Review Article

Cystic fibrosis in adults: diagnostic and therapeutic aspects*

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Abstract

Once considered a childhood disease, cystic fibrosis is now also a disease of adults. Increased longevity has resulted in the aging of the cystic fibrosis population. The consequent age-related medical problems among adults with cystic fibrosis have increased medical care needs. These needs are being met by a growing number of nonpediatric pulmonologists and other nonpediatric specialists. The objective of this review was to summarize the current knowledge about diagnosis and treatment in adult cystic fibrosis. In most cases, the diagnosis is suggested by manifestations of chronic sinopulmonary disease and exocrine pancreatic insufficiency. The diagnosis is confirmed by a positive sweat test result. Adult patients may, however, present pancreatic sufficiency and atypical clinical features, sometimes in combination with normal or borderline sweat test results. In such cases, identifying cystic fibrosis mutations and measuring nasal potential difference can have diagnostic utility. The standard therapeutic approach to pulmonary disease includes the use of antibiotics, airway clearance, exercise, mucolytics, bronchodilators, oxygen therapy, anti-inflammatory agents and nutritional support. Appropriate application of these therapies results in most cystic fibrosis patients surviving into adulthood with an acceptable quality of life.

Keywords: Cystic fibrosis; Diagnosis; Therapeutics; Mucoviscidosis.

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Introduction

Cystic fibrosis (CF) is a genetic disease of autosomal recessive inheritance. It is caused by mutations in a gene located on the long arm of chromosome 7.[1] This gene is responsible for encoding a 1480 amino acid protein known as the *Cystic Fibrosis Transmembrane Regulator* (CFTR) protein.[2,3] The CFTR protein constitutes a chloride channel in the apical membrane of the exocrine epithelial cells, regulating and participating in the transport of electrolytes through the cell membranes.[4] The clinical expression of the disease is quite varied. In general, CF presents as multisystemic impairment, characterized by a progressive loss of lung function, exocrine pancreatic insufficiency, liver disease, intestinal motility disorder, male infertility (obstructive azoospermia), and high concentrations of sweat electrolytes.[5,6]

Until less than 70 years ago, the disease, described by Andersen in 1938 as 'cystic fibrosis of the pancreas',[7] was almost always fatal within the first year of life. Over the years, advances in knowledge regarding the physiopathology and treatment of CF have increased the survival of these patients. In the United States, the mean survival is currently 36.5 years, and 43% of all CF patients are over the age of 18 years.[8]

The increase in longevity in CF patients has resulted in a greater proportion of age-related medical problems and complications related to disease progression, modifying the needs in health assistance. It especially demanded that different nonpediatric specialists be involved in the treatment of these patients. Since the pulmonary manifestations of the disease are progressive and constitute the principal determinant of its prognosis, nonpediatric pulmonologists play an important role in the multidisciplinary treatment of CF patients.[8]

The objective of this article was to review the principal diagnostic and therapeutic aspects of CF in adults.

Diagnosis

Table 1 shows the diagnostic criteria for CF. To be diagnosed with CF, an individual must present at least one phenotypical finding (Chart 1), have a family history of CF, or screen positive for CF in neonatal testing, as well as presenting laboratorial evidence of CFTR dysfunction – positive sweat test or positive nasal potential difference (NPD) – or have the two CFTR gene mutations known to cause CF.[5,9]

Table 1 - Diagnostic criteria for cystic fibrosis.

