Common clinical features of CF (respiratory disease and exocrine pancreatic insufficiency)

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Summary

First described as a disease of the pancreas, cystic fibrosis is a genetically inherited progressive disease affecting multiple organ systems. Pulmonary and pancreatic involvement is common in individuals with cystic fibrosis, and the former is attributable to most of the mortality that occurs with the condition. This chapter provides an overview of a clinical approach to the pulmonary and pancreatic manifestations of cystic fibrosis.

Introduction

Historically, references to the clinical presentation of cystic fibrosis (CF) date back to the 1650s to the early 1800. Subsequently in 1938, Dr. Dorothy Anderson first described this disorder in medical literature and named it “cystic fibrosis of the pancreas” on the basis of autopsies of malnourished children [1]. Since the discovery of the cystic fibrosis gene in 1989, there has been rapid understanding of the pathophysiology of the disease caused by the absence or defect of the CF gene product, and novel treatments for this multi-organ disease. Below, we provide a detailed review of the pulmonary and pancreatic clinical manifestations of CF.

CF lung disease

Pathophysiologic changes in CF arise from the time of conception, some are apparent in utero and progress to be clinically apparent later in life (figure 1) [2]. Although the CF lungs appear to be relatively normal at birth, the pulmonary complications lead to most morbidity and premature mortality seen in the disease [3-5]. Absent, or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein activity in the airway epithelial cells leads to abnormal chloride, sodium, and bicarbonate conductance [6]. This in turn may lead to depletion of airway...
surface liquid (ASL) resulting in ineffective mucociliary transport, accumulation of thickened mucus in distal airways and submucosal glands [7], and development of obstructive pulmonary disease [8]. The ductal dilation due to mucus blockage and the mucopurulent secretions coating the airways are hallmarks of CF airways disease, with the latter representing one of the earliest observed changes in infants and children with CF lung disease. Glandular hyperplasia in submucosal regions with surrounding inflammation in the peribroncholar regions may also be pronounced [6]. The obstructive changes in association with predominantly neutrophilic inflammation may be visualized as bronchial wall thickening and air trapping with high-resolution computerized tomography studies [9]. The clinical manifestations of CF lung disease can vary dramatically based on patient and disease factors, and can include chronic cough productive of tenacious mucus, dyspnea, and systemic features including malnutrition. The characteristic development of bronchiectasis is irreversible, and establishes a vicious cycle of reduced mucus clearance, inflammation and infection over the disease course [6,10]. A simplified pathway of the pathophysiology of CF lung disease is summarized in figure 2. For a more detailed description of the pathophysiology of CF lung disease, please see the accompanying manuscript in this journal issue.

Pulmonary disease status is most commonly tracked longitudinally through measurement of forced expiratory volume in 1 second as a percent predicted value (FEV1%) adjusted for demographic features. Though use of FEV1 as the primary measure of pulmonary health has been challenged, it remains an important measure for defining lung disease severity [11,12], diagnosis of pulmonary exacerbation [13,14], assessment of treatment response [15-17], and as an efficacy endpoint in clinical trials [18,19]. Low radiation computed tomography (CT) of the chest may be a more sensitive tool for disease progression, but the radiation exposure that CT requires remains a barrier for repeated measurements. Aside from spirometry, limited data exists describing either structural progression or the epidemiology of CF lung disease throughout a patient’s lifespan. Concurrent with improved survival, FEV1% predicted has improved dramatically over time in both children and adults with CF in the most recent birth cohorts based on data from the US CF Patient Registry [20]. This same data registry notes that the majority of US children who reach 18 years of age now have normal or mild lung disease [20]. Children less than six years are usually unable to perform spirometry reliably. Thus, FEV1 is first measured in children of school age and monitored serially. For those less than six years of age, other measures such as chest imaging, infant pulmonary function tests, and newer tools such as the lung clearance index (LCI) may be utilized [21-23]. Use of these more sensitive modalities may identify earlier pulmonary function abnormalities in infants and young children that may not otherwise be detected; although not routinely used in the clinic setting, these new tools may eventually be key to identifying early lung disease and following the evolution of CF lung disease.

**Figure 1**

Pulmonary exacerbations

CF lung disease is progressive, and individuals experience an annual decline in lung function as measured by FEV1% predicted of approximately 1%-3% per year; rates of decline however can be quite variable based on age, genotype, socioeconomic status, sputum microbiology and other clinical factors [24,25]. Lung function decline may be hastened by punctuating recurrent clinical events termed pulmonary exacerbations. Exacerbations in CF lung disease are frequent in both CF children and adults, and can clinically present as changes in respiratory or systemic status including cough, dyspnea, sputum quantity and character, reduced spirometric values, decreased appetite or energy, fever, or weight loss [14]. The cause of pulmonary exacerbation events are thought to result from a complex interplay of host immunity factors, airway microbiology, mucus production and airflow obstruction [14]. A number of viral (like influenza and respiratory syncytial virus) [26,27] and bacterial pathogens [28,29] have been implicated as triggers of acute pulmonary exacerbations; some have hypothesized that the inflammatory response to these infections lead to the clinical presentation [30,31].

Although pulmonary exacerbations are critical events in the course of CF lung disease, no clear diagnostic definition exists. A number of instruments have been proposed for diagnosis of a pulmonary exacerbation using a combination of symptomatic, clinical, laboratory, or treatment criteria [18,32,33], but no consensus has yet been reached. One of the most commonly used instruments in clinical trials has been the Fuch’s criteria (box 1). This definition has never been formally validated [18] but does provide a starting point.

