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Review Article

New Horizons in Cystic Fibrosis - A Review

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Abstract

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease among Caucasians. Remarkable advances in our understanding of the pathophysiology, diagnosis and treatment of CF have been made since the discovery of CFTR gene. Care of cystic fibrosis patients is complex and requires a team approach. Recent advances, novel treatments and the multidisciplinary team approach have improved survival in CF, transforming it into a predominantly adult disease. This review highlights the pathogenesis of cystic fibrosis and summarizes diagnosis, clinical manifestations and treatment guidelines.

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INTRODUCTION

Our understanding and treatment of cystic fibrosis has dramatically changed since the first description provided by Dr. Dorothy Anderson in the 1930s. Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease among Caucasians with an incidence of 1:3,000 in the United States. Today, it is increasingly more recognized among non-Caucasians in the United States with an incidence of 1:9,200 in Hispanics, 1:10,900 in Native Americans, 1:15,000 in African Americans and 1:30,000 in Asians [1]. The median predicted survival for CF has drastically improved over the past 25 years. According to the Cystic Fibrosis Foundation 2014 Registry Report, the median survival for CF patients in 2014 was 39. 3 years (95% CI, 37. 3-41. 4) compared to 20 years in 1980s [2]. This dramatic improvement in predicted survival is a result of immense progress in both treatments for cystic fibrosis and management of CF related diseases. As a result of improved survival, the CF Registry included more adults than children for the first time in 2014 (50. 7% adults 18 years or older and 49. 3%children under 18 years) [2]. The transformation of CF into an adult disease over the past two decades underscores the importance of familiarization with current CF treatment guidelines for adults with cystic fibrosis. The purpose of this article is to summarize the pathophysiology of CF, review diagnosis guidelines, current treatment guidelines for adults and recent advances in treatment.

Pathogenesis

Discovery of the cystic fibrosis transmembrane conductance regulator (CFTR) gene responsible for CF in 1989 has revolutionized our understanding of CF and led to breakthrough discoveries that have doubled predicted survival in patients [3,4]. Basic understanding of pathophysiology of this disease is essential to fully understand current and new therapies. The CFTR gene is located on the long arm of chromosome 7q31 [4]. The CFTR protein is a phosphorylation-dependent epithelial anion channel. CFTR is primarily located in the apical membrane, where it acts a chloride channel, bicarbonate channel and regulator of epithelial sodium channels. This allows it to regulate rate of anion movement across epithelia, and thereby determine trans-epithelial salt transport, fluid flow and ion concentrations [5,6]. CFTR is composed of two motifs, each containing a membrane-spanning domain and a nucleotide-binding domain that interacts with ATP. Additionally, a unique regulatory domain with multiple phosphorylation sites links the two motifs together. The membrane-spanning domain gives CFTR anion selectivity while the nucleotide-binding domain regulates channel gating [6]. The regulatory domain enables channel activity via phosphorylation at multiple sites that permit the nucleotide-binding domains to associate. Their association forms ATP binding sites that regulate channel gating [7].

There are now over 2,000 identified mutations in CFTR that are grouped into fiveclasses based on their effects on protein expression, structure and function (Figure 1). Class I mutations are nonsense mutations that introduce premature stop codons resulting in complete absence of functional CFTR. Class II mutations lead to misfolding or improper processing of CFTR protein resulting in degradation in most of the protein before it is able to reach the apical membrane [8]. Phe508del (F508del), a class II mutation, is the most common mutation and accounts for more than 70% of mutant alleles [3,4,9]. Class III mutations occur in the nucleotide-binding or regulatory domains and cause defective CFTR protein due to abnormal gating regulation. Class IV mutations occur in the membrane-spanning domain, and therefore affect chloride conductance. Class V mutations result in decreased production of CFTR protein due to splicing defects or missense mutations [8].

Mutations from class I and II lead to more severe lung disease and pancreatic insufficiency. However, the severity and

