Review Article

Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis

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Abstract:

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder that often occurs in patients with asthma or cystic fibrosis (CF) and is characterized by a hypersensitivity response to the allergens of the fungus *Aspergillus fumigatus*. In patients with CF, growth of *A. fumigatus* hyphae within the bronchial lumen triggers an immunoglobulin E (IgE)-mediated hypersensitivity response that results in airway inflammation, bronchospasm, and bronchiectasis. In most published studies, the prevalence of ABPA is about 8.9% in patients with CF. Since the clinical features of this condition overlap significantly with that of CF, ABPA is challenging to diagnose and remains underdiagnosed in many patients. Diagnosis of ABPA in CF patients should be sought in those with evidence of clinical and radiologic deterioration that is not attributable to another etiology, a markedly elevated total serum IgE level (while off steroid therapy) and evidence of *A. fumigatus* sensitization. Management of ABPA involves the use of systemic steroids to reduce inflammation and modulate the immune response. In patients who do not respond to steroids or cannot tolerate them, antifungal agents should be used to reduce the burden of *A. fumigatus* allergens. Recent studies suggest that omalizumab may be an effective option to reduce the frequency of ABPA exacerbations in patients with CF. Further randomized controlled trials are needed to better establish the efficacy of omalizumab in managing patients with CF and ABPA.

Key words:

Allergic bronchopulmonary aspergillosis, allergic fungal mycosis, cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive life-limiting multisystem disorder that results from defective functioning of the CF transmembrane conductance regulator (*CFTR*) protein.[1] *CFTR* is a complex glycoprotein (1480 amino acids) encoded by the *CFTR* gene, which is located on the long arm of chromosome 7 (7q31.2).[2] Physiologic activity of *CFTR* is necessary to maintain the normal consistency of respiratory and gastrointestinal secretions, which in turn is vital for innate immunity and proper digestion and absorption of nutrients.[3] In patients with CF, a genetic defect leads to defective functioning of the *CFTR* protein, which results in diverse pathologic manifestations including bronchiectasis, sinonasal polyposis, pancreatic insufficiency, and infertility.[4] Progressive destruction of lung parenchyma and decline in pulmonary function are the major life-limiting complications of CF.

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder that often occurs in patients with asthma or CF and is caused by hypersensitivity to the allergens of *Aspergillus fumigatus*.[5] *A. fumigatus* is a ubiquitous, spore-forming fungus that has been associated with multiple pulmonary disorders including ABPA, aspergilloma, invasive aspergillosis, allergic asthma, and hypersensitivity pneumonitis.[6] In patients with CF, growth of *A. fumigatus* hyphae within the bronchial lumen triggers an immunoglobulin E (IgE)-mediated hypersensitivity response with resultant bronchial inflammation and airway destruction and fibrosis (bronchiectasis). Patients often experience wheezing, pulmonary infiltrates, and a central (proximal) pattern of bronchiectasis.[7] Because of the overlapping features of ABPA with asthma, CF, and other diseases, this condition often remains underdiagnosed and there may be a long delay (of up to 10 years) between the first occurrence of symptoms and subsequent diagnosis.[8] In some countries, ABPA may be

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confused with other diseases, such as pulmonary tuberculosis, in nearly one-third of cases.[9]

Given that CF and ABPA have overlapping clinical, radiographic, and immunologic features, the diagnosis of ABPA in patients with CF remains challenging. Consequently, a number of international conferences have been organized and guidelines have been published to standardize the diagnosis and management of ABPA in CF patients.[10] Over the past one decade, newer therapies for ABPA in patients with CF have been developed and shown to be effective.[11] In this review, we present the epidemiology, clinical features, diagnostic evaluation, and management of ABPA in CF patients in the light of the currently available evidence.

Literature Search

In order to collate literature for this review, we performed a search of three large databases (PubMed, Ovid, and Medline) on March 23, 2016. Queries were performed using the keywords "Allergic bronchopulmonary aspergillosis" AND "Cystic fibrosis." We limited our search by restricting to articles published after the year 2000. This was done to ensure that only the most recently available data were collated for this review. Duplicate entries and articles which focused on pulmonary disorders other than ABPA were excluded. Abstracts of articles deemed relevant to this review were read by the authors of this study. We retrieved full texts of all the included publications (systematic reviews (SRs), clinical trials, observational studies, laboratory studies, and review articles) that discussed ABPA in patients with CF. Reference lists of these articles were also reviewed to include articles that were deemed relevant to this review. The total number of relevant publications identified and the overall literature review process are summarized in Figure 1. Information from these articles was organized into several key areas identified by mutual consensus among authors. A critical appraisal of the reviewed literature is provided herein.