Large population registries have demonstrated that pulmonary exacerbation rates in CF increase with age as individuals go through adolescence and young adulthood [13,14]. Exacerbation rates also increase with severity of lung disease, carrying a linear relationship in adulthood as lung function declines, and a non-linear relationship in children, whereby rates increase exponentially at lower lung function values [14]. Exacerbations are significant events in CF as they have been associated with decreased 2 and 5-year survival [34,35], and decreased lung function [36] (FEV1% predicted) including a failure to recover despite treatment [16,37]. Further, pulmonary exacerbations have been associated with development of cystic fibrosis

Box 1

Diagnostic criteria for a pulmonary exacerbation by Fuchs et al. [18]. Four out of the 12 features and physician decision to give IV antibiotics were required

“Exacerbation of respiratory symptoms”: a patient treated with parenteral antibiotics for any 4 of the following 12 signs or symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue of lethargy
- Temperature above 38 °C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10 percent or more from a previously recorded value
- Radiographic changes indicative of pulmonary infection
related diabetes (CFRD) [38], sleep disturbances [39], and health-related quality of life parameters [40]. Pulmonary exacerbations are important markers of disease severity [14] and serve as an outcome measure in CF clinical trials of diagnostic and therapeutic tools [41].

Most of the observational research has focused on CF pulmonary exacerbations defined by the use of intravenous antibiotics. However, CF pulmonary exacerbations occur along a wide spectrum from mild clinical events usually managed in outpatient settings with oral antibiotics to severe events requiring intravenous antibiotics and hospitalization including critical care. Mild exacerbations are not well studied or understood, and lack a clear definition; they may represent early stages of a more severe exacerbation, or a unique clinical presentation in itself [14].

Although the need for treatment of mild exacerbations has been questioned, observational data suggests that aggressive antibiotic treatment is associated with improved levels of lung function [42]. Management of CF lung disease is complex and requires a multifaceted approach of preventative, diagnostic, and treatment strategies. Airway clearance to mobilize secretions, prevention of chronic infection or eradication where possible (e.g. P. aeruginosa), optimization of nutritional status, and provision of psychosocial support all with patient involvement are critical aspects of CF care both in times of health and illness [8,43]. Additionally, patients may be treated with a combination of oral, intravenous, or inhaled therapies for pulmonary exacerbations based on severity and other patient factors. Evidence on the optimal approach to management of pulmonary health maintenance and treatment of pulmonary exacerbations is lacking, and is currently based on standards of care and management guidelines that have been developed by national and international CF societies [43-45]. Development of national registries [46-48] of CF patients since the 1960s have enabled clinical research [49-53] and the monitoring of care patterns, but have also highlighted the inconsistencies in clinical practices and outcomes between centers and countries [54,55]. Recent contemporary clinical trials are aiming to use rational study designs to construct an evidence based approach to CF pulmonary exacerbation management (NCT01349192, NCT01104402, NCT02781610), and may inform future research endeavors in CF lung disease.

**Pulmonary infection and microbiology**

Chronic endobronchial infections (bronchiolitis, bronchitis, and bronchiectasis) with a variety of pathogens are a hallmark feature of CF lung disease. Classic bacterial pathogens in the CF airways start with *Staphylococcus aureus* and *Haemophilus influenzae* in mild or early disease and the transition to *Pseudomonas aeruginosa*. *P. aeruginosa* is the archetypal pathogen in CF, establishes chronic infection in a large proportion of patients, and has been associated with significantly increased morbidity and mortality [36,56]. The deleterious outcomes of *P. aeruginosa* have led to the establishment of successful eradication programs over the past two decades, and indeed both the incidence and prevalence of *P. aeruginosa* have decreased in recent years [51,57].

Viral infections are also commonly identified in the airways of CF patients, and have been implicated in pulmonary exacerbations [58]. Fungal species including *Candida* and *Aspergillus* are also frequently identified, but limited data exist as to their causative role in CF pulmonary exacerbations and lung disease progression [59].

In addition to the classic pathogens, in recent years, microbial epidemiology has become increasingly complex with emergence of a number of additional pathogens including *Achromobacter xylosidans*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex and increased rates of Methicillin resistant *Staphylococcus aureus* (MRSA) [60-62] (figure 3). MRSA rates have risen dramatically and occur in upwards of 30% of patients
in specific US centers [60,63,64], although rates remain low in Europe, the UK, Canada, Australia and New Zealand. The risk of infection with many of these pathogens including *B. cepacia* complex increases with age in individuals with CF. The exact rates of infection vary between populations and CF pulmonary disease severity. The evolution of CF microbiology is thought to be related to selective antimicrobial pressures, a survivor effect in CF, and improved microbiologic diagnostics. Traditionally, CF patients were thought to acquire pathogens uniquely from the environment, but a number of transmissible strains have been identified. Notably, epidemiic or shared-strains of *Burkholderia cenocepacia* were associated with rapid clinical deterioration termed the "Cepacia syndrome" in pre and post-transplant CF patients [65,66]. A number of epidemic strains of *P. aeruginosa* have been identified and have variably been associated with increased morbidity and mortality [67-70]. More recently of concern, *Myxobacterium abscessus*, a highly resistant non-tuberculous mycobacteria with significant associated morbidity has been demonstrated to have potential for direct or in-direct person-person [71] transmission [72-74]. Identification of these transmissible pathogens in CF has led to the development and enhancement of infection prevention and control [75] measures as a key facet of CF patient care [76,77].