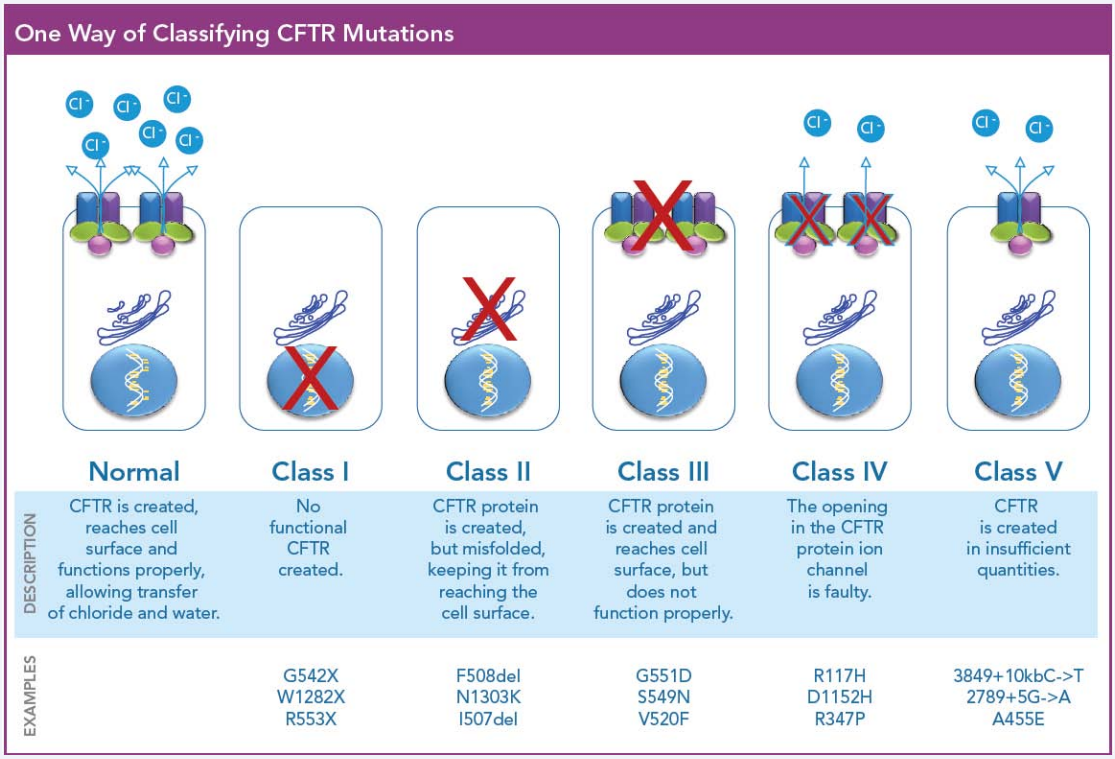

Figure 1 Cystic Fibrosis Foundation Patient Registry, 2014 Annual Data Report, Bethesda, Maryland, ©2015 Cystic Fibrosis Foundation (Used with permission).

progression of pulmonary disease in CF is considerably variable even among patients with same CFTR mutation. This difference may be due to patient factors such as sex, race, ethnicity, nutritional status and exposures to airborne toxins such as tobacco smoke [10,11]. Additionally, Schechter et al described strong association of socioeconomic status with outcomes in cystic fibrosis patients [12]. Although these environmental influences affect disease severity, the presence of additional gene modifiers has been shown to contribute significantly to clinical phenotype. As an example, genetic variation in the 5' end of transforming growth factor beta 1 (TGFb1) in CF patients with DelF508 mutation has been associated with severe lung disease [13]. Additionally, 14-3-3 proteins have been found to play an important role in biogenesis of CFTR protein [14]. Phosphorylation-dependent binding of 14-3-3 proteins to the regulatory domain of CFTR facilitates CFTR exit from the endoplasmic reticulum and trafficking to the apical membrane [14,15].

Diagnosis

The diagnosis of CF has vast implications for patients and their families. The broad spectrum of clinical disease and repertoire of over 2,000 different mutations have made diagnosis more difficult [9,10]. Diagnostic guidelines for CF were therefore established by the Cystic Fibrosis Foundation to standardize diagnosis of both infants with positive newborn screening (NBS) results and older patients presenting with an indistinct clinical picture. CF Foundation proposed the following diagnostic criteria state: "the diagnosis of CF should be based on the presence of 1 or more characteristic clinical features, a history of CF in a sibling, or a positive NBS test, plus laboratory evidence of an abnormality in CFTR gene or protein" [16,17]. The phenotypic features consistent with diagnosis of CF are shown in (Table 1). Either biological evidence of channel dysfunction such as an abnormal sweat chloride test or nasal potential difference and identification of a CF disease-causing mutation on each allele of the CFTR gene are acceptable evidence of a CFTR abnormality. Newborn screening depends on initial analysis of fetal blood for high values of immunoreactive trypsinogen (IRT) followed by genetic testing or repeat IRT [16].