Epidemiology

In a study by Sudfeld *et al.* using the John Hopkins Cystic Fibrosis Integrative Microbiology Database, close to 36% of individuals with CF were found to grow *A. fumigatus* in airway cultures, and the prevalence of *A. fumigatus* colonization increased from 1997 to 2007.[12] *Aspergillus* sensitization (AS) in patients with CF as diagnosed by the measurement of *A. fumigatus*-specific IgE has been shown to be nearly 32.8%.[13-19] Studies using skin prick testing have reported even higher estimates ranging from 42.8% to 65% in some series.[19-25]

Prevalence of ABPA in patients with asthma has generally been reported to be around 1%–3%.[26] In contrast, estimates of the prevalence of ABPA in patients with CF have been reported to be much higher.[19] Point estimates of prevalence vary widely depending on the diagnostic criteria used, population studied (children vs. adults), and geographic region of the study. Adult patients with CF tend to have a higher prevalence of ABPA as compared to children. For instance, Chotirmall *et al*. reported a 12% prevalence rate of ABPA in adult CF patients in Ireland using the CF Foundation (CFF) diagnostic criteria.[27] Using the same diagnostic criteria, Jubin *et al*. reported a prevalence rate of 9.4% in children with CF in France.[28] Moreover, the prevalence of ABPA in CF patients differs greatly from one region to the other. In the Epidemiologic Study of Cystic Fibrosis registry based on the United States and Canada, the prevalence of ABPA has been estimated to be only 2%.[26] On the other hand, a significantly higher prevalence of 7.8% has been noted in the Epidemiologic Registry of CF (ERCF) from Europe.[29] Finally, the prevalence of ABPA also varies significantly depending on the diagnostic criteria used for the diagnosis. As an example, Fillaux *et al.* reported the prevalence of ABPA in children with CF in France to be nearly 13.5%.[30] In another study from France, Fillaux *et al*. determined the prevalence of ABPA in children with CF using the CFF diagnostic criteria, which was strikingly lower (3.4%) than the previous estimate (13.5%).[31]

