allow for early intervention once derangements are noted. In addition, the annual nutritional assessment should optimally include body composition, bone density, glucose tolerance, and various biochemical and micronutrient levels (124–126). Early and aggressive nutritional support with adequate pancreatic replacement management should lead to both normal growth and better lung function (127, 128).

EARLY IDENTIFICATION AND TREATMENT OF CF COMPLICATIONS

Prolonged survival exposes CF patients to complications that were rarely encountered previously. It is of utmost importance to diagnose these complications as early as possible and provide appropriate therapy.

CF-related diabetes (CFRD) is the most frequent comorbidity diagnosed today (129), occurring in approximately 40% of adults, 25% of adolescents, and 9% of children (130). CFRD is associated with a rapid decline in lung function (131) and increased risk of death from respiratory failure (132). The early diabetic or impaired glucose tolerance period occurring several years before the development of overt CFRD may accelerate the decline in the clinical status of patients with CF (131, 133). CFRD is often clinically silent, screening using an oral glucose tolerance test is recommended for early diagnosis. Oral glucose tolerance tests should be done annually by 10 years of age, and testing should be done when the patient's status is clinically stable. CFRD is diagnosed when fasting plasma glucose is greater than 125 mg/ml and/or a 2-hour postglucose challenge is greater than 199 mg/dl. Hemoglobin A1c has insufficient sensitivity as a screening tool; however, a level greater than 6.4% is suggestive of CFRD. Clinical care of the patient with CFRD requires an interdisciplinary team and it is critical that an experienced endocrinologist be an integral member of the team. Insulin is the mainstay of pharmacologic therapy and caloric reduction should not be part of the management. Treatment with insulin enhances the nutritional state and temporarily improves pulmonary function and delays the decline in FEV_1 (134). Recent mortality data show that the disparity between CFRD and CF without diabetes is narrowing and that the previously noted difference between female and male CFRD mortality has disappeared, perhaps related to more aggressive screening and treatment (10).

ABPA is an important complication of CF, with prevalence ranging from 1 to 15%, increasing with age (135). It is a pulmonary hypersensitivity disease mediated by an allergic re-

sponse to respiratory colonization by *Aspergillus fumigatus* (136). ABPA is manifested by wheezing, pulmonary infiltrates, bronchiectasis, and fibrosis. The diagnosis of ABPA in CF is difficult, and may often be delayed, because many of the diagnostic criteria overlap with common manifestations of CF. The following minimal essential criteria for diagnosing ABPA in patients with CF have been proposed: (*1*) asthma or airflow obstruction, (*2*) immediate cutaneous reactivity to *Aspergillus* species, (*3*) elevated total serum IgE concentration ($\geq$ 417 IU/ml or $\geq$ 1,000 ng/ml), (*4*) elevated serum IgE to *A. fumigatus* and IgG to *A. fumigatus*, and (*5*) central bronchiectasis. The use of classic criteria for ABPA has been proposed as well, including peripheral blood eosinophilia (137). A CFF consensus conference recommended annual screening of serum IgE levels, arguing that early treatment would prevent lung function decline and irreversible lung damage (137). Quick diagnosis and treatment of ABPA with systemic steroids is of fundamental importance in ameliorating the progression of lung disease and preventing deterioration to a severe fibrotic stage (138–140).

Gastroesophageal reflux (GER) is relatively common in CF, with a reported incidence varying from 6.4 to 20% (141). Factors such as chronic cough, hyperinflation, high-fat diet, overnight percutaneous endoscopic gastrostomy feeds, delayed gastric emptying, postural drainage in head-down tilted position, and some medications may cause or exacerbate GER. Studies have implicated GER as an important cause of respiratory disease in patients with CF either by pulmonary aspiration of refluxed gastric contents or by neutrally mediated reflex bronchoconstriction secondary to irritation of the esophageal mucosa (142–145). These may contribute to deterioration in pulmonary function and progression of lung disease (123) and malnutrition resulting from prolonged emesis and dysphagia. A significant correlation between esophageal acid exposure and the number of coughs per 24 hours has been reported (122). Patients with reflux and cough had poorer lung function than those who did not. The possibility that acid blockade improves the clinical course of CF has prompted many physicians to aggressively treat GER symptoms even though there is insufficient evidence supporting its benefit on lung disease in CF.