The sweat chloride test remains the initial test of choice and gold standard for CF diagnosis despite its limitations. It was established in 1959 as a standardized procedure known as the Gibson-Cooke method [18]. The subsequent identification of chloride ions principle role in the pathogenesis along with the discovery of CFTR provided molecular rational for the sweat test in diagnosis of CF. Appropriate performance of the sweat test is of utmost importance and should only be performed by accredited CF care centers per CF Foundation recommendations. The test is performed via pilocarpine inotophoresis, which is used to stimulate sweat gland secretion. The sweat is collected and analyzed for chloride concentration. Universally, the test is considered abnormal when chloride concentration is greater than or equal to 60 mmol/L, intermediate between 40-59 mmol/L and normal when less than or equal to 39 mmol/L. Individuals with intermediate values should undergo repeat sweat chloride testing, detailed clinical assessment and DNA analysis for CFTR mutations [16]. Ancillary tests such as the nasal potential difference (NPD) that have been used in CF research have

Table 1: Phenotypic features consistent with a diagnosis of CF.

1. Chronic sinopulmonary disease, manifested by:
   a. Persistent colonization/infection with typical CF pathogens, including *Staphylococcus aureus, nontypeable Haemophilus influenza,* mucoid and nonmucoid *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and *Burkholderia cepacia*
   b. Chronic cough and sputum production
   c. Persistent chest radiograph abnormalities (eg, bronchiectasis, atelectasis, infiltrates, hyperinflation)
   d. Airway obstruction, manifested by wheezing and air-trapping
   e. Nasal polyps; radiographic or CT abnormalities of the paranasal sinuses
   f. Digital clubbing
2. Gastrointestinal and nutritional abnormalities, including:
   a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
   b. Pancreatic: PI, recurrent acute pancreatitis, chronic pancreatitis, pancreatic abnormalities on imaging
   c. Hepatic: prolonged neonatal jaundice, chronic hepatic disease manifested by clinical or histological evidence of focal biliary cirrhosis or multilobular cirrhosis
   d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and edema, complications secondary to fat-soluble vitamin deficiencies
3. Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis
4. Genital abnormalities in males, resulting in obstructive azoaspermia

Rosenstein B, Cutting G. The diagnosis of cystic fibrosis: a consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr. 1988; 132:589-595. Used with permission.

Table 2: Cystic Fibrosis Pulmonary Guidelines - Airway Clearance Techniques:

Technique	Method
Percussion and postural drainage (P&PD)	Postural drainage, percussion, and vibration of the chest
Positive expiratory pressure (PEP)	1. Expiratory breathing against pressure at 10-25 cm H2O to raise functional residual capacity or re-inflate collapsed lung 2. Resistor at 10-25 cm H2O to retard expiratory airflow and prevent complete exhalation; or 3. Expiration against a device that generates pressure of 40-100 cm H2O (high-pressure PEP)
Active-cycle-of-breathing technique (ACBT)	1. Thoracic expansion exercises 2. Controlled breathing to aerate alveoli and distal airways, move mucus to proximal airways 3. Forced expiratory technique to clear secretions
Autogenic drainage (AD)	Tidal breathing (controlled expiratory flow) at: 1. Low lung volumes to unstick mucus in peripheral airways 2. Mid-lung volumes to collect mucous in middle airways 3. High lung volumes to expel mucous from central airways
Oscillatory PEP (OPEP)	Intermittently interrupt expiratory flow, causes air to vibrate
High-frequency chest compression (HFCC)	Pulses of pressure through inflatable compressive vest to vibrate airways, which increases airflow at lung volumes to increase mobilization of sputum
Exercise	Regular vigorous activity designed to improve physical, heart, and/or muscle strength 1. Aerobic training (eg. cycling, running) for a set time at target intensity 2. Anaerobic training (eg. weight or resistance training, sprinting) for short time at high intensity

Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, *et al.* Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care. 2009; 54: 522-537. Used with permission [45].

recently been introduced to clinical practice for diagnosis [19]. NPD is avaluable tool for ruling out a diagnosis of CF in patients with inconsistent or intermediate sweat chloride test results. Unfortunately, testing availability remains limited for clinicians as only a few centers have been validated by the CF Foundation for NPD testing [16,19].