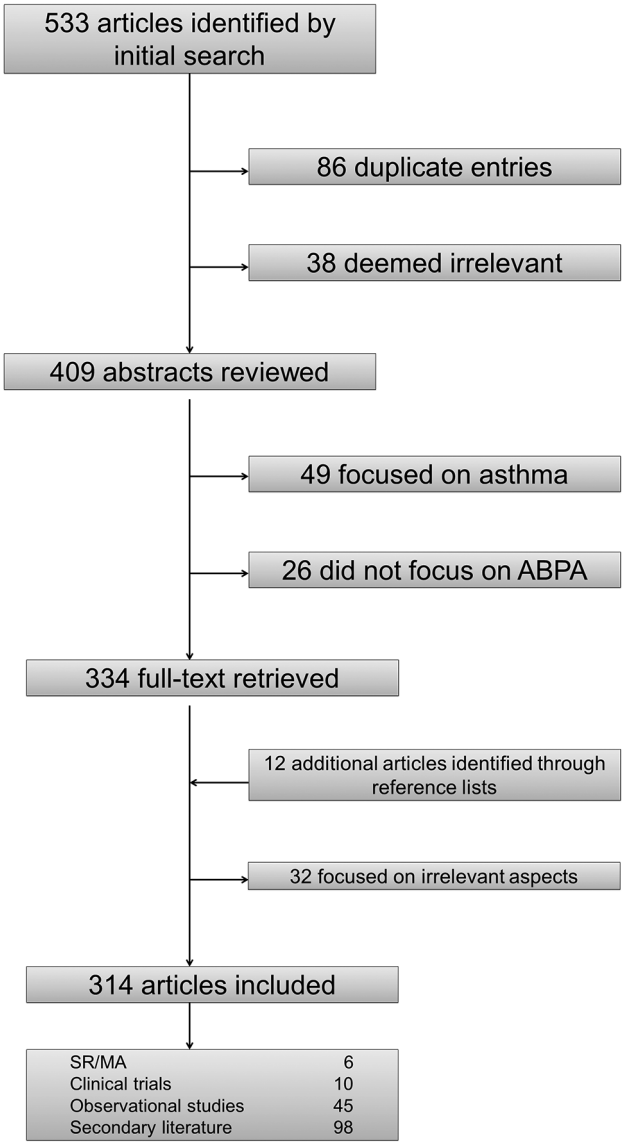

Figure 1: A flow chart depicting the inclusion and exclusion of articles for the purpose of this review. ABPA = Allergic bronchopulmonary aspergillosis; MA = Meta-analyses; SR = Systematic reviews

In a SR published in 2015, Maturu and Agarwal analyzed the results of 45 studies reporting the prevalence of ABPA and concluded that there was significant publication bias and heterogeneity among the published studies.[29] The prevalence of ABPA in these studies varied significantly ranging from 3% to 25% with a pooled prevalence of 8.9% (95% confidence interval: 7.4%–10.7%).

Pathogenesis

AS, defined as the presence of either immediate cutaneous hypersensitivity to *A. fumigatus* antigens or *A. fumigatus*-specific IgE antibodies in the serum, is the first step in the pathogenesis of ABPA.[32] In patients with ABPA, exposure to *A. fumigatus* spores and hyphae results in an IgE-mediated hypersensitivity response. This allergic response to *A. fumigatus* antigens leads to a number of clinical and immunologic manifestations, which culminate in ABPA. Before delving into the immunopathogenesis of ABPA, it would be useful to review the biology of *A. fumigatus* itself.

A. fumigatus is an ascomycete belonging to the subdivision Deuteromycotina within the fungal kingdom.[33] While *A. fumigatus* is considered the most common allergenic species within the *Aspergillus* genus, other species within this genus also have important medical importance. *Aspergillus clavatus* has been implicated in producing allergenic responses and possibly ABPA.[34] Moreover, *Aspergillus terreus* and *Aspergillus flavus* species have been reported to possess amphotericin B resistance.[35] This may have important therapeutic implications for patients.

A. fumigatus generally grows easily on routine bacteriological and mycological media and is capable of growing at temperatures ≥50°C. The ability to grow rapidly at 37°C is an important pathogenic feature and allows the rapid progression of invasive disease.[36] Moreover, *A. fumigatus* spores are very small in size (3–5 μm), which enable them to reach deeper into the smaller airways. At the same time, a thick hydrophobic protein coat allows these spores to evade phagocytosis by macrophages—the first line of immune defense against *A. fumigatus*.[37] Upon reaching the alveoli, spores germinate to produce fungal hyphae. Neutrophils and monocytes serve as the second line of defense for the body by killing fungal hyphae through opsonin-dependent and opsonin-independent mechanisms. On the other hand, *A. fumigatus* possesses a number of virulence factors to evade the immune system.[38] These virulence factors include superoxide dismutases, catalases, mannitol, proteases, ribotoxin, phthioic acid, phospholipases, gliotoxin, and a hemolysin. While these virulence factors have a definitive role in the pathogenesis of invasive aspergillosis, many of these proteins are antigenic and can be the target of immune responses in patients with ABPA.[39]

In patients with CF, *CFTR* dysfunction leads to abnormal mucociliary clearance of secretions. When such patients are exposed to *A. fumigatus* spores, impaired mucociliary clearance and defective innate immune responses lead to accumulation and persistence of fungal spores within the smaller airways.[40] Germination of spores leads to the formation of fungal hyphae and release of antigens, proteases, phospholipases, and other virulence factors. Such factors damage airway epithelial cells and allow a large dose of antigenic factors access to the interstitial and vascular compartments.[41] Antigen-presenting cells possessing human leukocyte antigen (HLA)-DR5 or HLA-DR2 process these antigens and present peptides in association with major histocompatibility complex Class II to $CD4^+$ T-cells located within the bronchoalveolar lymphoid tissue.[13] This results in the activation of T-cells and release of inflammatory cytokines that favor a $CD4^+$ Th_2 response. A predominant $CD4^+$ Th_2 response in patients with ABPA is thought to be related to genetically determined factors and explains why all patients with CF do not develop ABPA despite having *CFTR* dysfunction.[42]