Cystic fibrosis findings	Biochemical evidence of CFTR dysfunction
≥1 phenotypical finding	Positive sweat test
or	or
Positive neonatal screening plus	Positive NPD
or	or
Positive family history	2 mutations[a] in CFTR

CFTR: cystic fibrosis transmembrane regulator; and NPD: nasal potential difference. [a]The mutations in CFTR should be known as causes of CF. Adapted from Rosenstein & Cutting.[9]

Sweat test

The sweat test with quantitative iontophoresis with pilocarpine is the gold standard for the confirmation of CF diagnosis.[5,9,10] The collection methods are the Gibson-Cooke procedure and the Macroduct sweat collection system (Wescor, Logan, UT, USA). In both, the sweat is stimulated by iontophoresis with pilocarpine, after which it is collected with paper filter or gauze (Gibson-Cooke) or in a microbore tube (Wescor). The sample is then analyzed to determine the concentration of sodium chloride. The minimal acceptable sweat volume is 75 mg in the Gibson-Cooke procedure and 15 μL for the Macroduct system.[5,9]

Other methods, such as the conductivity measurement (non-selective measurement of ions) and the osmolarity measurement, can be used as screening tests. In this case, altered or erroneous values should be confirmed using a quantitative sweat test.[5,9]

The sweat test should always be interpreted in the clinical context. Chloride provides the best diagnostic discrimination. The measurement of sodium is useful as a quality control. Highly discordant values indicate problems in the collection or analysis. A chloride concentration higher than 60 mmol/L is consistent with a diagnosis of CF. Chloride values between 40 and 60 mmol/L are considered borderline.[5,9]

Every sweat test should be performed at least twice in each patient, preferably with an interval of weeks between tests. Every positive sweat test should be repeated or confirmed by the analysis of mutations. A sweat test producing a borderline value

Chart 1 - Phenotypical findings consistent with a diagnosis of cystic fibrosis.

1. Chronic sinopulmonary disease:
   a) Persistent colonization/infection with pathogens typical of cystic fibrosis, including *Staphylococcus aureus*, nontypable *Haemophilus influenza*, mucoid *Pseudomonas aeruginosa*, nonmucoid *P. aeruginosa*, and *Burkholderia cepacia*.
   b) Chronic cough and chronic expectoration.
   c) Persistent abnormalities on radiographic images of the chest (bronchiectasis, atelectasis, infiltrates, and hyperinflation).
   d) Airway obstruction with wheezing and air trapping.
   e) Nasal polyps, together with radiographic or tomographic abnormalities of the paranasal sinuses.
   f) Digital clubbing.
2. Gastrointestinal and nutritional abnormalities:
   a) Intestinal: meconium ileus, distal intestinal obstruction syndrome, and rectal prolapse.
   b) Pancreatic: pancreatic insufficiency and recurrent pancreatitis.
   c) Hepatic: chronic hepatic disease with clinical or histological evidence of focal biliary cirrhosis or multilobular cirrhosis.
   d) Nutritional: impaired development (protein-calorie malnutrition), together with hypoproteinemia and edema, complications secondary to liposoluble vitamin deficiency.
3. Salt-wasting syndromes: acute salt depletion and chronic metabolic alkalosis.
4. Male urogenital abnormalities resulting in obstructive azoospermia (bilateral congenital absence of the deferent ducts).

Adapted from Rosenstein & Cutting.[9]

should be repeated. If the result remains inconclusive, additional diagnostic tests should be carried out.[5]

Analysis of mutations

The identification of mutations known as the cause of CF in each of the CFTR genes, in the context of a clinical or family history consistent with CF, confirms the diagnosis. However, the finding of only one mutation or no mutations in the CFTR gene does not rule out a diagnosis of CF.[9] Cases of non-classic CF in which there is no evidence of mutation in the CFTR genes have been reported.[11-13] Therefore, the existence of complex genotypes, of modifying factors, and of attenuating mutations demand that clinical findings be taken into consideration during the process of making a diagnosis of CF.[14]

The analysis of mutations presents high specificity for confirming a diagnosis of CF.[9] However, its sensitivity for confirming CF is low, since there are a great number of mutations (over 1000) that are known to cause CF, and the commercial panels available for this analysis only study a minority of those mutations.[8] Few referral centers have access to panels that screen for a greater number of mutations or can perform the genetic sequencing for the diagnosis of the most atypical cases.[10]

Nasal potential difference

Abnormalities in the ionic transport in the respiratory epithelium of patients with CF are associated with an altered NPD pattern. Specifically, three characteristics distinguish CF: a) elevated basal NPD; b) greater inhibition of NPD after nasal perfusion with amiloride; and c) little or no change in NPD after perfusion of the nasal epithelium with a chloride-free isoproterenol solution.[9]