Until recently, our understanding of the CF airways microbiology had relied on culture-based methods, and a belief of airway sterility. The advent of non-culture-based methodology including the more widespread use of high throughput sequencing methods have identified that CF airways consist of a rich and complex polymicrobial milieu [78,79]. A number of non-classic anaerobic bacterial species have been identified in CF airways including *Prevotella*, *Veillonella*, and *Fusobacterium*, though their significance remains to be elucidated [80,81]. Although the constituents of the airway microbiome can be largely cultured using enriched methods [82], standard microbiologic laboratory methods do not enable this degree of identification. Emerging evidence suggests that CF patients have a vast microbrial community that decreases in diversity with increasing age and lung disease severity [83,84]. Further research is required to understand the complex interplay of the airway microbial milieu with the natural history of lung disease in CF.

**CF pulmonary complications**

In addition to progressive obstructive lung disease, cystic fibrosis (CF) patients are prone to various non-infectious pulmonary complications. These issues have become increasingly common with improved survival in CF and can impact disease trajectory.

**Hemoptysis**

Hemoptysis is common in CF, with an annual incidence of 1-2% and 4.1% of patients experiencing massive hemoptysis during their lifetime [85-87]. The pathogenesis involves chronic airway inflammation leading to local angiogenesis and hypertrophy of the systemic bronchial arterial circulation. Adjacently, bronchial inflammation can weaken arterial walls leading to intermittent hemorrhage [85,88,89]. Although bleeding can occur in younger patients, the incidence increases in adults and with advanced lung disease, with CF Foundation data showing that 61% of CF patients with massive hemoptysis (> 240 mL per 24-hour period or clinical instability) had an FEV1 <40% predicted [85,88-90]. The clinical presentation of CF-associated hemoptysis can be varied, with some patients having scant bleeding and minimal associated symptoms, and others life-threatening hemorrhage. Because of the spectrum, management should begin by assessing bleeding severity. Guidelines recommend that CF patients contact their provider if blood volume is ≥ 5 mL, or for smaller volumes (scant) if it represents their first episode. Scant bleeding can often be managed in the outpatient setting, whereas massive hemoptysis invariably requires hospitalization [86,91]. Unfortunately, as noted in the US CF Foundation’s pulmonary guidelines for hemoptysis, much of our clinical approach is not supported by high quality evidence [86]. Given the absence of evidence, recommendations regarding management needed to focus on a Delphi approach with experts in pulmonary medicine, radiology, surgery and interventional radiology [86]. Management requires a multifaceted approach supporting gas exchange and addressing decisions for individual treatments including bronchial artery embolization (BAE). Firstly, because hemoptysis is often precipitated by acute CF exacerbation, antibiotics are recommended for patients with at least mild (≥ 5 mL) hemoptysis, or smaller volumes if other concerning features are present [18,43,86,87,92]. Whether to initiate or continue other treatments is based on bleeding severity and risks/benefits of the particular therapy. For massive hemoptysis, hypertonic saline should be discontinued due to risk of airway irritation, as should mechanical clearance therapies for risk of clot disruption [86,93]. In mild-to-moderate hemoptysis, the strategy should be individualized for a given patient. Our clinical approach is to hold inhaled treatments (pulmozyme, hypertonic saline, inhaled antibiotics) for 24–48 hrs, introducing them one at a time and evaluating patient tolerance. Studies have evaluated the role of BAE for CF-associated hemoptysis. BAE risks including ischemic complications (infarction of the spinal column due to embolization of the anterior spinal artery or pulmonary infarction) should be recognized, along with the fact that most CF-associated hemoptysis abates without intervention. Furthermore, particularly with advanced CF lung disease, the bronchial circulation may participate in gas exchange, thus presenting additional risk of respiratory failure after BAE in those with limited pulmonary reserve [94-96]. After assessment of risks and benefits, BAE is recommended for CF patients with massive or persistent hemoptysis and clinical instability. Unlike in the general population, testing to localize CF-associated hemoptysis prior to BAE [bronchoscopy, computed tomography (CT)] is rarely necessary [86]. Instead, some, but
not all, advocate that all large and suspicious bronchial arteries should be embolized, although firm recommendations are lacking \[86,97\]. BAE success rates are high, initially controlling bleeding in 75–97% of CF patients, but recurrent hemoptysis does occur in 23–46% \[85-89,96,98\]. Observational research from registry data suggest that massive hemoptysis in CF is associated with lung function decline, increased healthcare utilization, and a 1-year mortality of 35% \[85,96\]. Even in patients with milder disease (FEV1 > 50% predicted), the 2-year relative risk of dying after massive hemoptysis is approximately 7. Given the guarded prognosis, an episode should lower the threshold for lung transplantation referral \[99\].

Pneumothorax

Spontaneous pneumothorax affects 3.4% of CF patients with annual incidence of 0.64% \[100\]. CF-associated pneumothoraces result from airway inflammation and mucus impaction leading to air trapping, alveolar overdistention, and rupture \[100–102\]. Subpleural bleb rupture represents a less common mechanism \[103–105\]. The incidence of pneumothorax increases with age and lung disease severity, with US CF Foundation data showing that 75% of patients suffering pneumothorax had FEV1 < 40% predicted. Other associated risk factors (some reflecting severe lung disease) are in Table 1 \[100\].