Activation of $CD4^+$ Th_2 cells leads to the activation of a humoral immune response, which entails production of IgE-producing B-lymphocytes and plasma cells. In addition, the release of cytokines, such as interleukin-4 (IL-4), IL-5, and IL-13, results in enhanced formation and differentiation of eosinophils and isotype switching of B-cells to IgE.[43] Interestingly, experimental studies have shown that B-cells from patients with ABPA have higher sensitivity to IL-4 and spontaneously produce larger amounts of IgE, IgG, and IgA antibodies against *A. fumigatus* antigens.[44] Some laboratory evidence suggests that this may be accounted for by polymorphisms in the IL-4 receptor α-chain (IL-4Rα), which result in a gain-of-function effect and promote exaggerated synthesis of IgE antibodies.[45]

Attachment of IgE to mast cells and cross-linking of IgE molecules result in mast cell degranulation and release of histamine, leukotrienes (LTB), and other mediators, which precipitate bronchospasm and other manifestations of a hypersensitivity response. Eosinophils are also important effector cells in patients with ABPA and are recruited by cytokines, such as LTB_4, platelet-activating factor, eotaxin, monocyte chemoattractant protein-3 (MCP-3), and Regulated on Activation, Normal T cell-Expressed and Secreted (RANTES).[46] Eosinophils possess Fc receptors for IgE, IgG, and IgA; binding of *A. fumigatus*-specific IgG, IgA, and IgE molecules to these receptors and their cross-linking results in degranulation of eosinophils. Release of major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin from eosinophils damages airway epithelial cells and further aggravates bronchial inflammation [Figure 2].[47]

Airway epithelial cells also contribute to the inflammatory response in ABPA by producing pro-inflammatory cytokines including IL-6, IL-8, and MCP-1.[48] Moreover, continuous damage to the epithelial cell layer triggers repair processes, which induce an influx of extracellular matrix proteins into the airway lumen. *A. fumigatus* spores and hyphae can attach to these matrix proteins and persist indefinitely within the smaller airways.[49] Attachment of fungal spores and hyphae to the smaller airways allows *A. fumigatus* antigens to continuously aggravate inflammatory responses as well as elaborate factors that worsen damage to airway epithelial cells and induce mast cell degranulation. Over a long period of time, ongoing bronchial inflammation and pulmonary damage result in the development of bronchiectasis.[50]

Here, it should be noted that some of the immunopathogenic responses seen in patients with ABPA are similar to those

seen in patients with atopic asthma. However, patients with ABPA tend to have a greater burden of *A. fumigatus* allergens, which accumulate and persist within the smaller airways.[51] Moreover, patients with ABPA usually have IgE antibodies directed against *A. fumigatus* antigens Asp f2, Asp f4, and/or Asp f6. This is in contrast with patients with atopic asthma, who usually possess IgE antibodies directed against Asp f1 and/or Asp f3 antigens.[39,52-55] In addition, B-cells and mast cells from patients with ABPA demonstrate hyperresponsiveness, which may be partly accounted for by polymorphisms in the IL-4Rα chain.[56] Finally, patients with ABPA have HLA haplotypes which promote exaggerated $CD4^+$ Th_2 responses and continued synthesis of IgE. HLA-DR2 and HLA-DR5 restriction in patients with ABPA has been reported by Chauhan *et al*.[57] More specifically, studies have shown that HLA-DRB1*1501 and HLA-DRB1*1503 confer the highest risk of developing ABPA.[58] Conversely, HLA-DQ2 (HLA-DQB1*0201 in particular) provides relative protection against the development of ABPA.[59]

