



Asthma in Cystic Fibrosis: Definitions and Implications of This Overlap Syndrome

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Abstract

Purpose of Review Cystic fibrosis (CF) is a multisystem, autosomal recessive disease that leads to progressive loss of lung function. Respiratory symptoms for both CF and asthma include cough, wheezing, and dyspnea. There is debate within the CF community on how to best define and distinguish CF-asthma overlap syndrome (CFAOS) from asthma-like features, though CFAOS is well-recognized. We aim to review the epidemiology, diagnosis, and treatment of asthma in CF and explore areas where further research is needed.

Recent Findings There has been considerable improvement in the understanding and treatment of asthma over the past two decades leading to novel therapies such as biologic agents that target the airway inflammation in asthmatics based on their asthma phenotype. These therapies are being studied in CFAOS and are promising treatments.

Summary This review provides a comprehensive overview of the definition, epidemiology, diagnosis, and current treatment of CFAOS.

Keywords Asthma · Cystic fibrosis · Cystic fibrosis-asthma overlap syndrome

Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
CF	Cystic fibrosis
CFAOS	CF-asthma overlap syndrome
CFF	Cystic Fibrosis Foundation

CFTR	Cystic fibrosis transmembrane conductance regulator
CPET	Cardiopulmonary exercise test
ESCF	Epidemiologic Study of Cystic Fibrosis
FEV ₁	Forced expiratory volume in 1 s
ICS	Inhaled corticosteroid
LABA	Long-acting beta ₂ -agonist
LAMA	Long-acting muscarinic antagonist
PEFR	Peak expiratory flow rate
SABA	Short-acting beta ₂ -agonist

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Introduction Including Epidemiology

Cystic fibrosis (CF) is a rare, life-shortening, multisystem, genetic disease that results in progressive loss of lung function over time. It occurs when there are mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene resulting in a defective CFTR protein. Because the CFTR protein serves as a chloride channel in epithelial cells lining the respiratory tract, loss of function results in thick, dehydrated secretions and causes recurrent pulmonary infections and chronic airway inflammation. Respiratory symptoms can include cough, wheezing, and dyspnea, especially

during pulmonary exacerbations of CF. The 2017 Cystic Fibrosis Foundation (CFF) Consensus Guidelines provides updates for the diagnostic criteria of CF [1].

Asthma, on the other hand, is a common but complex and heterogeneous disease. Like CF, asthma is associated with chronic airway inflammation but with different underlying mechanisms. Distinct “asthma phenotypes” have been described. Over the last decade, an increasing number of genome-wide association studies have identified genetic variants that are strongly associated with asthma, as well as studies identifying the role of early environmental exposures plays in the development of disease [2–4]. The diagnosis of asthma is characterized by airway hyperresponsiveness, which leads to recurrent symptoms of cough, wheezing, shortness of breath, and chest tightness in response to stimuli with evidence of reversible bronchoconstriction [4]. Asthma often presents in childhood, although confirmatory diagnosis under 5 years of age is difficult because viral illnesses can also cause wheezing in young children.

The overlapping symptoms of CF and asthma present a diagnostic dilemma for clinicians. Investigators in the North American Epidemiologic Study of Cystic Fibrosis (ESCF) found that childhood wheezing in CF is common, occurring in over 60% during the first 6 years of life, and is associated with significantly lower lung function at 6–7 years of age when compared to children with no wheezing [5]. The ESCF suggests that asthma in CF occurs when there are episodes of acute airway obstruction, often seasonal in nature, and reversed by bronchodilators, a personal history of atopy or a strong family history of asthma, and/or laboratory evidence of eosinophilia. The concurrent diagnosis of asthma is determined by the opinion of the treating physician when symptoms of asthma contribute significantly to the individual’s lung disease [6]. Prevalence of asthma in the 2018 National Cystic Fibrosis Patient Registry Annual Data Report is 31.5%, peaking during adolescence, and then decreasing among adults. The 2018 NHIS Data estimates the national prevalence of asthma in the general population in the US to be 7.7%.