Pneumothoraces in CF are associated with significant morbidity, mortality, and increased health care utilization \[100,106–108\]. US CF Foundation data show a median survival after pneumothorax of about 30 months and a 2-year mortality of 48.6%, with estimated attributable mortality of 6.3–14.3% \[100,109\]. CF-associated pneumothoraces can be found incidentally, but the majority of patients present with pain, breathlessness, or respiratory failure \[102,110,111\]. Diagnosis is usually established with chest radiograph, although CT may be required for small pneumothoraces or in patients with pleural adhesions \[104\].

Management is aimed at safe resolution and prevention of recurrence \[86,102,112\]. All patients with large pneumothoraces or clinical instability should be hospitalized. Initial management is similar to the general population, by tube thoracostomy for large pneumothoraces or smaller pneumothoraces with clinical instability.

Other treatment decisions should address gas exchange and initiation/continuation of medical therapies. CF-associated pneumothoraces can occur during exacerbations, but mandatory antibiotics are not imposed by current guidelines, with this decision instead guided by other clinical features \[86\]. Although aerosolized treatments may pose a risk of airway irritation, guidelines do not require discontinuation at the time of presentation \[86,93\]. Mechanical clearance therapies should be evaluated on a case-by-case basis; for all pneumothoraces, it is appropriate to discontinue intrapulmonary percussive ventilation. For large pneumothoraces, discontinuation of other clearance therapies should be considered, with this decision factoring in the requirement for mucus clearance, the presence or absence of chest tube(s), and other clinical factors. Gas exchange should be supported with supplemental oxygen as needed avoiding non-invasive or positive pressure ventilation if possible due to the concern of converting a pneumothorax into a tension pneumothorax.

Recurrence of CF-associated pneumothoraces is common, with rates of initial chest tube failure or subsequent relapse ranging between 37–90% \[86,102,113,114\]. Preventing recurrence is challenging and a variety of strategies have been employed including sclerosant agents, pleural abrasion, pleurectomy, and Heimlich valves \[115–119\]. The decision for pleurodesis is influenced by the recurrence risk weighed against the risks of intervention. Additionally, although lung transplantation can be successfully performed in patients with previous pleurodesis, this does impact the complexity of the operation \[120,121\]. Therefore, CF guidelines recommend reserving pleurodesis for patients with recurrent, large pneumothoraces. In most cases, surgical pleurodesis is preferable, and ideally should be discussed with the CF centers associated lung transplantation center. Regardless, due to the prognostic implications, the occurrence of pneumothorax in CF patients should prompt consideration for referral to a lung transplantation center \[99\].

### Pulmonary Hypertension

Pulmonary hypertension is an important complication of CF, occurring in between 20–63% of patients depending on the population and definitions \[122–130\]. The pathophysiology involves chronic hypoxic vasoconstriction leading to progressive remodeling and destruction of the pulmonary vascular bed \[131–133\]. CF patients with severe lung disease and hypoxia are most frequently affected \[134–136\].

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**Table 1**

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<th>Risk factors associated with pneumothorax in cystic fibrosis patients [100]</th>
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<td>Severe lung disease</td>
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<td>Pancreatic insufficiency</td>
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<td>Low socioeconomic status</td>
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<td>Dornase alfa use</td>
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<td>Inhaled tobramycin use</td>
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<td>Allergic bronchopulmonary aspergillosis</td>
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<td>Enteral feedings</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Burkholderia cepacia complex</td>
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<td>Aspergillus fumigatus</td>
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Although CF-associated pulmonary hypertension is typically mild, there is a subset of patients that develop higher pressures than would be expected for their degree of lung disease [129,132,137]. Therefore, providers should consider screening with transthoracic echocardiogram patients with advanced lung disease, hypoxia, or signs of right heart failure, or at the time of lung transplant evaluation [135].

The management of CF-associated pulmonary hypertension primarily involves optimization of CF-specific pulmonary therapies. Given the pathophysiology, special attention to ensure adequate oxygenation is required, including assessment for both exercise- and sleep-induced hypoxia, both of which are common with advanced parenchymal disease. Pulmonary vasodilators offer conceptual benefit and have been studied in small series, but are not currently an accepted modality but further research may demonstrate efficacy.

Given its association with severe lung disease, CF-associated pulmonary hypertension carries a poor prognosis. Many studies have found it to be a risk factor for death, with a median survival as low as 8 months after diagnosis, along with increased waitlist mortality among those listed for transplantation. Although more recent studies have not confirmed pulmonary hypertension as an independent risk factor for mortality, with the caveat studies utilizing echocardiograms to diagnose pulmonary hypertension in CF, it can be considered a marker of advanced disease that should prompt consideration of referral for lung transplantation.

Advanced lung disease, respiratory failure, and lung transplantation

Worldwide, patients with CF are surviving longer, and an increasing proportion of the CF population is now adults [20,138]. Most CF patients in the United States (US) transition to adult care with near-normal lung function, but progressive respiratory failure remains the primary cause of death for the majority [20,139]. As patients with CF age, lung function declines and eventually the FEV₁ reaches a threshold associated with increased pulmonary symptoms and increased mortality. Transplant-free survival after FEV₁ reaches < 30% predicted has increased over time. In observational survival data from three single-center CF cohorts, with patients eligible in 1977-1989 in Canada, 1975-1994 in the US, and 1990-2003 in the United Kingdom, median transplant-free survival after FEV₁ < 30% predicted was 2 years, 3.8 years and 5.3 years, respectively [140-142]. In a recent national US cohort study with patients eligible in 2003-2013, median transplant-free survival after FEV₁ < 30% was 6.6 years [143]. While this level of survival with advanced lung disease is greater than that seen in earlier years in similar persons with CF, there remains an approximately 10% per year probability of death once the FEV₁ has fallen below 30% of predicted [143].