Clinical Features

Patients with ABPA classically present with wheezing and often have evidence of bronchospasm and airway hyperresponsiveness in the preceding 6 months. Some patients may complain of coughing up mucus plugs or sputum containing brown, black, or green specks.[60] In patients with CF, ABPA often presents with worsening pulmonary function and evidence of new infiltrates on chest radiographs or computed tomography (CT). Sputum smear showing *A. fumigatus* hyphae or sputum culture growing *A. fumigatus* are nonspecific findings and may be seen in CF patients with or without ABPA.[61] Laboratory findings suggestive of ABPA include peripheral eosinophilia and markedly elevated total serum IgE levels. Skin prick testing to *A. fumigatus* antigens is positive in all patients with ABPA, though it is nonspecific and is detectable in nearly 20%–25% of patients with persistent asthma.[62] Serum precipitins to *A. fumigatus* are also detectable, and serum levels of *A. fumigatus*-specific IgE and IgG antibodies are elevated.[63] Patients with long-standing ABPA have evidence of central bronchiectasis (typically within the central two-thirds of lung parenchyma) on CT scans. On plain chest radiographs, patients may have evidence of fleeting opacities or infiltrates. Other signs described in the literature include ring sign (circumferential bronchial wall thickening), tram-track appearance (nontapering, dilated bronchi appearing as parallel lines), and/or finger-in-glove sign (mucus plugging within dilated bronchi).[64] While many radiologic findings seen in ABPA can be caused by CF itself, there are some features that are relatively specific for ABPA. These features include central varicose or cystic bronchiectasis, infiltrates that completely resolve with steroid treatment, and high-attenuation mucus plugs.[65]

A staging system of ABPA has been published in the literature, although it was originally formulated for patients with asthma and ABPA.[66] The stages in this system are not arranged in a chronologic order and patients do not sequentially pass from one stage to the next. This five-staging system for ABPA is summarized in Table 1 (adapted from Stevens *et al*.[10]).

Diagnosis

Traditionally, diagnosis of a classic case of ABPA has been based on the following essential criteria: (1) Asthma or airflow obstruction; (2) positive skin reactivity to *A. fumigatus*; (3) serum total IgE level > 1000 ng/mL; (4) elevated serum *A. fumigatus*-specific IgE and IgG; and (5) central bronchiectasis.[67] However, these criteria have been formulated and used extensively in patients with ABPA and asthma. Patients with CF have pulmonary function abnormalities at baseline and develop recurrent pulmonary exacerbations due to a wide variety of causes. Diagnosis of ABPA in such patients is challenging and the need for having distinct diagnostic criteria has been long recognized. Consequently, the CFF consensus criteria for the diagnosis of ABPA in patients with CF were formulated and published in 2003 [Table 2].[10]

As per the CFF consensus criteria, minimal diagnostic criteria for ABPA in CF patients require evidence of acute or subacute clinical deterioration not attributable to another etiology, total serum IgE level >1200 ng/mL while off steroids, immediate cutaneous reactivity to *A. fumigatus* antigens or demonstration of *A. fumigatus*-specific IgE antibodies *in vitro*, and one of the following: (1) Serum precipitins to *A. fumigatus*; (2) demonstration of *A. fumigatus*-specific IgG antibodies *in vitro*; or (3) new or recent abnormalities on pulmonary radiologic imaging, which do not respond to antibiotics and chest physiotherapy. Moreover, patients who have a high suspicion of ABPA, but in whom the total serum IgE level is 200–500 ng/mL, the total serum IgE level should be repeated in 1–3 months.

Management

The goal of management in patients with CF and ABPA is to prevent the development of lung fibrosis and retard decline in pulmonary function.[68] Treatment of ABPA involves addressing two different aspects of the disease: (a) Attenuating the immunologic response and inflammation; and (b) reducing the burden of *A. fumigatus* allergens present in the airways. The

Table 1: Stages of allergic bronchopulmonary aspergillosis*

Stages	Description
I	Acute stage characterized by pulmonary infiltrates, markedly elevated total serum IgE level, and peripheral blood eosinophilia; responds well to steroids, and steroids can be tapered off
II	A stage of remission in which patients do not have pulmonary infiltrates and do not require steroids
III	A relapse of the disease (similar to Stage I) that responds well to steroids, leaving little to no radiographic evidence of pulmonary scarring
IV	A stage of steroid-dependent disease in which the total serum IgE level is variable and radiographic infiltrates may or may not be present; patients require inhaled and systemic steroids for treatment
V	A stage of "burnt out" disease in which permanent fibrotic damage is evident on radiographic studies with irreversible impairment of pulmonary function; such patients have inadequate response to steroids

*These stages are not sequential phases of the disease

Table 2: Cystic Fibrosis Foundation – Consensus Conference criteria for diagnosis of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis

Classic case	Minimal diagnostic criteria
Acute or subacute clinical deterioration that is not attributable to another etiology	Acute or subacute clinical deterioration that is not attributable to another etiology
A serum total IgE level of >2400 ng/mL unless patient is receiving systemic steroids*	A serum total IgE level of >1200 ng/mL*,†
Presence of IgE antibodies to *A. fumigatus in vitro* or immediate cutaneous hypersensitivity to *Aspergillus*‡	Immediate cutaneous hypersensitivity to *Aspergillus*‡ or presence of IgE antibodies to *A. fumigatus*
Precipitating antibodies to *A. fumigatus* or serum IgG antibody to *A. fumigatus* by an *in vitro* test	One of the following Precipitins to *A. fumigatus* or IgG antibody to *A. fumigatus in vitro*
New or recent infiltrates (or mucus plugging) on chest radiography or computed tomography that do not respond to antibiotics and standard physiotherapy	New or recent abnormalities on chest radiography or computed tomography that do not respond to antibiotics and standard physiotherapy

Adapted from: Stevens *et al*.[10] *If a patient is receiving steroids, check serum total IgE levels when the patient is off steroid treatment, †If allergic bronchopulmonary aspergillosis is suspected and serum total IgE level is between 480 ng/mL and 1200 ng/mL, repeat testing in 1-3 months, ‡Cutaneous reactivity to *Aspergillus* is indicated by a wheal of 3 mm (or more) in diameter with surrounding erythema following a skin prick test in a patient who is currently off systemic antihistamines. *A. fumigatus* = *Aspergillus fumigatus*

former can be achieved through the use of anti-inflammatory and immunomodulatory drugs, while the latter is accomplished by employing antifungal therapy.

Treatment guidelines for the management of ABPA in CF have been based heavily on expert opinion and observational data.[10] Systemic corticosteroids and itraconazole have been considered the mainstay of therapy for ABPA.[69] Adjunctive measures, such as the use of inhaled corticosteroids, bronchodilators, anti-LTB drugs, and environmental manipulation, are also frequently employed.[70] More recently, small-scale studies have shown that omalizumab may be an effective treatment for patients with ABPA.[71]

Systemic corticosteroids are considered the first-line therapy for patients with CF and ABPA.[10] Prednisolone at a dose of 0.5–2.0 mg/kg/day (or an equivalent steroid) should be employed as an initial therapy in all patients. After a period of 1–2 weeks, dosage should be modified to prednisolone 0.5–2.0 mg/kg every other day. Subsequently, the dose of corticosteroids should be reduced slowly based on the patient's clinical response. In general, corticosteroids should be tapered off over a period of 2–3 months. Some patients may relapse during the corticosteroid taper; in such cases, increasing the dose of corticosteroids and addition of itraconazole is usually useful.[70] Once patients demonstrate signs of clinical improvement, corticosteroids should be tapered off.

Corticosteroids are useful in ABPA owing to their anti-inflammatory and immunosuppressive effects. Corticosteroids reduce the expression of phospholipase A_2, pro-inflammatory cytokines, and other inflammatory mediators through their interaction with glucocorticoid response elements.[72] Furthermore, corticosteroids also reduce the serum IgE level by downregulating immunoglobulin production, increasing the apoptosis of B-lymphocytes, and reducing the expression of integrins and other adhesion molecules.[73]