While bronchodilators and inhaled corticosteroids (ICS) are mainstays in the treatment of asthma, there is little evidence to suggest their benefit in the treatment of CF in the absence of asthma. Administration of inhaled beta₂-agonists can help relieve airway hyperresponsiveness and prevent bronchospasm associated with other inhaled therapies such as hypertonic saline and inhaled antibiotics. The presumption is that wide-scale and long-term use of inhaled beta₂-agonists in 96% of individuals in the registry is an adjunctive therapy for airway clearance. The CFF guidelines recommend against the routine use of ICS in individuals 6 years and older without a diagnosis of asthma or allergic bronchopulmonary aspergillosis (ABPA) [7]. Even so, ICS prescription without a diagnosis of asthma or ABPA occurred in almost 39% of

individuals according to the 2018 National Cystic Fibrosis Patient Registry Annual Data Report, highlighting the treatment dilemma clinicians face with the overlapping symptoms of CF and asthma and the potential for a subgroup that might benefit from ICS.

Diagnosis of Asthma in Individuals with CF

Asthma is typically a clinical diagnosis based on variable respiratory symptoms, including episodic wheeze, cough, and shortness of breath, which is usually in response to specific triggers. The documentation of variable expiratory airflow limitation, allergy tests, markers of airway inflammation, and imaging studies helps support the diagnosis [4]. Clinical symptoms and expiratory airflow limitation may improve either spontaneously, usually with the removal of the trigger, or in response to treatment. Unfortunately, making a diagnosis of asthma in CF is not straightforward as individuals with CF often exhibit many of the same symptoms, variable expiratory airflow limitation, and imaging findings without actually having concomitant asthma [8]. Table 1 summarizes the diagnostic testing used to identify asthma and how they may be used to identify CFAOS.

Clinical Presentation

Symptoms of episodic wheeze, cough, and shortness of breath suggest a diagnosis of asthma. The probability of asthma increases if individuals present with more than one of these symptoms and if symptoms are worse at night, vary in frequency and intensity over time, and are triggered by outside factors such as respiratory viral infections, exercise, changes in the weather, smoke or strong fragrances, and exposure to specific environmental allergens [4]. In CF, cough is a prevalent symptom and can vary in frequency and intensity over time. Wheezing and shortness of breath are both symptoms that can occur in CF, especially in the context of an acute pulmonary exacerbation, and are, therefore, nonspecific. Physical examination is also usually not helpful unless individuals have evidence of atopic diseases such as eczema. Family or personal history of atopic disease, including eczema or allergic rhinitis in individuals with CF, may help diagnose asthma but is more related to the strong association between allergic inflammation and asthma [8, 9].

Spirometry/Peak Expiratory Flow

Excessive variability in forced expiratory volume (FEV₁) or peak expiratory flow is a diagnostic feature of asthma [4]. Airflow variability in asthma refers to improvement or worsening of lung function over time, such as days or visits, or in response to reversibility tests, and it is often associated with an

Table 1 Summary of diagnostic testing by condition

	Cystic fibrosis	Asthma	Cystic fibrosis -asthma overlap syndrome
Clinical presentation	• Productive cough • Wheezing • Extra-pulmonary manifestations • Sudden onset shortness of breath with infections	• Dry cough • Wheezing • Sudden onset shortness of breath, especially in association with known triggers • Atopic exam finding may be present • Family history of asthma, atopy, or eczema	• Productive and/or dry cough • Wheezing • Atopic exam finding may be present • Family history of asthma, atopy, or eczema • Sudden onset shortness of breath, especially in association with known triggers • Sudden onset shortness of breath with infections • Many overlapping symptoms
Spirometry/peak expiratory flow	• Daily variability noted in CF • Predominantly small airways disease	• Excessive variability noted	• Limited data on the use of spirometry to distinguish CF, asthma, and CFAOS
Bronchodilator responsiveness	• Up to 60% have a bronchodilator response • May have an association with CFTR dysfunction	• Reversible response with SABA administration, 200 cc and 12% increase in FEV₁ or FVC when compared to pre-SABA measurements	• Inadequate to distinguish CF, asthma, and CFAOS
Bronchial provocation testing	• 40 to 50% have a response to bronchial provocation • May have an association with CFTR dysfunction • Positive response is associated with more severe lung disease, older age, and more rapid decline in lung function	• Characteristically responsive to challenge • Not specific to asthma	• Inadequate to distinguish CF, asthma, and CFAOS
Exercise testing	• Exercise is used as a form of chest physiotherapy • Correlates with increased peak flow and FEV₁, and decreased sputum impedance	• Used for the diagnosis of exercise-induced asthma • Increased shortness of breath and wheezing	• Need further investigation
Allergy testing	• Frequently reactive to fungi, especially <i>A. fumigatus</i>	• May have antigen-specific aeroallergens, including fungal and non-fungal allergens • May be more beneficial in atopic patients • Elevated in eosinophilic asthma	• Unclear role
Fractional concentration of exhaled nitric oxide	• Decreased levels		• Need further investigation