Progressive respiratory failure in CF can manifest as hypoxemia and/or hypercarbia. End-stage CF-related lung disease can also be marked by several of the issues discussed above including rapid decline in FEV₁, hemoptysis, recurrent pneumothoraces, pulmonary hypertension, refractory pulmonary exacerbations requiring intravenous antibiotics and severe malnutrition [86,139]. Pulmonary exacerbations can precipitate a rapid decline in lung function and respiratory failure, especially among patients with an already severely reduced baseline FEV₁. As noted above, hemoptysis that is treated with repeated BAE has been associated with precipitation of acute on chronic hypercarbic respiratory failure and death, specifically among patients with an already severely reduced FEV₁ [95]. Supportive therapy for hypoxemic and/or hypercarbic respiratory failure in CF can be similar to treatments used in patients without CF, including non-invasive mechanical ventilation with bi-level positive airway pressure or invasive mechanical ventilation via an endotracheal tube [144,145]. Among CF adults with chronic respiratory failure, treatment of acute on chronic respiratory failure with invasive mechanical ventilation is associated with poor outcomes [145,146]. Mechanical ventilation can still be used as a bridge to lung transplantation in carefully selected patients [99]. Extracorporeal membrane oxygenation (ECMO) is a potential therapeutic option for patients with CF and acute or progressive chronic respiratory failure as a bridge to lung transplantation [147]. Patients with end-stage CF lung disease become increasingly deconditioned and malnourished as their condition worsens. The use of ECMO without mechanical ventilation (ambulatory, or "awake" ECMO) allows patients to improve physical conditioning through rehabilitation and continue eating to support nutritional requirements [147-149]. ECMO remains an uncommonly used modality for use in selected cases of transplant candidates; given the complexity and challenges of this intervention, it is only used in centers with appropriate staff and expertise.

Lung transplantation is an option for treating end-stage lung disease in CF and provides a known survival benefit [150]. Although lung transplantation carries short-term risks and a limited longevity, survival after lung transplantation is improving for patients with CF. The most recent median survival estimate for patients with CF following lung transplantation is 8.6 years, and the 1-year conditional median survival (for patients surviving at least one year post-transplant) is 11.1 years [151]. Lung transplantation has moved from the category of palliative therapy to an effective treatment that can add a substantial number of years to a patient’s life. The International Society for Heart and Lung Transplantation (ISHLT) recommends referral for lung transplant evaluation when a patient has a 2-year predicted survival of < 50% [99], but prediction of 2-year mortality in CF is problematic [34,35]. Referral for lung transplant evaluation is frequently considered in patients with CF once the FEV₁ is < 30%, but FEV₁ is not included in the international recommendations for listing patients with CF (table II) [99]. With improving survival for
patients with CF and FEV₁ < 30% [143], the timing of lung transplant referral and listing has become more challenging. In a recent US national cohort study, 2003–2013, almost 40% of patients with CF and FEV₁ < 30% die without lung transplantation [143]. A retrospective analysis of 256 deaths among patients with CF in France, 2007–2010, revealed that half of the deaths (n = 129) occurred in patients who did not undergo lung transplantation [152]. Among the patients who died without listing for lung transplantation despite having indications for transplant, transplantation was never considered in 39% of patients by their care teams; in cases where transplant had been considered, 25% of patients who died without listing had refused lung transplantation [152]. With the increasing survival benefit of lung transplantation, efforts to increase referral and listing of patients with CF should be prioritized.

In patients with end-stage CF lung disease, the burden of symptoms (especially pain and depression) and treatments can be tremendous for patients and their caregivers [153,154]. Listing for lung transplantation can complicate decisions related to management of symptoms and active treatment of the end-stage lung disease [153,45,155]. Despite the complexity of management, multidisciplinary palliative care in CF should focus on symptom management, communication, and support of the patient and family [153].

**Asthma as a complication of CF**

The diagnosis of comorbid asthma with CF is a challenge because of overlapping symptom profiles [156], greater day-to-day variation in measures of pulmonary function in patients with CF than in normal controls [157], and variable response to bronchodilators [158–161] and standard asthma therapies [162,163] among patients with CF. The North American Epidemiologic Study of Cystic Fibrosis (ESCF) has attempted to describe asthma in CF - “The diagnosis of asthma is suggested by the following: episodes of acute airway obstruction reversed by bronchodilators (especially if seasonal), a strong family history of asthma and/or evidence of atopy (such as eczema or hay fever), or laboratory evidence of allergy such as eosinophilia or elevated IgE” [164]. The prevalence of asthma in CF in the European Epidemiologic Registry of CF was 15–26% and varied depending on lung function; in both children and adults, there was more frequent identification of asthma-like symptoms among patients with lower FEV₁% predicted [165]. Although one could postulate that asthma would develop in patients with CF at rates that are comparable to patients without CF, there is debate about whether F508del heterozygous patients have increased susceptibility to or protection from asthma [156,166,167].