An elevated NPD, accompanied by a family history of CF or a clinical profile suggestive of the disease, support the diagnosis of CF. However, the absence of an increase in the NPD does not rule out a diagnosis of CF, since a false-negative result can occur in the presence of an inflamed epithelium. It is recommended that the NPD be evaluated at least twice - at different time points.[9] However, this technique is available only in highly specialized centers and requires rigorous standardization.[8]

Complementary tests

In the initial diagnostic evaluation, other complementary tests are used. In a secondary way, they contribute to the diagnosis, to evaluating the severity of the disease, and to planning specific ther-

apeutic approaches. They include the evaluation of pancreatic function, lung function, sputum microbiology, facial sinuses, and the male genitourinary system (screening for obstructive azoospermia).[10]

The adult patient

Although the diagnosis of CF is usually made during the childhood (in the first year of life in 70% of cases), the frequency of the diagnosis in adult life has increased.[8]

In general, patients diagnosed in adult life present non-classic forms of CF. Although such patients present chronic respiratory disease, it is less severe than that seen in patients with early-onset CF, and the incidence of infection with *Pseudomonas aeruginosa* is lower, as is the frequency of pancreatic insufficiency, in late-onset CF patients than in those diagnosed during childhood. Another factor that contributes to the diagnostic difficulty is that a considerable number of these patients present normal or borderline sweat test results.[15-17]

One group of authors described 28 cases of patients living in Salvador, Brazil and diagnosed with CF in adult life.[18] The mean age was 31.1 years, 53.7% were black or mulatto, and 43% presented *P. aeruginosa* in the sputum culture. The authors emphasized the importance of investigating CF in adult patients with recurrent respiratory infection, sinusitis, and bronchiectasis. Another group of authors described 54 patients diagnosed with CF in adult life in Campinas, Brazil.[19] In that study, the mean age was 41.8 years, and the forced expiratory volume in one second (FEV_1) was 52%. In addition, 85% of the patients presented chronic productive cough, 6% presented fatty diarrhea or fat in the stool, and 48% presented *P. aeruginosa* in the sputum culture.

Despite these differences, the CF diagnostic criteria for children are the same as those used for adults.[9] In addition to repeating the sweat test, in general the diagnosis demands that a more comprehensive analysis of mutation be made. Although determining the NPD might be useful, the difficulty in standardizing the test is a limiting factor in clinical practice.[15] In the absence of gastrointestinal symptoms, the differential diagnosis should include ciliary dyskinesia, deficiency of immunoglobulin G, and Young's syndrome.[5]

Treatment

Since CF is a complex disease, the treatment must be holistic. The use of the multidisciplinary approach model to treat the disease is based on the observation that the creation of comprehensive care centers for CF is related to the progressively better prognosis pf the patients.[8,20] Therefore, the recommendations for the adult centers follow the successful multidisciplinary model of the pediatric centers.[8]

Despite the great advances in the knowledge regarding CF, the treatment of the disease continues to focus on resolving symptoms and correcting organ dysfunction.[21,22]

Although CF is a multisystemic disease, pulmonary impairment is the principal cause of morbidity and mortality.[23] Although the course of the pulmonary component of the disease is invariably one of progressive deterioration, an appropriate therapeutic approach can slow its progression.[23,24]

The standard therapeutic regimen for the pulmonary manifestations includes the following: a) antibiotic therapy; b) exercise and bronchial hygiene c) mucolytic agents; d) bronchodilators; e) anti-inflammatory agents; f) nutritional support; and g) oxygen supplementation.[8,23-25]

Antibiotic therapy

Antibiotics are the cornerstone of the treatment for the pulmonary component of CF. Patients with CF should be routinely evaluated, ideally every four months, and testing should include microbiology and antibiogram of the sputum.[8]