Abbreviations: CF cystic fibrosis, CFTR cystic fibrosis transmembrane conductance regulator, CFAOS cystic fibrosis-asthma overlap syndrome, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, SABA short-acting beta₂-agonists

obstructive airflow limitation. In CF, bronchiectasis and airway collapse, mucous plugging, airway mucosal edema, stimulation of autonomic nerve fibers, and airway smooth muscle contraction all contribute to the obstructive lung disease and airflow variability commonly seen [10, 11]. Large day-to-day variations in FEV₁ can be seen in CF without a change in clinical symptoms and also in the setting of acute exacerbations and is therefore not useful in differentiating lung disease from CF or concomitant asthma [12]. Peak expiratory flow is a measure of the flow rate through the large airways, and it may be used in asthma to diagnose airflow variability and monitor for signs of acute exacerbations [13]. However, CF disease primarily involves the small airways, so peak expiratory flow is not often used [14]. One study compared the effect of

inhaled bronchodilators or placebo on the peak expiratory flow of individuals with CF who had a positive methacholine challenge test and those that did not have a positive methacholine challenge test. This study revealed that only individuals with bronchial hyperresponsiveness had improved peak expiratory flow with the use of a bronchodilator when compared with placebo [15]. Variability in peak expiratory flow as a means to differentiate asthma in CF needs further investigation.

Bronchodilator Responsiveness

Variability in FEV₁ or peak expiratory flow associated with obstructive airflow limitation that is reversible with

administration of inhaled bronchodilators such as albuterol strongly suggests the diagnosis of asthma in non-CF individuals [4]. Studies of inhaled bronchodilators in CF have shown a variable response. Most studies of inhaled bronchodilators in CF show approximately 50–60% of participants have a significant response [10] regardless of having concomitant asthma, atopic disease, or family history of atopy [16]. One study [17] found that reversible airflow obstruction was associated with younger age and severe genotype but no association with a family history of asthma, serum IgE, or blood eosinophils. Other studies have shown a paradoxical reduction in FEV₁ with bronchodilator administration, possibly from the collapse of airways with decreased smooth muscle tone [10]. One study used newborn pigs with CF to show that CFTR regulates airway smooth muscle tone, seemingly independent of airway inflammation and mucus plugging [18•]. If bronchodilator response in CF may be related to the loss of CFTR function in airway smooth muscle cells. One study measured CFTR function, lung function, and airway distensibility 48 h after administration of the CFTR potentiator ivacaftor [11•]. CFTR potentiation improved CFTR function, airflow obstruction, and airway distensibility, and the authors concluded, because these changes occurred so quickly, they are likely due to relaxation of the airway smooth muscle from increased CFTR function. The effect of bronchodilators in people with CF may also be associated with genetic variability in inflammatory markers. One recent study showed an association between the interleukin-8 gene variant rs4073 and the response to inhaled bronchodilators in CF from specific mutations in the interleukin-8 gene [19]. Bronchodilator responsiveness alone is not adequate to distinguish asthma from CF disease.

Bronchial Provocation Testing

Bronchial provocation testing assesses for airway hyperresponsiveness, a finding often seen in asthma. Agents used in provocation testing include inhaled methacholine, histamine, and mannitol. While airway hyperresponsiveness characterizes asthma, it is not specific for asthma. Bronchial hyperresponsiveness is evident in 40–60% of individuals with CF in both pediatrics and adults [20, 21]. The cause of airway hyperresponsiveness in CF may be partly due to CFTR deficiency in airway smooth muscle cells and from the inflammatory environment of the CF airways. CFTR deficiency or dysfunction in airway smooth muscle cells causes diminished calcium release in response to histamine and airway remodeling from smooth muscle hyperplasia leading to airway smooth muscle mediated constriction [22]. Inflammation in the CF airway is predominantly neutrophil driven and associated with the production of TNF α , interleukin-8, and interleukin-13, all of which cause upregulation in the contractile function of airway smooth muscle [22]. One recent study evaluated the

contractile properties of intrapulmonary airway smooth muscle cells in people with CF [23•] by dissecting airway smooth muscle strips from human control and CF intrapulmonary airways and testing their response to methacholine, isoproterenol, and interleukin-13. These findings suggest an increase in CF airway smooth muscle mass and impaired β -adrenergic-induced relaxation in the presence of interleukin-13. Airway hyperresponsiveness in CF is also associated with more severe lung disease, a more rapid decline in FEV₁, increased age and is overall a poor prognostic finding [24]. Individuals with CF and airway hyperresponsiveness may also be more likely to develop bronchospasm with certain inhaled antibiotics [25].