Itraconazole is an azole antifungal drug that should be used in patients with ABPA who: (a) Respond poorly to corticosteroids; (b) relapse during tapering of corticosteroids; (c) develop corticosteroid toxicity; or (d) become corticosteroid dependent.[10,70] Since corticosteroids do not possess antifungal properties, therapy with corticosteroids alone does not affect the burden of *A. fumigatus* present in the airways. Itraconazole, being an azole antifungal drug, inhibits fungal 14α-demethylase enzyme leading to depletion of ergosterol, accumulation of sterol precursors, and alteration in the structure of the fungal plasmalemma.[74] As itraconazole possesses antifungal properties, it inhibits the growth of *Aspergillus* species and reduces the overall allergen burden. This in turn helps attenuate the overall inflammatory response in patients with ABPA. However, itraconazole does not possess any anti-inflammatory or immunomodulatory property of itself.[75] Therefore, it should not be used as the first-line therapy and should only be instituted in conjunction with corticosteroids. The usual dose of itraconazole is 5 mg/kg/day which may be administered in one or two divided doses. In general, a 3–6 month course of itraconazole therapy is sufficient. Liver function tests should be obtained at baseline, 1 month, and for every 3 months thereafter, or if there is a suspicion of liver dysfunction.[76] Routine monitoring of itraconazole levels is not recommended, but testing for itraconazole level should be considered for patients who respond poorly to itraconazole and those in whom there is a suspicion of inadequate absorption or noncompliance.[10] In some patients with CF who do not achieve adequate serum itraconazole levels, especially those with severe pancreatic insufficiency, use of a cyclodextrin-based liquid formulation (if available) or higher dosage itraconazole capsules may be useful.[77] Following the completion of itraconazole therapy, it is necessary to keep patients in regular follow-up to assess whether itraconazole therapy actually reduced the frequency of ABPA relapses.

Other adjunctive measures are also employed frequently in the management of patients with CF and ABPA. Use of inhaled bronchodilators and inhaled steroids may be reasonable in such patients as they ameliorate bronchospasm and modulate the local inflammatory response.[78] Manipulation of patients' environment to reduce the burden of *A. fumigatus* spores may be also tried.[79] While such a prophylactic maneuver seems intuitive, it has not been proven to reduce the frequency of relapses.

The management of patients with CF and ABPA is sometimes confounded by the fact that several clinical features of ABPA overlap with those of CF exacerbation due to bacterial infection, asthma, or a variety of other causes.[80] Due to this reason, the decision to treat a CF patient for ABPA may be uncertain in some clinical situations. As per the CFF consensus conference guidelines, patients with a definitive diagnosis of ABPA should receive treatment for ABPA. Likewise, patients who have only serologic evidence of AS with stable pulmonary function and no new clinical features should not be treated for ABPA. However, in cases where patients have evidence of AS and worsening pulmonary function, with or without radiographic infiltrates, a trial of treatment for CF-related pulmonary infection should be given first. In patients who do not respond to therapy and have evidence of AS, treatment for ABPA and/or asthma exacerbation should be instituted. Most patients who develop pulmonary decompensation with new radiographic infiltrates, serum IgE level between 500–1000 IU/mL, history of AS, and no response to therapy for CF exacerbation have ABPA and respond well to treatment for ABPA.[10]

Recent studies have explored the use of other antifungal agents in the treatment of ABPA with encouraging results. In a retrospective study, Hilliard *et al*. reported the use of voriconazole monotherapy in 13 patients with ABPA.[81] Voriconazole therapy afforded a significant improvement in pulmonary function tests and serologic tests. In another retrospective study, Chishimba *et al*. reported the efficacy of voriconazole and posaconazole in twenty patients with asthma and ABPA.[82] Both drugs were found to produce a significant improvement in radiologic and serologic parameters. Based on its theoretical efficacy, nebulized amphotericin B has been used to successfully treat ABPA in a 14-year-old CF patient awaiting lung transplantation.[83] In a small case series from Belgium, Proesmans *et al*. reported the efficacy of nebulized amphotericin B in treating 7 patients with ABPA (2 of whom had ABPA associated with CF).[84] While these reports are encouraging, further prospective, controlled studies are needed to better establish the efficacy and safety of these agents for the treatment of ABPA in patients with CF.

Omalizumab, a humanized anti-IgE monoclonal antibody, has recently received much attention as a potentially useful steroid-sparing agent. Several observational studies have reported the efficacy of omalizumab in reducing the need for steroids and overall exacerbation rates in patients with ABPA.[85-88] Tillie-Leblond *et al*. reported the use of omalizumab in 16 adult patients with asthma and ABPA.[89] Omalizumab significantly reduced the need for steroids and the overall number of exacerbations in this study. In another study by Emiralioglu *et al*., the use of omalizumab in six patients with CF and ABPA reduced the total serum IgE levels, improved respiratory symptoms, and decreased the need for steroids.[90] A small randomized, double-blinded, placebo-controlled trial (with a cross-over design) of omalizumab in adult patients with asthma and ABPA was published in 2015. This trial showed that omalizumab successfully reduced the frequency of exacerbations and decreased surface-bound IgE and FcεR1 (high-affinity receptor for crystallizable fragment [Fc] region of IgE) levels.[91] However, a large multicenter, double-blinded, placebo-controlled trial (www.clinicaltrials.gov identifier number NCT00787917) of omalizumab in CF patients with ABPA was terminated prematurely by Novartis® pharmaceuticals due to poor enrollment and retention of patients. Consequently, a recent Cochrane SR concluded that the use of omalizumab in CF patients with ABPA cannot be unequivocally recommended given the absence of validated data from randomized controlled trials.[92]