Antibiotics can be used in four specific clinical situations in CF: a) in the treatment of infectious exacerbations; b) in the eradication or long-term treatment of infection with *Staphylococcus aureus*; c) in the early eradication of *P. aeruginosa* infection; and d) in the suppressive treatment of chronic *P. aeruginosa* infection.[26]

Patients with CF can present periodic worsening of the pulmonary manifestations due to respiratory infections, to exposure to air pollutants or to bronchial hyperreactivity.[27] Depending on the severity of the clinical profile, oral or intravenous antibiotics are used in the intermittent treatment of the exacerbations.[26] For patients presenting exacerbations that are more severe, treatment with intravenous antibiotics for 14-21 days is recommended, and

hospitalization is generally necessary.[25] The choice of the antibiotics is based on the review of the sputum cultures and on the most recent antibiogram results.[21,24] The targets of the antibiotic therapy include the pathogens specifically related to CF, such as *P. aeruginosa*, *S. aureus*, and *Burkholderia cepacia*.[23] As *P. aeruginosa* is the most frequently pathogen isolated in adults with CF,[8,28] treatment with fluoroquinolones for the mild exacerbations, whereas the combination of a beta-lactam antibiotic with an aminoglycoside is indicated for the treatment of severe exacerbations.[8]

Generally, *S. aureus* is the first bacterium cultivated in the respiratory secretion of children with CF, remaining a major pathogen in adults.[29] The approaches for the treatment of *S. aureus* include, in addition to antibiotic therapy during exacerbations, a short course of antibiotics when the sputum culture is positive and prolonged antibiotic therapy from the moment of diagnosis.[22,29] Many authors recommend the early eradication of this bacterium, using an antibiotic course for two to four weeks, even in the absence of symptoms.[22] Although successful eradication is achieved in 75% of cases, recurrence of the infection occurs after the discontinuation of the antibiotics.[30] Continuous antibiotic therapy with flucloxacillin, initiated from the time of diagnosis, has been shown to result in lower rates of *S. aureus*-positive cultures, less cough, and lower rates of hospitalization.[31] However, continuous anti-staphylococcus treatment can increase the incidence of infection with *P. aeruginosa*.[32] At present, there is insufficient evidence to define the use of prophylactic antibiotic therapy for *S. aureus* infection.[33]

The acquisition and persistence of *P. aeruginosa* in the lower respiratory tract of CF patients are associated with higher rates of morbidity and mortality.[34] Initially, the isolated strains have a nonmucoid appearance and are sensitive to multiple antibiotics.[35] These strains of recent infection can be eradicated with aggressive treatment with antibiotics. However, over time, *P. aeruginosa* strains of the mucoid phenotype, which are associated with a more accelerated decline in lung function and a greater risk of death, emerge. Chronic infection with *P. aeruginosa* of the mucoid phenotype is typically impossible to eradicate, and the goal of the antibiotic therapy then turns to suppression of the pathogen.[36] Therefore, when *P. aeruginosa* is the bacterium initially identified, early and aggressive treatment to eradicate the pathogen and prevent chronic infection has been recommended. However, in the management of the early eradication of *P. aeruginosa*, uncertainty remains regarding the best therapeutic regimen and its duration. A practical alternative to this approach consists of administering the combination of oral ciprofloxacin and inhaled colistin for a period of three to six weeks. In patients presenting recurrence or in those with initial identification of mucoid strains, a more prolonged (three-month) course is recommended.[37] The use of inhaled tobramycin for 28 days has also been shown to achieve a significant rate of eradication.[38] It has also been demonstrated that the combination of intravenous antibiotics and inhaled antibiotics is effective in eradicating such bacteria, although this strategy presents economic and logistic disadvantages.[37]