Exercise Testing

Exercise challenge testing is an objective way of testing for airway hyperresponsiveness in people suspected of having asthma. Despite people with CF and asthma, both reacting similarly to the inhaled agents used in bronchial provocation testing, they tend to respond differently to exercise. Most studies show an increase in peak expiratory flow, lung function as measured by FEV₁, and bronchodilation, and a decrease in sputum mechanical impedance after exercise in CF. The CFF considers exercise therapy an airway clearance therapy equivalent [26, 27]. Eucapnic voluntary hyperventilation is another form of bronchial provocation testing used to detect exercise-induced bronchoconstriction in asthma. One small pilot study [28] compared eucapnic voluntary hyperventilation testing to cardiopulmonary exercise test (CPET) to detect exercise-induced bronchoconstriction in CF. Two out of the ten patients studied were positive for exercise-induced bronchoconstriction based on eucapnic voluntary hyperventilation compared with none of the patients testing positive that underwent CPET-based exercise testing.

Allergy Testing

The presence of atopy may support the diagnosis of asthma but is not specific for asthma and may not be present in all asthma phenotypes [4]. Skin prick testing and serologic evaluation of antigen-specific IgE for aeroallergens are two common methods to test for the presence of atopy. Early studies seem to show a high prevalence of reactivity to aeroallergens in CF primarily because of a far greater number of reactions to fungal antigens, especially *A. fumigatus* [29, 30]. Reactivity to *A. fumigatus* is common in both atopic asthma and CF; however, only a small number of these individuals may develop allergic bronchopulmonary aspergillosis (ABPA). According to the 2018 National Cystic Fibrosis Patient Registry Annual Data Report, the prevalence of allergic bronchopulmonary aspergillosis in CF is around 5.4%, much lower than the overall reactivity to *A. fumigatus*, which may be closer to 75% [9]. Although ABPA affects both people with atopic asthma and

CF, studies have not been able to show an association between the presence of ABPA and atopy in CF [30]. The cause of the high prevalence of reactivity to aeroallergens seen in CF is still unclear. It may be due to recurrent pulmonary infections predisposing CF airways to heightened immunologic reactivity to inhaled allergens or damaged airway epithelium in CF may allow access of aeroallergens [30, 31].

Fractional Concentration of Exhaled Nitric Oxide (FE_{NO})

Individuals with eosinophilic asthma characterized by T_H2 airway inflammation have higher levels of FE_{NO}. Airway epithelial cells, endothelial cells, and inflammatory cells, including eosinophils, produce nitric oxide. Measurement of an elevated FE_{NO} in eosinophilic asthma is associated with a good short-term response to inhaled corticosteroids and is predictive of exacerbation risk [4]. However, an elevated FE_{NO} is not specific for asthma, is not elevated in all asthma phenotypes, and, therefore, is of limited use in the diagnosis of asthma. FE_{NO} levels are decreased in people with CF even early in life, and this may be the result of predominantly neutrophilic airway inflammation and underlying CFTR dysfunction [32, 33]. We are unaware of any study using FE_{NO} to distinguish CFAOS from asthma-like features in CF.

So, How Do We Diagnose CF-Asthma Overlap?

There is no gold standard for diagnosing CFAOS. CFTR dysfunction has a complex effect on the airways, potentially causing airflow obstruction, variability, hyperresponsiveness, and reaction to aeroallergens irrespective of a concomitant diagnosis of asthma. Airflow response to exercise and the fractional concentration of exhaled nitric oxide is often different between CF and certain types of asthma. Still, studies are lacking to distinguish asthma from asthma-like features in CF disease. For now, it appears the best approach is to use (1) clinical history, including personal and family history of atopic disease, (2) supporting objective measurements of airflow reversibility, (3) confirmation of atopic disease with skin prick testing or serologic evaluation for reactivity to antigen-specific IgE for aeroallergens, and (4) most importantly, improvement in symptoms with appropriate treatment of suspected asthma. The specific treatments of CFAOS will be discussed in the coming section.