In order to avoid the addition of unnecessary treatments and their potential adverse effects, it is important for physicians to recognize the complexity of diagnosing asthma in CF. Airflow obstruction, bronchial hyperreactivity [168] and wheezing are common pulmonary manifestations of CF [156]. The underlying mechanisms of airflow obstruction in CF include airway edema due to chronic infection and inflammation, autonomic nerve stimulation related to epithelial damage from infection, airway smooth muscle contraction caused by inflammatory mediators, obstruction by abnormally tenacious secretions, bronchospasm, and secondary fibrosis [156,161,169,170]. Bronchodilator responsiveness is present intermittently for most patients with CF [161], but many patients with bronchodilator responsiveness do not have associated atopy [171] or a clinical diagnosis of asthma [156].

The most common asthma phenotype in patients without CF includes the development of antigen-specific IgE antibody to aeroallergens, contributing to both acute asthmatic symptoms
and chronic airway inflammation [172]. The presence of IgE-mediated reactions to environmental antigens (aside from Aspergillus) may identify the patients with an asthmatic phenotype of CF [172]. Unfortunately there remains no gold standard for diagnosing asthma in patients with CF, but atopy may be the key to identifying some of the patients with concurrent asthma and CF [156,172].

Exhaled nitric oxide (NO) measured orally is typically increased in patients with asthma and is normal in patients with CF; exhaled NO measured nasally is typically reduced significantly in patients with CF when compared to those with asthma or controls [173]. Unfortunately, inter-subject variability in exhaled NO is substantial for CF patients, which limits the utility of using exhaled NO cut-points to diagnosis asthma in this population [172,174].

Bronchial hyperreactivity is a response to inhaled directly-acting smooth muscle constricting agents (e.g. methacholine or histamine). Studies have shown high rates of bronchial hyperreactivity in both children [175] and adults [176] with CF, but results of bronchial provocation testing are variable over time in the CF population [177]. Abnormal response to bronchial provocation testing has been associated, however, with worse pulmonary function in patients with CF [177,178].

In the US CF Foundation Patient Registry in 2014, a median of 96.1% of patients across CF care centers were prescribed inhaled beta-agonists, irrespective of concurrent asthma diagnosis [20]. A Cochrane Review of inhaled bronchodilators documented the net benefit of both short- and long-acting beta-agonists in patients with CF and either bronchodilator responsiveness or bronchial hyperreactivity [179]. Based on the good level of evidence for a moderate benefit, the US CFF guidelines recommended the chronic use of inhaled beta-agonists for all patients with CF over the age of 6 years [170]. Importantly, 10-20% of patients with CF have worsened maximal expiratory flow rates or FEV1 after the administration of bronchodilators, which is thought to be the result of the collapse of large airways in the setting of smooth muscle relaxation [159,161,169]. Consideration of beta-agonist use for patients with CF on a case-to-case basis, with re-evaluation over time, should depend on the patient’s clinical and/or objective response to the agent [156]. For patients with CF, without a diagnosis of asthma or allergic bronchopulmonary aspergillosis (ABPA), there is insufficient evidence to support the routine use of inhaled corticosteroids to improve lung function or reduce exacerbations [170]. Therefore, diagnosis of asthma in CF versus asthma symptoms due to CF-related lung disease affects treatment decisions. Clinicians should carefully consider asthma-specific therapies in atopic patients with CF, and have vigilance surrounding discontinuation of these therapies if there is a lack of benefit is appropriate [180].

**Allergic bronchopulmonary aspergillosis**

Allergic bronchopulmonary aspergillosis (ABPA) results from an IgE-mediated (and also IgG-mediated) allergic response to *Aspergillus fumigatus*, which leads to bronchial airway obstruction [181]. ABPA is a relatively uncommon but important pulmonary complication CF; prevalence estimates range from 1 to 15% of the CF population, with most showing < 5% of CF patients affected [20,182-184]. Symptoms and signs of ABPA in patients with CF include wheezing, increased cough, exercise intolerance, pulmonary infiltrates, high attenuation mucus plugs, central bronchiectasis and pulmonary fibrosis with decreased FEV1 [182]. The course of ABPA is one of recurrent exacerbations [185]. ABPA may be associated with greater decline in pulmonary function [186] and can progress to respiratory failure [187-189].

Clinical deterioration that does not respond to antibiotic treatment should raise suspicion for ABPA in CF. Minimal diagnostic criteria for ABPA in CF were developed at the international Cystic Fibrosis Foundation Consensus Conference in 2003 (table III) [182]. Other investigators have attempted to describe ABPA in CF [183,184,190-194]. Total IgE level and the response of IgE to steroids have been suggested as valuable criteria for diagnosing ABPA in CF [182,183,191,195,196]. Skin testing and serum precipitating antibodies to *A. fumigatus* are sensitive markers of ABPA in CF [183,191]. Diagnosis of ABPA in CF may require asthma or airflow obstruction in the North American Epidemiologic Study of Cystic Fibrosis (ESCF), but instead included