CENTERED CARE: REGULAR AND FREQUENT ROUTINE EVALUATION

The first report that documented the advantage of care in a CF center came from Denmark. Survival of patients treated in Copenhagen at the only CF center in Denmark was significantly better than survival of patients treated by local physicians (146). Subsequent reports from the United Kingdom showed that patients treated in CF clinics had better pulmonary function, nutritional status, and chest radiography scores than those treated in nonspecialized healthcare settings (147). A retrospective multicenter study showed that earlier referral of children with CF to specialist care is associated with significantly better FEV_1 and lower prevalence of *P. aeruginosa* at the age of 13 years (148). Another study showed that patients treated in a CF center had significantly higher rates of colonization with *P. aeruginosa* and *Burkholderia cepacia*; nevertheless, they were in a significantly better clinical condition compared with those who were treated in general clinics (147).

Centered care by a dedicated team of trained and experienced health professionals is essential for optimal patient management and outcome (147, 149–151). Care involves frequent clinical evaluations and monitoring for complications by physicians and other healthcare workers specifically trained in the management of CF (149). Data from the CFF database (10) and the German Cystic Fibrosis Quality Assessment Project (11) indicate that significant differences can be observed between centers regarding the clinical condition of patients. Analysis of pulmonary function data from the 194 U.S. centers showed that the patients at the top 25% centers had significantly better nutritional state than those treated in the centers in the lower quartile. The upper quartile sites were characterized by more clinic visits and more routine tests, such as spirometry and sputum cultures leading to more antibiotic therapy (150). A similar study in a pediatric patient population demonstrated that the centers with highest lung function scores for their patients were characterized by more clinic visits, more respiratory tract cultures, and frequent treatment of patients, particularly those considered to have mild lung disease (151).

ADHERENCE TO THERAPY

For many patients with CF, daily treatments with physiotherapy, inhalations, oral medicines, and nutritional support are time consuming and tiresome (152). Although no study has correlated poor adherence with worse outcome, it is likely that the consequences of poor adherence and avoidance of therapies may be associated with accelerated decline in lung function and the need for increased interventions with antimicrobials. Assessment of adherence to treatments should be done at every routine clinic visit and methods to increase adherence should be implemented when necessary (153–155).

For patients with minor or no symptoms, the feeling or appearance of well-being creates the false sense that the disease is not active, thereby reducing the motivation for adherence to prescribed daily regimens. In addition, therapy aimed at preventing complications is not associated with the direct perception of its efficacy in contrast to treatments for symptoms. Methods to increase adherence to therapy include education about the pathophysiology of the disease, the aims and mechanism of action of therapies, and the importance of adherence. Studies using behavioral techniques to increase adherence to treatment components have been conducted with varying results (156). Cell phone intervention was recently proposed to improve adherence in adolescents with CF (157).

Creating therapeutic alliances with the patients and their families is crucial to encourage patients' empowerment. Although the concept of the therapeutic alliance has its roots in psychoanalytic literature, it is an essential component of all types of therapy. Therapeutic alliance refers to the mutual collaboration established between a caregiver and a patient to overcome any resistance that might block the healing process. RICH (Respect, Information, Connection, and Hope) are the ingredients of empowerment (158). Providing *information* to patients about their disease, therapies, and prognosis in an appropriate language and in a *respectful* way will build a therapeutic alliance (*connection*) that is essential to promoting patients' empowerment and to supporting better adherence to therapies. Emphasizing to the patient the improvement in the survival of patients with CF, which is associated with adherence to recommended treatments, may provide motivation (*hope*) that will help the patient cope with the time-consuming and tiresome therapies.

SUMMARY

Significant improvement in the survival of patients with CF has been achieved in the last decades. The improved clinical status of the patients is mainly the result of a better understanding of the natural course of infection and inflammation in CF that has led to the implementation of strategies that increase the life

expectancy and quality of life of the patients. These strategies include prompt diagnosis, timely and aggressive nutritional support, augmentation of MCC and improved mucous drainage, initiation of antimicrobial and antiinflammatory therapy as soon as possible, early treatment of acute exacerbations, implementation of effective hygienic measures in and outside CF centers, and prompt identification and treatment of CF-related complications. Treatment at a specialized CF center by a multidisciplinary dedicated team, including frequent visits, and periodic routine tests are essential to detect and treat early changes. Adherence to these therapies is challenging and it should be discussed with the patients at every clinic visit. Creating therapeutic alliance with the patients and their families is essential to promoting patients' empowerment and supporting better adherence to therapies. Maintaining patients in optimal status will allow them to benefit from future treatments designed to correct or modify the basic genetic defect associated with CFTR by gene replacement therapy or pharmacological interventions currently under development. These new therapies are expected to further increase life expectancy of the patients.

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