The use of inhaled antibiotics has been employed as a form of suppressive treatment of chronic *P. aeruginosa* infection, with evidence of improvement in the clinical course and functional outcome.[39] Initial studies used aminoglycosides, especially tobramycin, at doses of 60-80 mg (nebulized, two to three times a day). Colistin has been widely used in Europe at doses of 500,000-1,000,000 IU (nebulized, twice a day). A preparation of inhaled phenol-free tobramycin, administrated at doses of 300 mg twice a day, for 28 days with a free interval of 28 days, is the form of treatment that has been the most widely studied in clinical trials. Despite these advances, there is still a lack of evidence to define the best drug for chronic suppression.[26]

The evidence for the chronic use of oral antibiotics in adults with CF is quite inconclusive, and this strategy is therefore not recommended.[8] However, it has been demonstrated that treatment with oral macrolide improves the lung function and lowers the frequency of exacerbations in patients with *P. aeruginosa*. The principal adverse effects demonstrated are nausea and diarrhea. Hepatotoxicity and ototoxicity have also been observed. Macrolides appear to exert their effects by acting on the pathogenic bacterium (affecting the formation of the *P. aeruginosa* biofilm) and on the host (immunomodulatory effects). The benefit of the prolonged use of azithromycin seems to extend to patients without *P. aeruginosa* infection. There is a great heterogeneity in the response to azithromycin. The studied doses

of azithromycin are 250-500 mg/day and 250 mg (weight < 40 kg) or 500 mg three times a week.[40]

Exercise and bronchial hygiene

Mechanical measures to increase mucociliary clearance are one of the fundamental pillars of CF treatment.[24] There are a variety of respiratory therapy techniques used for bronchial hygiene.[23] The conventional techniques include postural drainage and thoracic percussion in different anatomical positions, so as to facilitate the removal of secretions using the force of gravity. Despite the evidence of the benefits of these techniques, they can result in hypoxia (particularly in patients with severe diseases) or gastroesophageal reflux. In addition, these techniques are time-consuming and cannot be carried out without assistance, making the patients dependent on their caregivers and resulting in low compliance. As the patient enters adulthood, autonomy becomes a priority. More recently, respiratory therapy techniques that permit bronchial hygiene without assistance have been developed. Such techniques include the following: autogenic drainage; modified autogenic drainage; active cycle of breathing; forced expiration; positive expiratory pressure using a mask; use of oral oscillatory devices; high frequency thoracic compressions; and intrapulmonary percussive ventilation. The patient should be guided in the choice of techniques/combinations of techniques and should be instructed in the correct performance of the maneuvers. The frequency and duration of the treatment should be individualized. Patients with minimal respiratory symptoms might require only one session of respiratory therapy a day, whereas patients with more severe pulmonary disease or with a great quantity of secretion might require three or more session a day.[24]

Physical activity increases airway clearance and constitutes an important adjuvant to bronchial hygiene measures. Exercise attenuates the decline in lung function, improves cardiovascular performance, increases functional capacity, and improves quality of life. Therefore, exercise is recommended for adult patients with CF.[8] Patient with more severe pulmonary disease should be evaluated in order to determine whether there is a need for oxygen supplementation during physical activity.[41] Pulmonary rehabilitation regimens provide benefits in patients with CF.[8]

Mucolytic agents

The abnormal viscosity of the sputum in CF is caused by neutrophil-induced release of extracellular DNA. The use of inhaled recombinant human DNase decreases the viscosity of the sputum in CF by degrading the extracellular DNA into small fragments. In patients over the age of 5 and presenting anFEV_1 higher than 40% of predicted, DNase has been shown to be beneficial, reducing the rate of exacerbation of pulmonary disease by 22% and improving FEV_1 by 5.8%. In patients with more severe pulmonary disease (FEV_1 < 40% of predicted), lung functional benefits have been observed, but there was no reduction in exacerbations. The recommended dose of DNase is 2.5 mg (nebulized, once a day). The principal adverse effects are hoarseness, voice alteration, and pharyngitis. In the majority of cases, these symptoms are self-limiting.[24]