Treatment of CFAOS

The management of both CF and asthma has dramatically changed over the past several decades. CFAOS is becoming a more well-characterized disease state, and the therapies for managing CFAOS are an active area of investigation. Individuals

who are living with CF experience airway inflammation from both CFTR-associated and Th1 or Th2 mediated processes. CFAOS is well-recognized in the CF community, and current therapies used are the same for individuals with asthma without a diagnosis of CF. The goals of treatment include targeting the underlying inflammatory process, controlling symptoms, and preventing exacerbations and hospitalizations. The current categories of therapy for CFAOS include beta₂-agonists, inhaled corticosteroids, anti-leukotrienes, muscarinic antagonists, systemic corticosteroids, and biologics. Table 2 outlines the current treatments for CF, asthma, and CFAOS.

Short-Acting Beta₂-Agonists

The use of short-acting beta₂-agonists (SABA) for bronchodilation is a mainstay in the treatment of CF. Patients with CF use SABAs for improvement of pulmonary hygiene, prevention of bronchospasm associated with CF-specific inhaled medications, and control of symptoms during an acute pulmonary exacerbation of CF.

SABAs are historically the first-line therapy for all individuals diagnosed with asthma who do not have CF, regardless of severity. The National Asthma Education and Prevention Program (NAEPP) guidelines support the preferential use of SABA in the management of asthma when there is a sudden onset of symptoms and/or an exacerbation [34]. However, the recent GINA guidelines recommend changes in the management of intermittent asthma that differ from NAEPP. In place of an as-needed SABA, the GINA guidelines recommend utilizing an as-needed inhaled corticosteroid in addition to a SABA or an as-needed combination inhaled corticosteroid and long-acting beta₂-agonist for the management of acute symptoms [4].

The practice pattern of using SABAs as needed for the management of sudden onset symptoms in CF is typical, regardless of the diagnosis of concomitant asthma. In 1995, 82% of people in the ESCF used a SABA, while only 31.5% carried a diagnosis of CFAOS [35]. Literature supports the use of SABAs for CFAOS. A study by Eggleston et al. demonstrated that twice-daily SABA use in individuals with CF with a positive methacholine challenge had significant increases in peak expiratory flow rate (PEFR) when compared to placebo control [15]. However, reversible airway obstruction has not necessarily translated into a diagnosis of asthma in CF, and more compelling evidence would be a family history of asthma and atopic symptoms as detailed above [17]. Other studies showed a trend towards increased lung function with the administration of a SABA. However, it did not reach statistical significance and did not include the diagnostic criteria for asthma [36]. A Cochrane review including 66 publications and 369 participants with CF also found improvement in FEV₁ with the administration of a SABA [37]. More information on the role SABAs play in the management of CF and

Table 2 Summary of drug class use by condition

Drug Class	Cystic fibrosis	Asthma	Cystic fibrosis-asthma overlap syndrome ⁷
Short-acting beta ₂ -agonists	• Before airway clearance • Acute exacerbations • Prevention of bronchospasm before inhaled antibiotics and/or hypertonic saline	• Sudden onset symptoms • Acute exacerbations • Smart puffs prior to activity known to cause symptoms	• Before airway clearance • Sudden onset symptoms • Acute exacerbations • Prevention of bronchospasm before inhaled antibiotics and/or hypertonic saline
Long-acting beta ₂ -agonists	• May have a role in management during acute exacerbations • May be a potential alternative to SABA, but strong evidence lacking	• Used in combination with ICS for acute symptom onset in intermittent asthma • Used in combination with ICS for persistent asthma	• Frequently used in combination with ICS for persistent asthma in patients with CF
Inhaled corticosteroid	• Not recommended in the absence of asthma diagnosis	• Standard of care for persistent asthma with or without a LABA • May consider using in intermittent asthma for as needed symptoms	• Equivocal data for use, although frequently used by clinicians
Leukotriene antagonists	• May improve PEFR in individuals 5 to 18 years old	• May consider using as an alternative to ICS for mild persistent asthma, but inferior efficacy	• May be beneficial in patients with atopic features or prominent eosinophilia
Long-acting muscarinic antagonist	• Safe and effective • Add on therapy	• Safe and effective • Add on therapy	• May be safe and effective, more studies needed
Systemic steroids	• Recommend only in individuals with ABPA • Use considered in severe acute exacerbations	• Use in acute exacerbations • Routine use as maintenance therapy recommended against, except in severe persistent asthma	• Insufficient data about long-term use • Recommend using the shortest effective duration for acute exacerbations
Biologics	• Not investigated in individuals with CF without asthma or ABPA • Role in CF with ABPA is unclear, need further investigation	• In severe asthma, improves FEV₁ and decreases exacerbations and the need for hospitalization • Lowers the dose of long-term systemic steroid dose	• Case reports have demonstrated improvement in FEV₁ • Multiple current investigations ongoing

Abbreviations: ABPA allergic bronchopulmonary aspergillosis, FEV₁ forced expiratory volume in 1 s, ICS inhaled corticosteroids, LABA long-acting beta₂-agonists, PEFR peak expiratory flow rate, SABA short-acting beta₂-agonists

CFAOS is expected from a Cochrane review currently being conducted by Smith et al.