DNA analysis in establishing CF diagnosis is most useful for those individuals with sweat chloride values in the intermediate range. Two or more disease-causing CFTR mutations should be located on different alleles as CF is an autosomal recessive disease. Current CF mutation screening panels effectively identify 90% of CFTR mutations in Caucasians. Screening panels are significantly less effective in other populations with Hispanic, African or Asian origins due to some variation in CF-causing mutations [16]. Only 127 of the 2007 CF mutations on the current CF Mutation Database have been confirmed as disease causing [9,20]. CF Foundation recommends testing for the 23 CF mutation panel developed by the American College of Medical Genetics (ACMG). These mutations have been demonstrated to cause sufficient loss of CFTR function to confer CF disease, and are therefore noted as conclusive genetic evidence for diagnosis of CF [16]. Stabilization of the 14-3-3-CFTR interaction as shown by Loes and colleges serves as a basis for design of novel therapies for CF [16].

Clinical Manifestations

Clinically, cystic fibrosis leads to changes in sinuses, lungs, pancreas, liver and reproductive tract as a direct result of abnormal secretions due to CFTR malfunction. Pulmonary disease remains the most striking and primary cause of mortality. Liver disease/failure accounted for 2.8% of mortality in 2014 [2]. According to

2014 Cystic Fibrosis Foundation Patient Registry, the majority of patients were asymptomatic or minimally symptomatic at the time of diagnosis. The most common symptomatic presentation at time of diagnosis among infants (under age 1) was meconium ileus or intestinal obstruction, while those diagnosed after age 1 most commonly presented with acute or persistent respiratory abnormalities [2].

Sino-pulmonary manifestations

The respiratory manifestations in CF are widely variable. Classically, patients develop productive cough, dyspnea, digital clubbing, hyperinflation of lungs on radiograph and air trapping with obstructive ventilator limitation. There are multiple proposed mechanisms for airway disease in cystic fibrosis including impaired mucociliary clearance, acidification of airway-surface liquid, impaired bacterial killing and clearance, and increased inflammation [21,22]. During early childhood, dysfunction of CFTR results in airway colonization with pathogenic bacteria. Common pathogens include *Haemophilus influenzae*, *Staphylococcus aureus*, *Burkholderiacepacia* complex (BCC), *Pseudomonas aeruginosa* and recently increasing *Stenotrophomonas maltophilia* [23,24]. Pseudomonas is particularly troublesome as it forms biofilms that inhibit penetration of antimicrobial agents and confer the mucoid phenotype [22,24]. Consequently, chronic bacterial airway infections result in progressive destruction of airways by promotin gneutrophilic inflammation and mucous production. Advancing cystic fibrosis lung disease leads to progressive bronchiectasis. In late stages, pneumothorax and hemoptysis can be potentially fatal complications [25].

The prevalence of paranasal sinus disease is widespread in CF. Greater than 90% of CF patients reveal evidence of sinus involvement on CT scan [26]. Several studies have noted increased prevalence of sinus aplasia or hypoplasia in CF patients with verified genetic mutations signifying that chronic rhinosinusitis results at least in part from abnormal fetal development of the sinuses, along with impaired mucociliary clearance and chronic neutrophilic inflammation from pathogen colonization [27]. Obstructing nasal polyposis is increasingly more common among CF patients compared to normal population and reaches an incidence of almost 50% in adolescence [26].

Gastrointestinal manifestations

Impaired CFTR function within the pancreatic ducts causes mucinous impaction and obstruction that interferes with pancreatic enzyme secretion, effectively causing exocrine pancreas insufficiency. Over time, the obstructed pancreatic enzymes cause autolysis and progressive destruction of pancreatic islet cells leading to endocrine pancreas dysfunction (i. e. cystic-fibrosis related diabetes) [24,28]. Pancreatitis is a less common complication of CF occurring in 1.24% of CF patients in one large cohort. It was more frequently noted in patients with pancreatic sufficiency (10. 3%) compared to those with pancreatic insufficiency (0. 5%) [29]. This difference has led to the recognition of correlation between genotype and pancreatic phenotype. The pancreatic sufficiency phenotype strongly correlates with milder mutations (class IV and V) that normally cause reduced CFTR activity rather than complete inactivation [30,31]. Pancreatic insufficiency is by far the most common gastrointestinal manifestation of CF. It affects85% of CF patients in the United States and is often present from birth [28,31]. The lack of pancreatic enzymes causes maldigestion and malabsorption that leads to severe fat-soluble vitamin deficiency (vitamins A, E, D and K) and malnutrition if left undiagnosed [31]. This contributes to the low bone density and increased fracture rates in CF patients [32].