Nebulization of the hypertonic saline solution increases ciliary transport, improves the rheological properties of the sputum, and improves the hydration of the surface of the airways. Nebulization with 3-7% saline solution improves mucociliary clearance and lung function in a short period of time.[42] One recent clinical trial studied the nebulization of 4 mL of 7% hypertonic saline solution, administered for 48 weeks.[43] The authors demonstrated a significant improvement in lung function, a 56% reduction in the rates of exacerbation, and no worsening of the bacterial infection or the inflammation. Therefore, in CF patients, nebulization of hypertonic saline solution, preceded by bronchodilator inhalation, is a safe, affordable treatment, providing therapeutic benefits that appear to be independent of the use of DNase.[43]

Although nebulized N-acetylcysteine has been used to reduce the sputum viscosity in CF patients, there is little evidence to support its use. In addition, N-acetylcysteine might be an airway irritant and cause bronchospasm. Nor is there any basis for the use of oral N-acetylcysteine.[23,24]

Bronchodilators

Bronchial hyperreactivity is quite common in CF patients, occurring in approximately half of the CF population. Therefore, inhaled bronchodilators have been used as part of the standard treatment in CF.[24] $_2$The agents most frequently employed are the short-acting $_2$agonists. They are generally used prior

to respiratory therapy in order to facilitate airway clearance.[8] The majority of the patients present functional improvement after the administration of a short-acting $_2$agonist. Although data regarding the use of ipratropium bromide as a bronchodilator in CF patients are limited and controversial, the majority of the studies report modest functional benefit. Therefore, bronchial hyperreactivity should be assessed in all patients with CF, and a therapeutic bronchodilator test should be performed.[23]

Anti-inflammatory agents

The search for an anti-inflammatory strategy that stops the progression of the pathophysiological process in CF has been the target of numerous studies. Despite such efforts, a drug that is efficient and safe for this purpose has not yet been identified.[44]

Although oral corticosteroids at a dose of 1-2 mg/kg on alternate days seem to retard the progression of the pulmonary disease, the benefits are offset by the significant adverse effects, especially cataract development and growth impairment. There is as yet little evidence for the use of systemic corticosteroids to treat CF exacerbations. However, systemic corticosteroids have been used as a therapeutic resource in patients with severe exacerbations, especially in the presence of bronchial hyperreactivity.[23]

Inhaled corticosteroids have also been studied in CF with the objective of reducing the inflammatory process and decreasing lung injury. However, the current evidence is insufficient to establish whether there is benefit in its use.[45]

High doses of ibuprofen (20-30 mg/kg/day) were studied in CF patients and were found to lower the rate of FEV_1 decline, reduce the number of hospitalizations, and improve the nutritional state. However, at such doses, ibuprofen also doubled the incidence of renal insufficiency and gastrointestinal hemorrhage, thereby limiting its use. There is also the need to monitor serum levels of the medication administered. One review article demonstrated the lack of evidence to recommend the use of ibuprofen in clinical practice.[46]

Other anti-inflammatory drugs have been much less widely studied in CF. Although montelukast reduces the eosinophilic inflammation in CF, the clinical evidence on the subject is inconclusive.[44]

Nutritional support

The nutritional state plays an important role in the clinical course of CF. Impairment of the nutritional state results in alterations in lung function and affects patient survival. Nutritional intervention should begin early, avoiding deterioration of the lung function and having a positive effect on survival. Every CF patient should be regularly evaluated in order to monitor the nutritional state and ensure an adequate caloric intake.[20] The recommendation includes a high-fat diet, with 35% to 40% of the calories coming from fat.[8] Patients with CF might need 120% to 150% of the estimated minimum daily requirement. An approximate estimate of the energy needs can be made using the following equation: total energy expenditure = basal metabolic rate × 1.1 (poor absorption factor) × 1.5 to 1.7(activity factor) + 200 to 400 kcal/day.[47]

Commercial oral supplements can be used in select cases.[8] These patients can be monitored by determining the 3-day intake or by using a 24-h recollection survey, together with anthropometric evaluation (body mass index, arm circumference, mid-arm muscle circumference, triceps skinfold thickness, and weight loss percentage), analysis of body composition (electrical bioimpedance), and peripheral muscle strength (handshake strength) determination. The goal is to maintain a body mass index of 20-25 kg/m^2, a body mass index lower than 19 kg/m^2 indicating significant malnutrition and the need for aggressive nutritional intervention. Treatment for exocrine pancreatic insufficiency and CF-related diabetes mellitus are also important components of the nutritional approach.[47]