Long-Acting Beta₂-Agonists

Long-acting beta₂-agonists (LABA), when used in combination with inhaled corticosteroids, improve asthma control and asthma-associated deaths [38]. Both the NAEPP and GINA guidelines recommend the use of LABA in conjunction with an inhaled corticosteroid for maintenance therapy in persistent asthma [34]. The use of LABA in CFAOS is less studied. Hordvick et al. investigated LABA use in individuals with an acute exacerbation of their CF, who had a forced vital capacity greater than 40% predicted and required hospitalization, and showed improvement in FEV₁ when compared to both placebo and SABA [39]. Other studies demonstrated improved symptoms and PEFR when LABAs replaced SABAs in patients with CF [40]. However, a recent Cochrane review found that LABAs do not improve FEV₁ or CF quality of

life at baseline [41]. Although LABA use is common in CFAOS, more studies are needed to clarify their role in the treatment of CFAOS.

Inhaled Corticosteroids

The pathophysiology of asthma has been an intense topic of investigation for decades, which has led to numerous groundbreaking discoveries. Our current understanding of mechanisms in asthma has led to asthma classifications based on clinical phenotypes. Multiple asthma phenotypes exist and include Th1 and atopic Th2 mediated inflammation [42•]. Airway inflammation plays a vital role in the underlying disease process, acute exacerbations of asthma, and chronic airway remodeling. Due to the role airway inflammation plays in asthma, ICSs are an essential therapy in the long-term management of asthma [4].

Although individuals with CF have airway inflammation due to abnormal functioning of the CFTR protein, diverse lung microbiomes, and recurrent infections, the utilization of

ICS in CFAOS is based on similar underlying airway inflammation as in asthmatics without CF [43]. A double-blinded, randomized control trial investigating the role budesonide plays in histamine-induced bronchial hyperactivity in CF showed significant improvement in airway hyperresponsiveness after 6 weeks of therapy. Still, it failed to show a significant change in lung function [44]. A retrospective analysis out of Belgium noted a significantly lower rate in the decline of FEV₁ in individuals with CF on an ICS [45]. However, another randomized control trial investigating the withdrawal of ICS versus placebo did not demonstrate significant differences between the two groups in terms of exacerbations, lung function, or SABA use [46]. Along these same lines, a recent Cochrane review noted, “Evidence from these trials is of low to very low quality and insufficient to establish whether ICS are beneficial in cystic fibrosis, but withdrawal in those already taking them has been shown to be safe.” [47] Given the equivocal data for the use of ICS in CFAOS, further investigation is needed to confirm if the benefit outweighs any potential risks associated with treatment.

Leukotriene Antagonists

Step therapy for asthma includes leukotriene antagonists, and the NAEPP and GINA guidelines support their use [4, 34]. In asthma, leukotriene antagonists are initiated instead of low-dose ICS or in conjunction with ICS or ICS-LABA combination therapy. Leukotriene inhibitors function as either leukotriene receptor antagonist or leukotriene synthesis inhibitors. Leukotriene inhibitors are considered an alternative to ICS; however, monotherapy with leukotriene inhibitors is inferior to ICS therapy [48]. Leukotriene inhibitors play a role in reducing inflammation by reducing serum eosinophils. The decrease serum eosinophils correlate with a trend towards improvement in exercise capacity in individuals with CF [49]. In one small study of sixteen children with CF (ages 5–18 years), montelukast, a leukotriene receptor antagonist, helped reduce symptoms and improve PEFR [49]. Given these findings, it may be useful to consider leukotriene inhibitors when there is prominent eosinophilia or an atopic component to CFAOS. It must also be stated that the United States Food and Drug Agency recommends caution with leukotriene inhibitors due to described psychiatric side effects predominantly reported in children but also adults. However, long-term clinical trials are needed to determine if this clinical association is accurate [50].