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**Table III**

**Diagnosis of allergic bronchopulmonary aspergillosis (ABPA) in cystic fibrosis**

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<th>Criteria</th>
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<tr>
<td>Acute or subacute deterioration not attributable to another cause¹</td>
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<tr>
<td>Elevated total serum IgE concentration (&gt; 500 IU/mL or &gt; 1200 ng/mL)</td>
</tr>
<tr>
<td>Immediate cutaneous reactivity² to <em>Aspergillus</em> species or elevated serum IgE to <em>A. fumigatus</em>, and</td>
</tr>
<tr>
<td>IgG to <em>A. fumigatus</em> or precipitins to <em>A. fumigatus</em>, or</td>
</tr>
<tr>
<td>New abnormalities on chest radiography (pulmonary infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard chest physiotherapy</td>
</tr>
</tbody>
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¹Screening may also identify asymptomatic individuals with ABPA.
²Wheal > 3 mm in diameter with surrounding erythema.
bronchoconstriction as a minor criterion; ESCF also included peripheral eosinophilia > 1000 eosinophils/μL and response to steroids as minor criteria for ABPA diagnosis [184]. Peripheral blood eosinophilia is a component of diagnosing ABPA in patients without CF, but peripheral eosinophilia is common in patients with CF without ABPA [183] and may be related to chronic *Pseudomonas aeruginosa* infection [182]. Central bronchiectasis may be a late finding in ABPA in CF and patients can be seropositive for ABPA without evidence of more advanced lung scarring [192]. Sputum culture with *A. fumigatus* is supportive of a diagnosis of ABPA but is not diagnostic [185]. Due to the potential for progression to respiratory failure, the US CF Foundation Guidelines recommend that CF physicians should maintain a high degree of suspicion for ABPA in patients with CF who are older than 6 years of age [182]. Annual screening for ABPA is recommended using total serum IgE levels and peripheral eosinophil counts [191]. If total serum IgE concentration is > 500 IU/mL, further testing (i.e. cutaneous reactivity to *Aspergillus* species, serum IgE to *A. fumigatus*, serum IgG to *A. fumigatus* or precipitins to *A. fumigatus*, and/or chest imaging) is recommended to determine whether the minimal diagnostic criteria for ABPA are present [182]. If the total serum IgE concentration is 200–500 IU/mL, then the IgE level should be repeated in 1–3 months if there is clinical suspicion for ABPA and further testing could be indicated [182]. Early treatment of ABPA, prior to the development of associated bronchiectasis and fibrosis, may slow the natural history of the disease and improve the prognosis [185].

Treatment recommendations for ABPA in CF are based on limited available data, but treatment should be considered when a patient is symptomatic without another explanation for the decompensation and has serologic and/or radiographic evidence of ABPA [182]. Frequently, treatment for a CF pulmonary exacerbation with antibiotics, prior to or concurrently with ABPA therapy, is indicated [182,185]. Treatment of ABPA is focused on decreasing inflammation and reducing the allergen burden [185]. High dose oral corticosteroids are the mainstay of treatment for ABPA, which remains true for ABPA in CF [185]. Systemic steroids in patients with CF have potentially greater toxicities than in patients with ABPA and asthma because of the increased risk of diabetes/diabetes control, osteoporosis and worsening pulmonary infections in this patient population. Itraconazole is sometimes used as a steroid-sparing agent in relapsed ABPA in CF [182,185]. Inhaled corticosteroids have been studied in ABPA and may provide some benefit in reduction of oral steroid doses [185,197]. Omalizumab is an anti-IgE recombinant humanized monoclonal antibody more recently being used in select ABPA cases with some reported success though no recommendations relating to its use in CF exist due to lack of efficacy and safety data [198–200]. Some suggest exploring the patient’s environment to remove significant mold exposures, but this is not based on any evidence for efficacy [182].

In summary, ABPA is an important pulmonary complication in CF and routine surveillance is indicated to identify individuals early in their course. Multiple diagnostic approaches have been described in the literature. Treatment of exacerbations of ABPA in CF requires consideration of simultaneous treatment for pulmonary exacerbation due to CF. The primary therapy for ABPA in CF is oral corticosteroid treatment.

**Exocrine pancreas**

Pancreatic exocrine disease has been recognized since the initial clinical recognition of the disease and has led to the clinical finding of “cystic fibrosis of the pancreas” the disease’s primary moniker in 1938, as noted above, due to the combined cystic and fibrotic disease noted in post-mortem pancreases from pediatric autopsy studies highlighted in Dr. Dorothy Anderson’s early work in CF [1]. Pancreatic exocrine disease is one of the earliest, often occurring in the first few months of life, and most consistent clinical manifestations of the disease [201]. The mechanisms by which defects in CTRR affect the pancreas and lead to pancreatic exocrine insufficiency have been advanced by a number of key animal models (CF pig and CF ferret). CTRR protein is present on the apical membrane of pancreatic duct epithelial cells; abnormal or absent CTRR protein in the duct likely leads to altered chloride absorption and bicarbonate secretion. Bicarbonate secretion into the duct leads to an osmotic gradient that facilitates pancreatic duct fluid flow [202]. With defective CTRR, the pancreatic fluid is low in bicarbonate with subsequent lower pH and reduced volume with increased protein concentration leading to zymogen degranulation [203] and activation and duct obstruction. This in turn leads to auto-digestion of the exocrine pancreas with replacement with inflammation and fibrosis with eventual fatty infiltration. Severe pancreatic destruction can be confirmed on Computed Tomography of the abdomen. The onset of this destructive cascade occurs early [204] in utero. In a study of 60 autopsy specimens from fetuses and infants who died at under 4 months of age [204], abnormalities were seen as early as 17 weeks gestation. Severe exocrine pancreatic dysfunction has been noted in up to 85% of newborns [205]. The disease of the exocrine pancreas is progressive; for those patients not diagnosed early in infancy, they may develop it in subsequent years. Data from the 2015 US CF Foundation Patient Registry notes that 87.1% of the 28,983 CF patients reported in the registry were taking pancreatic enzyme supplementation – this characteristic has often been used as a surrogate for actual pancreatic insufficiency.