Oxygen supplementation

The pulmonary component of CF is progressive and, in its most advanced phases, is accompanied by hypoxemia and pulmonary hypertension.[23] The treatment for hypoxemia is crucial for slowing the progression of the pulmonary hypertension. However, there are only limited data on oxygen therapy in CF.[8] Therefore, the criteria used for continuous oxygen therapy in CF are extrapolated from studies of chronic obstructive pulmonary disease: arterial oxygen pressure lower than 55 mm Hg, during waking and on room air; arterial oxygen pressure lower than 59 mm Hg, in the presence of lower limb edema; polycythemia; electrocardiographic/

echocardiographic evidence of dilated right heart chambers; or pulmonary hypertension. Some CF patients also present hypoxemia only during exercise or while sleeping. Oxygen therapy during exercise is indicated if oxygen saturation drops below 90%. Nocturnal oxygen therapy is indicated if the oxygen saturation is lower than 90% for 10% or more of the total sleep time.[8] Continuous positive airway pressure during sleep might be required in some specific situations. Noninvasive mechanical ventilation can be a temporary support measure for the patients with chronic respiratory insufficiency who are awaiting a lung transplant.[24]

Approach to extrapulmonary manifestations

Patients with CF and presenting the exocrine pancreatic insufficiency phenotype should receive supplementation of pancreatic enzymes in meals and snacks. The initial adult doses of enzymes are approximately 500 U of lipase/kg/meal and 250 U of lipase/kg/snack. The doses should be adjusted according to the clinical needs up to the maximum of 2500 U of lipase/kg/meal and 1250 U of lipase/kg/snack. Patients with pancreatic insufficiency are predisposed to poor absorption of the liposoluble vitamins A, D, E, and K. The supplementation of these vitamins is routinely recommended.[8]

From 20 to 25% of CF patients develop hepatic disease. However, only 6% to 8% evolve to cirrhosis. Hepatic function tests present low sensitivity and specificity for the diagnosis. An ultrasound scoring system could facilitate the identification of chronic hepatic disease in adults. There is evidence of the benefits of ursodeoxycholic acid in CF-related hepatic disease. The appropriate dose is 20 mg/kg/day in two intakes. Liver transplant has been a major therapeutic strategy for treating CF patients with advanced chronic hepatic disease.[8]

The prevalence of diabetes mellitus and glucose intolerance increases with age. The clinical state and lung function deteriorate in the years preceding the diagnosis of diabetes, thereby worsening survival. Regular monitoring through oral glucose tolerance tests permits early intervention with insulin.[48,49]

The prevalence of osteoporosis varies from 38% to 77% in adult CF patients. The principals of preventing bone disease consist of intense vigilance, especially during puberty, accompanied by physical exercise and supplementation with calcium, as well as with vitamins D and K. Oral or intravenous bisphosphonates are useful for treating established disease.[50]

Infertility is seen in 95% of all men with CF. Male infertility results from abnormalities in the reproductive tract, resulting in obstructive azoospermia.[51,52] The absence of spermatozoa confirms infertility. Spermatozoa can be obtained using techniques such as microsurgical aspiration of sperm from the epididymis, percutaneous aspiration of sperm from the epididymis, and testicular biopsy. Such patients can impregnate their partners through assisted conception involving intracytoplasmic injection of spermatozoa into the oocyte. However, that is a costly process, available only in large centers, and the success rate is only 12 to 45% per cycle.[53]