Cystic fibrosis-related liver disease has become more prevalent as a result of improvement in survival since the 1980s. There is a wide spectrum of hepatobiliary manifestations observed in CF as a result of abnormal composition, consistency and flow of bile due to CFTR dysfunction [31,33]. The most common hepatobiliary diseases include asymptomatic elevation of liver enzymes, microgallbladder, hepatic steatosis, focal biliary cirrhosis, multilobular cirrhosis, cholelithiasis and cholecystitis. Less frequently, common bile duct stenosis, neonatal cholestasis, sclerosing cholangiti and cholangio carcinoma can occur. The abnormal bile composition and dysfunctional flow causes obstruction of small biliary ductules that leads to secondary hepatocyte injury. The resulting inflammation induces collagen synthesis by stellate cells that initially causes focal biliary cirrhosis and then progresses to multilobular cirrhosis over several years [33-35]. Post-mortem studies have noted incidence of focal biliary cirrhosis as high as 70% in adults with CF, but less than a third of them developed clinically significant liver disease [34].

CF patients experience multiple other gastrointestinal manifestations. About 30% of patients report gastroesophageal reflux disease [2]. Distal intestinal obstruction syndrome (DIOS) is a unique manifestation to CF that can occur at any age as a direct result of fecal obstruction of the ileocecum. Patients classically present with abdominal distention and palpable right lower quadrant mass [33]. DIOS likely results from impaired gut motility, thick mucous secretions and decreased water secretion due to CFTR dysfunction. This underlying mechanism is also responsible for the increased incidence of constipation and obstipation experienced by CF patients [33]. The intestinal dysmotility and thick mucous secretions, along with chronic use of azithromycin, also increased small intestinal bacterial overgrowth in CF [33]. Rectal prolapse is reported in less than 1% of patients [2]. Additionally, CF patients have an increased incidence of celiac disease, inflammatory bowel disease and multiple gastrointestinal malignancies compared to the general population [36,37].

Bone disease

The multiple factors contributing to bone disease in CF include malabsorption of vitamin D, poor nutritional status, physical inactivity, glucocorticoid therapy, delayed pubertal maturation, and chronic airway inflammation resulting in increased serum cytokine levels [32]. Multiple reports have shown significantly decreased bone mineral density (BMD) in CF patients compared to age-matched controls. Additionally, several cross-sectional studies have observed a nearly two-fold increase in fracture rate and increased prevalence of kyphosis [38,39]. Vertebral and rib fractures can be debilitating for CF patients because they produce chest wall deformities that reduce lung function and

inhibit effective cough [32]. This hinders airway clearance and accelerates the course of CF-related lung disease. Additionally, severe bone disease can lead to exclusion from life-saving lung transplantation [32,40]. CF Foundation recommends screening all adult CF patients with dual-energy X-ray absorptiometry [32].

Infertility

Lastly, infertility is a major concern and affects 95% of males with cystic fibrosis. Male infertility is caused by aspermia secondary to abnormal organogenesis of vas defers [41]. Sexual potency is not affected and spermatogenesis can be reduced, but is generally not absent [41,42]. Partial sparing of spermatogenesisallowssome CF patients to reproduce via microscopic epididymal sperm aspiration with intracytoplasmic sperm injection [42]. Females with CF generally have normal reproductive function.

Treatment

Cystic fibrosis has been transformed into an adult disease as a result of improved understanding of pathophysiology, multi-disciplinary treatment approach by CF care centers and advances in treatment. This dramatic shift has led to the publication of CF adult care guidelines by the Cystic Fibrosis Foundation. Comprehensive care by a multi-disciplinary team (including physician, nurse, respiratory therapist, dietitian and social worker) at a CF Care Center is strongly recommended in adults and pediatrics [43]. Patients should have frequent contact with their Adult CF Care Team and at least one comprehensive evaluation by each team member per year. Health maintenance such as vaccination and age appropriate cancer screening should also be addressed by care team or in collaboration with independent primary care provider [43]. The foundation of treatment for all CF patients focuses on antibiotic therapy, airway clearance and nutritional support.

Chronic therapy for maintenance of lung health

Pulmonary status of CF patients should be monitored regularly with spirometry, yearly microbiologic assessment of expectorated sputum with antibiotic susceptibility testing and Posterioanterior/Lateral chest radiography every 2-4 years [43]. Chronic therapy for maintenance of lung health should be based on severity of lung disease. Forced expiratory volume in 1 second (FEV1), based on percentage of predicted, is acknowledged as the most useful objective measure of pulmonary status [43,44]. FEV1greater than 90% of predicted is considered normal lung function, 70-89% of predicted is mild impairment, 40-69% of predicted is moderate impairment and less than 40% of predicted is severe impairment.