Decreases in duodenal bicarbonate inactivate pancreatic enzymes and precipitating bile salts with subsequent loss of bile salts [206]. This in turn leads to inadequate lipid solubilization and increased fecal fat losses. The symptoms are driven in part by the exposure of the colon microflora to increased luminal fat content. Fat-soluble vitamin deficiencies that are seen include vitamins A, D, E, and K. Even in the setting of pancreatic
The diagnosis of exocrine pancreatic insufficiency is usually suspected through neonatal screening, and clinically suggested by signs and symptoms of fat malabsorption and reduced fatsoluble vitamin levels in the blood. Screening was implemented to try to prevent symptoms of nutritional failure particularly in infants and steatorrhea with greasy stools and flatus worsened by a high fat diet. Given the high rate of penetrance of this clinical manifestation of the disease, pancreatic insufficiency is usually suspected on screening and diagnosed in infancy. Direct measurement of pancreatic enzyme levels in the duodenum is possible but challenging and invasive. The traditional approach to diagnosing pancreatic insufficiency is by performing a 72 hour quantitative fecal fat collection using a standardized high fat diet (a high fat diet of 100 grams of fat/day or 3 g/kg/day). Stool is then collected utilizing stool markers (FD&C blue dye, two 250 mg capsules); this allows one to capture stool between two different blue dye markers separated by 72 hrs of oral ingestion. Absorption of dietary fat and nitrogen is markedly abnormal in CF patients with pancreatic insufficiency with as little as 40–50% of fecal fat absorbed without treatment [209]. In recent studies assessing the coefficient of fat absorption, the short-term placebo arms of the clinical trials noted a change of coefficient of fat malabsorption from 56.4 (SD = 24.93) with placebo to 86.8 (SD = 8.09) with pancreatic enzyme use [change = −34.1 (SD = 23.03)] [210]. Similar changes have been observed in other recent placebo controlled trials of enzyme efficacy [211-213]. An alternative approach to diagnosing pancreatic insufficiency in CF is to measure stool fecal elastase. Fecal elastase is one of over 20 enzymes excreted by the pancreas with the unique property of not being altered by gut transit [214] and is low in CF (< 200 μg/g) stool. In a large cross-sectional US study, 87% of CF patients (denominator was 1215) had a fecal elastase level of less than 100 μg/g stool [215], the current diagnostic threshold for pancreatic insufficiency. It is important to know that in the first year of life, fecal elastase can be quite variable – infants with levels between 50 and 200 μg/g of stool should be treated with pancreatic enzyme replacement but also re-measured at one year of age [216]; some of these children will have levels over 200 μg/g stool after 1 year of age. The reason for this variability is unclear. Data also supports the use of low daily weight gain (< 50th percentile) and abnormal steatorrhea in a clinical setting where fecal elastase is not available to diagnose pancreatic insufficiency in CF babies [217]. Unfortunately, the utility of identifying mild pancreatic insufficiency with fecal elastase is challenging.

Pancreatic enzyme replacement therapy (PERT) is used to supplant the lack of endogenous enzyme secretion in those patients diagnosed with pancreatic insufficiency. Standard recommended starting doses of PERT are as follows: 2500 U of lipase per kg per meal (or 10,000 U of lipase/kg per day). An alternative approach is to dose based on the grams of fat ingested on average per day (4000 U of lipase per g of fat per day). Clinicians must be aware that symptoms suggesting malabsorption with or without treatment with PERT may have alternative causes in CF like small bowel bacterial overgrowth, gastroesophageal reflux disease, *Clostridium difficile* induced colitis, inflammatory bowel disease, celiac disease, constipation, and distal intestinal obstruction syndrome in addition to rarer conditions like bowel cancer and volvulus. Careful clinical assessment must be done to rule out alternative causes of gastrointestinal symptoms by physical exam, laboratory testing (i.e. obtaining *Clostridium difficile* stool toxin level) and imaging.

Other clinical manifestations of the exocrine pancreas (notably episodic acute pancreatitis and pancreatic sufficiency) are seen in milder phenotypes of CF, specifically class IV and V mutations in CFTR [218]. These patients can develop late onset exocrine pancreas failure or experience recurrent acute pancreatitis. To assess association of milder CF genotypes with these clinical presentations, one can go to the John's Hopkins University CFTR2 website and get registry-based data that describe the clinical phenotype associated with the genotype (http://www.cftr2.org/). Clinicians should monitor pancreatic sufficient patients to ensure that they have not transitioned from partial pancreatic exocrine function to pancreatic exocrine failure. Evaluation of CF patients with pancreatitis should include exclusion of biliary stone disease and toxins (alcohol) as a cause.

**Conclusions**

CF is a multisystem genetic disorder with an evolving clinical phenotype with the advent of new therapies. The majority of the morbidity and mortality in CF is associated with the pulmonary manifestations of the disease. Given the complexity of pulmonary involvement and myriad of associated complications related to the disease, CF patients tend to get the majority of their care in specialized CF centers. These approved centers offer multidisciplinary care including physicians with expertise in pulmonary medicine, infectious diseases, diabetes, endocrinology, gastroenterology, hepatology, specialized nursing staff, nutritionists/dieticians, respiratory therapist, social workers and mental health experts. Given the increasing survival of CF patients due to improvements in care, primary care physicians and general practitioners will increasingly encounter CF patients in their practice settings, and increased collaboration between CF specialists and primary care physicians and general practitioners is encouraged.
References


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