Long-Acting Muscarinic Antagonist

Long-acting muscarinic antagonists (LAMA) are known to cause bronchodilation via their effects on airway muscarinic receptors. The use of LAMAs in both adults and children with CF is safe and well-tolerated [51–53]. One randomized controlled trial in individuals with CF demonstrated significant

improvement in FEV₁ with long-term tiotropium when compared to placebo [54]. The use of LAMAs in asthmatics without CF is efficient and is, at a minimum, safe to use in individuals with CF [55]. Since LAMAs function as bronchodilators without anti-inflammatory properties, initiation of LAMA therapy in CFAOS may play a role as a third-line agent as part of additive therapy to an ICS; however, additional studies on CFAOS patients are needed.

Systemic Corticosteroid Therapy

Glucocorticoids function primarily as immune suppressants by inhibiting the expression of inflammatory genes and subsequent inflammatory cell recruitment and activation. These mechanisms are recently reviewed [56]. Oral corticosteroids are often employed in the treatment of cystic fibrosis to quell bronchoconstriction due to inflammation. Early studies noted that in individuals with CF, alternate day corticosteroids were associated with a significantly higher FEV₁ at 48 months as compared to placebo. Unfortunately, significant side effects were noted that included lower height and abnormal glucose metabolism [57]. Given the unacceptable side effect profile with long-term systemic corticosteroid use, short courses of oral corticosteroids have primarily been used for the treatment of acute exacerbations of CF.

There are more investigations on systemic corticosteroid use for the management of exacerbations of CF than in CFAOS. Studies investigating the use of glucocorticoids in the treatment of individuals with acute exacerbations of CF requiring hospitalization revealed a trend towards improvement, although it was not statistically significant [58]. The failure to demonstrate significant improvement may have been due to the study being underpowered. A small case series including four hospitalized children with acute respiratory distress due to an exacerbation of CF, who failed to respond to intravenous antibiotic therapy with systemic corticosteroids, were administered high-dose pulse corticosteroids, which was associated with clinical improvement with an acceptable side effect profile [59]. However, this treatment method needs further testing with controlled studies. Systemic corticosteroid use in the treatment of acute exacerbation is common at some institutions despite low-quality evidence. A questionnaire study published in 2007 investigating practice patterns of CF-specific physicians in the UK noted that 100% of responders prescribed systemic corticosteroids as an adjunct to systemic antibiotics for the treatment of acute exacerbations [60].

The CFF guidelines recommend against the use of chronic systemic corticosteroids in CF. Although there is little data available to support this recommendation, there exists a high degree of concern over the risks associated with long-term glucocorticoid use. CF is a multisystem disease with complications from pancreatic insufficiency, bone disease, CF-related diabetes, and chronic colonization of multiple strains of bacteria and

fungi in the airways. The use of chronic systemic corticosteroids could potentially worsen the co-morbidities in people with CF without significant clinical improvement. Overall, there is insufficient data available for the benefit of systemic corticosteroids in CFAOS. Given this lack of data, the CFF recommends systemic corticosteroid use only in specific conditions such as ABPA, asthma exacerbation, or severe CF exacerbations and to use the shortest duration possible [61].

Advanced Therapies

Advanced therapies improve the quality of life of individuals with asthma. Biologic therapies significantly decrease the frequency of exacerbations and improve FEV₁ in asthma not associated with CF. Advanced treatments include immunosuppressive therapies such as monoclonal antibodies to IgE, IL-4, and IL-5. These generally are reserved for severe asthmatics with a Th2 phenotype characterized by elevated peripheral eosinophils, high serum IgE, or elevated FE_{NO}, and are reviewed in detail elsewhere [62, 63].

Omalizumab

Omalizumab is a monoclonal antibody directed towards IgE. IgE antibodies are produced upon exposure to specific antigens and bind to receptors on either mast cells or basophils. The binding of IgE to the high-affinity FcεRI receptors expressed on the surface of mast cells or basophils induces the release of multiple inflammatory mediators, such as histamine and arachidonic acid metabolites, which are critical modulators of the allergic response. Details of the mechanism of action for omalizumab are reviewed in detail elsewhere [64].

Omalizumab was the first approved biologic for moderate to severe asthma, and multiple studies demonstrate improvement in outcomes. Two trials particularly exemplify the clinical benefit of omalizumab. Humbert et al. recruited over 400 patients, which included 12 to 75 years old, with inadequate control of their asthma on ICS/LABA combination therapy. Omalizumab decreased rates of exacerbation and emergency room utilization while increasing the quality of life and morning PEFR [65]. Braunstahl and colleagues lead an international, registry-based, observational trial, including 14 countries and recruiting over 900 poorly controlled atopic patients with asthma, and reported a decrease in clinically significant exacerbations and a decrease in oral corticosteroid use [66]. Overall, omalizumab improves FEV₁ and decreases the frequency of exacerbations, hospitalizations, and use of rescue inhalers and systemic corticosteroids in patients with severe asthma and elevated IgE. However, some differences in response may be age-dependent [67].