Airway clearance therapy (ACT) is a key component of lung health maintenance in CF patients, as their impaired ability to clear pathogenic organisms from the airways can lead to progressive decline in lung function from acute exacerbations. The CF Foundation recommends ACT for all CF patients. Variable forms of airway clearance therapy are described (see Table 2) and range from physiotherapy to high-frequency chest compressions. ACT should be individualized to each patient based on age, severity of lung disease and patient preference as none have demonstrated superiority to others [45]. Additionally, aerobic exercise is recommended as an adjuvant therapy to improve airway clearance [45].

Additional therapies to maintain lung health in adults include hypertonic saline, dornase alfa and bronchodilators. Chronic use of hypertonic saline 7% twice daily has been shown to improve lung function and decrease exacerbations of CF lung disease [46]. The beneficial effects of hypertonic saline are likely derived from improved airway clearance due to increasing airway hydration and induction of cough [46]. Likewise, dornase alfa improves lung function and reduces exacerbations by augmenting airway clearance. Dornase alfa is a recombinant human DNase that breaks down free DNA and thereby decreases viscosity of airway secretions to facilitate airway clearance [47]. Dornase alfa is recommended for CF patients 6 years of age and older, even if they have asymptomatic lung disease [44]. Bronchodilators have become part of the therapeutic regimen as majority of CF patients demonstrate bronchial hyper-responsiveness. They are commonly used to provide symptomatic relief, as pretreatment for chest physiotherapy, and with hypertonic saline to facilitate airway clearance [43,44].

Chronic antibiotic therapy has been employed to suppress *P. aeruginosa*, as it is the organism most commonly responsible for decline of lung function. Both aerosolized tobramycin and aztreonam are recommended for CF patients 6 years and older with lung disease and pseudomonas aeruginosa persistently present in airway cultures. Chronic use has been shown to reduce exacerbations, improve lung function and quality of life [43,44]. There is insufficient evidence to recommend for or against the use of other inhaled antibiotics such as ceftazidime, colistin and gentamicin [44]. The use of chronic oral antipseudomonal antibiotics lacks sufficient evidence with the exception of azithromycin. Chronic oral azithromycin (250 mg daily or 500 mg three times weekly) is recommended for CF patients 6 years and older with pseudomonas aeruginosa persistently present in airway cultures to improve lung function and reduce exacerbations. The beneficial effect of azithromycin seems to be derived from both its antimicrobial and anti-inflammatory properties. Therefore, the CF Foundation recommends that use of chronic azithromycin be considered in even those patients without persistently present pseudomonas aeruginosa in airway cultures [44]. There is insufficient evidence to recommend for or against the use of chronic oral anti-staphylococcal antibiotics in patients with staphylococcus aureus persistently present on airway cultures [44].

Acute exacerbation of cystic fibrosis lung disease

Progressive decline in lung function results from recurrent pulmonary exacerbations. *Pseudomonas aeruginosa* is the most common colonizing pathogen responsible for deterioration in lung function in adults. Therefore, acute exacerbations should be treated with two antipseudomonal antibiotics. However, the use of a single antibiotic to treat acute exacerbation may be adequate in CF patients with mild disease. Specific antibiotic selection should be based on most recent sputum culture [43,48]. The use of intravenous (IV) antibiotics is preferred due to differences in the volume of distribution and rate of elimination in CF patients [49]. Intravenous antibiotics should not be administered in a nonhospital setting unless equivalent resources and support

can be assured [48]. The CF Foundation has noted that there is insufficient evidence to recommend optimal duration of antibiotic therapy, but routine practice is to complete treatment with 14-21 days of IV antibiotics. Routine use of corticosteroids is not recommended as part of treatment of an acute exacerbation. Chronic therapies for maintenance of lung health should be continued and airway clearance therapy should be increased during acute exacerbations [48].

Aggressive and long-term use of antibiotics has been shown to slow decline in lung function and improve survival, but it has also increased the burden of antimicrobial resistance and antibiotic toxicity [44]. Antimicrobial resistance plays an important role in cystic fibrosis as it contributes to persistence of bacteria within lungs of CF patients and worse survival [50,51]. Bacterial resistance is based on the antibiotics minimum inhibitory concentrations (MIC) reached with systemic therapy. Aerosolized antibiotics can achieve significantly higher sputum concentrations than intravenous antibiotics [52]. Development of new aerosolized antibiotics such as azetreonam and colistimethate has improved treatment of multi-drug resistant infection. However, there is no clinically relevant definition of resistance based on aerosolized therapy and antimicrobial resistance may still develop [52]. Non-antibiotic treatments such as gallium, antimicrobial peptides, and anti-biofilm compounds should be considered to decrease antimicrobial resistance [51].