Although there are reports of reduced female fertility in CF, this has been questioned. The choice of contraceptive is difficult and must be individualized. The use of oral contraceptives can result in a worsening of diabetes, as well as poor absorption and hepatic dysfunction. However, the use of broad spectrum antibiotics might affect the absorption and the efficiency of the oral contraceptives. The outcomes for the fetus and mother during gestation in CF patients are generally favorable. Gestation is at increased risk in CF patients with advanced pulmonary disease (FEV_1 < 50% of predicted), diabetes mellitus, or malnutrition. However, the cut-off points for the clinical contraindication of conception is not established.[53]

Transition from the pediatric team to the adult team

The process of transferring the health care of CF patients between teams that deal with different age brackets is an important strategy to be developed in all CF treatment centers. In addition to the advantage of an approach that is aimed more at specific age-related clinical problems, the adult program should prioritize the independence and autonomy of the individual. Although it has been suggested that the transition should occur between the ages of 16 and 18, there should be flexibility, taking into consideration the maturity and clinical status of the patient.[54] In general, the transition requires clinical stability of the disease. Patients presenting severe exacerbations or terminal disease, as well as those

who are on a transplant waiting list, are not candidates for transition.[8]

Lung transplant

Lung transplant is known to be related to greater survival and better quality of life in patients with advanced pulmonary disease. Due to the suppurative nature of CF, there is a need for bilateral pneumonectomy to avoid infection in the grafted lung. The most widely used technique is bilateral lung transplant through a sequential bilateral surgical procedure using a cadaver donor. Lobe transplantation from a living donor is an alternative, especially for patients who cannot wait for a cadaver donor, although it requires that the receptor be of short stature and presenting volume proportionality with the organs to be grafted.[55] The criteria for patient candidacy are as follows: FEV_1 < 30% than the predicted; severe hypoxemia; hypercapnia; progressive functional damage or increase in the duration and frequency of hospital treatment for exacerbations; life-threatening pulmonary complications such as hemoptysis; and increased antibiotic resistance of the bacterial pathogens.[56] Due to the longer survival of CF patients, the use of FEV_1 < 30% of predicted has been questioned as a criterion for transplant candidacy.[55] The rate of decline in lung function has been proposed as a more reliable criterion. A new model for reference and prediction of mortality has been proposed, based on the score of multiple clinical and functional variables. The 5-year post-transplant survival rate has been reported to be 50%.[55]

Advances and perspectives

A recent study of CF patients between the ages of 2 and 18, without *P. aeruginosa* colonization, showed that vaccination with a bivalent vaccine made from *P. aeruginosa* flagellum was efficient in reducing the risk of *P. aeruginosa* infection and might therefore increase survival among such patients.[57]

The principal of gene therapy involves the introduction of RNA or DNA into the epithelial cells of the airways in order to compensate for the genetic defect. Technical difficulties include the need for continuous re-administration due to the turnover of the target cells. In addition, the genetic material must overcome the systemic and local pulmonary defenses. The use of viral vectors for the administration of genetic material presents greater transduction efficiency. However, no means of avoiding the immunological response that appears with the re-administration has been found. Although the use of non-viral vectors provokes a much less intense immunological response, it presents lower transduction efficiency. In addition, the low expression of CFTR and the episodic course of the pulmonary disease make it difficult to use conventional outcomes as measures of the efficiency of the gene therapy. Therefore, gene therapy has not yet become a clinical reality despite the numerous clinical trials.[58,59]

One prospective treatment is stem-cell therapy. Various cell populations derived from adult bone marrow or from umbilical cord blood might locate a variety of organs and acquire phenotypical and functional characteristics of specific adult organ cells. That would permit the genetic defect to be corrected through the regeneration of the respiratory epithelial cells.[60] However, knowledge of pulmonary stem cells is quite limited, and such research is still in the initial phase.[58,59]

Conclusions

Since CF has now become an adult disease as well, its treatment requires the involvement of pulmonologists and other nonpediatric specialists. The standard treatment for the pulmonary component of the disease includes antibiotic therapy, bronchial hygiene, exercise, mucolytic agents, bronchodilators, oxygen therapy, anti-inflammatory agents, and nutritional support. The appropriate use of these measures results in greater survival and a better quality of life for adult CF patients.

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