Most investigations of omalizumab efficacy in patients with CF have a concomitant diagnosis of ABPA, although

some reports include CFAOS. The benefit of omalizumab in CF complicated by ABPA is not clear. Studies have indicated mixed results on improvement in FEV₁, systemic corticosteroid use, and quality of life in patients with CF and ABPA [68, 69]. However, the role omalizumab plays in CFAOS is limited to case reports and patients with confounding ABPA diagnosis. One case report describes a decrease in systemic corticosteroids and hospitalizations and an increase in quality-of-life score in CFAOS. Still, the patient also carried a diagnosis of ABPA, confounding the interpretation of the results as improvement in ABPA control or asthma control. Regardless, large, randomized controlled trials are needed to define further the role omalizumab plays in the treatment of CFAOS [70].

Mepolizumab

Mepolizumab, a monoclonal antibody that neutralizes IL-5 and prevents binding of IL-5 to the α-chain of the IL-5 receptor complex, is an effective add on therapy in severe eosinophilic asthma. However, investigations into its use in CFAOS are limited [62, 71]. In a recent case series, mepolizumab improved lung function, decreased the rate of acute exacerbations, and lowered the need for oral corticosteroid treatment in CF [72]. Large multicenter randomized controlled trials are needed to evaluate the efficacy of the various biologic therapies in the CF-asthma population with asthma overlap driven by T2 inflammation.

Benralizumab

Benralizumab is a monoclonal antibody to the IL-5 receptor. It has two primary functions, which include blocking the recruitment and activation of eosinophils as well as depleting eosinophils from the circulation, bone marrow, and target organs [62]. In severe asthmatics, benralizumab decreased the frequency of acute exacerbations and increased FEV₁ when compared to placebo in patients with elevated eosinophils counts and frequent exacerbations. Importantly, investigations into the efficacy of benralizumab in severe asthma have either not defined the inclusion of CF or listed CF as an indication for exclusion [62, 63, 73, 74]. The effects of benralizumab on airway remodeling in asthma, which will include patients with CF, are currently under investigation by Pierre-Olivier et al.

Future Research Directions

The treatment of CF has dramatically changed over the past decade with the invention of CFTR modulators. CFTR modulators include potentiators of the CFTR gating channel and correctors of CFTR protein folding [75, 76]. Treatment with CFTR modulators is personalized and based on the genetic mutations of the individual. In the fall of 2020, the Federal Drug Administration approved the first triple combination

CFTR modulator, elexacaftor-tezacaftor-ivacaftor (ELX/TEZ/IVA), which is made up of two CFTR correctors and one potentiator respectively. ELX/TEZ/IVA improves FEV₁, BMI, quality of life scoring, and reduces rate of pulmonary exacerbations in individuals with CF disease and at least one copy of the F508del mutation [77]. At the time of this manuscript writing, no publications are available investigating the role CFTR modulators play in CFAOS or the effects they may have on asthma-like features in CF by effectively treating the underlying dysfunction of the CFTR protein.

Conclusions

The diagnosis of CFAOS is often difficult due to the underlying abnormalities of the CF airways causing asthma-like features. The best approach may be to use clinical history combined with supporting objective measurements of airflow reversibility, confirmation of atopic disease with skin prick testing, or serologic evaluation for reactivity to antigen-specific IgE for aeroallergens, and, most importantly, improvement in symptoms with appropriate treatment of suspected asthma. Further studies are needed to allow for better differentiation of CFAOS from asthma-like features in CF disease.

Use of SABA, ICS, LABA, and LAMA is quite common in CF even in patients without a diagnosis of CFAOS despite a lack of data showing effectiveness. Further studies are needed, particularly in people with CFAOS, to determine benefit. While advanced therapies such as monoclonal antibodies to IgE, IL-4, and IL-5 are being used and studied in CFAOS, large multicenter randomized controlled trials are needed to evaluate their efficacy. Finally, one future area of interest is the effect highly effective CFTR modulators such as ELX/TEZ/IVA may have on patients with CFAOS and asthma-overlapping features of CF.

Declarations

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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