Lung transplantation

The median survival for lung transplant patients with CF is 8. 3 years. Lung transplantation for CF patients has more favorable long-term survival than patients with other pulmonary conditions [40,53]. Referral criteria for lung transplantation include an FEV1 less than 30% of predicted or rapid decline in FEV1, exacerbation of pulmonary disease requiring ICU stay, increased frequency exacerbations of antibiotic therapy, recurrent pneumothorax and recurrent hemoptysis that is not controlled by embolization [10,25,43]. *Burkholderia cepacia* complex does not colonize people without CF, but can cause infection in individuals who are immunocompromised. Most transplant centers exclude patients with growth of *Burkholderia cepacia* complex on airway cultures. The survival rate post-transplant is approximately 50% [43].

Nutrition and pancreatic enzyme

Appropriate nutrition should not be neglected in CF patients given the strong correlation with long-term survival [54]. CF Foundation recommends that patients with pancreatic insufficiency consume a high-calorie diet with unrestricted fat and have regular evaluation by a dietitian [55]. Additionally, fat-soluble vitamin (*i,e.* A, D, E, and K) supplementation is recommended, as pancreatic insufficiency patients are prone to malabsorption [43]. Pancreatic enzyme supplementation should be initiated in patients that demonstrated evidence of steatorrhea such as diarrhea, foul-smelling stools, weight loss, flatus and fat-soluble vitamin deficiency. Newly diagnosed adults should undergo 72-hour fecal fat collection, and initiate pancreatic enzyme supplementation if it demonstrates fecal fat excretion greater than 7% [35]. Enzyme dosing can be calculated based on amount of fat ingestion and will normally range from 500-4,000 lipase units per gram of fat ingested per day [55]. Enzyme supplementation should be given with meals and snacks, and dose should be incrementally increased if symptoms of steatorrhea persist. Doses higher than 4,000 lipase units per gram of fat ingested per day increase risk of fibrosing colonopathy, and should therefore be decreased as soon as possible [43,55]. Fibrosing colonopathy results from ingestion of large quantities of pancreatic enzyme supplements, and can result in colonic strictures. The mainstay of treatment is reduction in pancreatic enzyme dose and adequate nutritional support. In some cases enteral elemental feeding, total parenteral nutrition or surgical intervention may be necessary [55].

CF related liver disease

The most common CF-related liver disease is cholestasis, which may sequentially progress to focal biliary cirrhosis and multilobular cirrhosis. Screening for liver disease should be done on yearly basis with panel of liver function test and careful examination of the liver and spleen at each clinic visit. A multidisciplinary team including CF center staff, gastroenterologist/hepatologist, surgeon experienced in hepatobiliary surgery and radiologist is recommended for the management of liver disease [33,43]. The goal of therapy should be to minimize ongoing liver damage and prevent progression to cirrhosis. Treatment of hydrophilic bile acid, ursodeoxycholic acid (UDCA), improves biochemical indexes of liver injury and pruritus by increasing bile flow in CF related cholestasis. However, no conclusive evidence has shown that UDCA improves mortality or alters progression to cirrhosis [33]. Nevertheless, the use of UDCA is recommended for CF patients who have cholestasis-fibrosis-cirrhosis. Patients should be entered into clinical trials when possible so that useful outcome data can be gathered [33,43]. Taurine is not recommended for treatment of CF-related liver disease [33]. Patients with CF-related liver disease should be immunized with complete series for hepatitis A and hepatitis B virus [33].

Decompensated cirrhosis and liver failure are uncommon in cystic fibrosis, but are likely only going to increase over the next decade as median survival continues to improve. Liver transplantation should be considered in CF patients with decompensated cirrhosis/liver failure. Early referral should be considered for CF patients with relatively well preserved pulmonary function [33,43].

CF related diabetes mellitus

Cystic fibrosis-related diabetes (CFRD) occurs in 40-50% of adults and shares features of type 1 (insulin insufficiency) and type II diabetes (insulin resistance). Screening for CFRD should be performed yearly using the 2-hour 75-gram oral glucose tolerance test beginning by age 10 years in all CF patients. Hemoglobin A1c is not a sufficiently sensitive screening test for diagnosis of CFRD [43,56]. The CF Foundations recommends quarterly evaluation by a specialized multidisciplinary team with expertise in diabetes and CF, quarterly hemoglobin A1c measurement and annual monitoring for microvascular complications per the American Diabetes Association guidelines once diagnosis of CFRD has been established. Patients should be treated with insulin therapy, as oral agents are ineffective and not recommended. Patients should receive ongoing diabetes

self-management education and monitor blood sugars at least three times daily once on insulin therapy [56]. Moderate aerobic exercise for at least 150 minutes per week should be strongly encouraged. Nutritional management does not include calorie restriction in CFRD because of the importance of adequate caloric intake to maintain body mass index in CF patients. Patients should continue a high calorie-diet with unrestricted fat and goal of maintaining good nutritional status [56].

CFTR modulating therapies

Novel treatments in cystic fibrosis have aimed to correct the dysfunctional CFTR protein by enhancing normal biogenesis, facilitating translocation to cell surface, increasing channel activity and decreasing channel turnover/destruction. The first major breakthrough was the development of VX-770 (Ivacaftor), a CFTR potentiator that increases activity of defective CFTR proteins in patients with Gly551Asp (G551D) mutation. It demonstrated clear restoration and improvement of CFTR function. Phase 3 clinical trials and observational studies have shown normalization of sweat chloride test, improvement in FEV1 % of predicted, increase in body mass index and decrease in hospitalizations with ivacaftor therapy in patients with G551D mutation [57-59]. Use was initially limited as the G551D mutation is only present in 4-5% of CF patients. However, subsequent studies have expanded use of ivacaftor to patients with non-G551D class III gating mutations, in addition to class IV and V mutations. Clinical trials have shown improvement in lung function with ivacaftor monotherapy in patients with at least one copy of Arg117His (R117H), a class IV mutation [59-61]. However, ivacaftor has shown limited clinical benefit in patients with the most common mutation, Phe508del (F508del). Fortunately, a corrector molecule VX809 (lumacaftor) was introduced to enhance folding and facilitate translocation of CFTR to cell surface. Lumacaftor has been shown to effectively increase the amount of CFTR protein on the cell surface *in vitro*, but monotherapy has shown limited effect in human trials [60]. The second major breakthrough came with lumacaftor-ivacaftor combination therapy. Two phase 3, randomized, double-blinded, placebo-controlled studies assessing the effect of lumacaftor-ivacaftor combination therapy in a total of 1108 patients with homozygous F508del (class II mutation) showed significant improvement of FEV1 % of predicted [62]. This has expanded CFTR modulating therapy options to a majority of CF patients. Both Ivacaftor and lumacaftor have demonstrated safety and tolerability.

Emerging therapies

The development and implementation of CFTR modulators has opened new horizons in CF treatment. Their goal is to restore robust CFTR function, and thereby dramatically improve clinical outcomes. Combination therapy with lumacaftor-ivacaftor has not demonstrated significant benefit in heterozygous F508del, but stronger potentiatorsare already in the pipeline. One example is VX-661, a second corrector molecule with longer half-life than lumacaftor [63]. Early trials show promising results in patients with F508del/G551D genotype on combination therapy with VX-661 and ivacaftor. The most recent breakthrough in CF treatment is the introduction of read-through agents that selectively override premature stop codons seen in class I mutations. PTC-124 (Ataluren) is a read-through agent currently undergoing phase 3 clinical trial with promising results [8]. If effective, ataluren will expand CFTR modulator therapy to class I mutations. Combination therapy with new and more potent CFTR modulators has brought us closer to restoring robust CFTR protein function. Additionally, recent advances in gene therapy have made complete restoration of CFTR and cure of cystic fibrosis more realistic. Use of CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9 (CRISPR-associated nuclease 9) genome editing system has been shown to correct CFTR locus by homologous recombination in cultured intestinal stem cells of CF patients [64,65]. More recently the CRISPR-Cas9 genome editing system has been used in induced pluripotent stem cells from CF patients with homozygous F508del. It precisely corrected the mutation and showed recovery of normal CFTR expression and function in subsequently differentiated airway epithelial cells [66].

CONCLUSION

New therapies and advances in treatment since the discovery of CFTR gene responsible for CF have revolutionized care of cystic fibrosis and dramatically improved survival. Care of cystic fibrosis patients uniquely employs a multidisciplinary team approach, while providing personalized medicine based on genotype and phenotype. New horizons in CF treatment have predominantly focused on CFTR modulators to restore robust CFTR function. These novel therapies are a prime example of personalized medicine that targets underlying dysfunction of CFTR protein based on patient's unique genetic mutation. Continued discovery of stronger CFTR modulators, along with promising results from gene therapy trials, further increases the likelihood of possibility of a cure.

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