Natural Course and Outcome

In patients with CF, development of ABPA has been associated with a progressive decline in pulmonary function. In a prospective study of 122 children with CF, Kraemer *et al*.

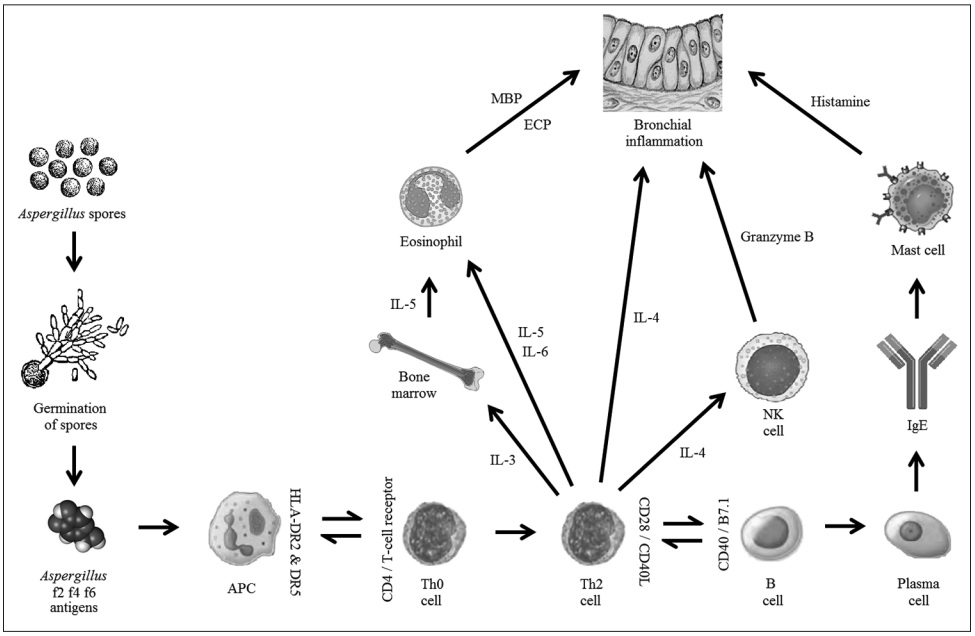

Figure 2: A diagram depicting the model of pathogenesis of allergic bronchopulmonary aspergillosis. APC = Antigen-presenting cell; ECP = Eosinophil cationic protein; HLA = Human leukocyte antigen; IL = Interleukin; MBP = Major basic protein; NK = Natural killer

assessed the effect of ABPA on pulmonary function.[93] They reported that development of ABPA in patients with CF was associated with a rapid decline in all parameters of pulmonary function including forced expiratory indices (forced expiratory volume in 1 s [FEV_1] and forced expiratory flow at 50% vital capacity). Moreover, decline in pulmonary function was worst among CF patients with ABPA when compared to CF patients free from *Pseudomonas aeruginosa*, CF patients infected with *Pseudomonas aeruginosa*, and CF patients with atopy but no evidence of ABPA. In an epidemiologic study based on data from the ERCF, Mastella *et al*. found that the presence of ABPA in CF patients was associated with a lower FEV_1 at all ages.[29] Interestingly, in a retrospective cohort study, Amin *et al*. showed that colonization of CF patients with *A. fumigatus* (in the absence of ABPA) is an independent risk factor for hospitalization.[95] However, unlike ABPA, chronic infection with *A. fumigatus* does not adversely affect pulmonary function by itself.[11]

Future Directions

Guidelines for the management of ABPA hitherto have been mostly based on observational, low-quality evidence, and there is a general dearth of well-designed controlled trials to guide the management of ABPA in patients with CF.[10,80] Fortunately, a number of trials are currently ongoing to address key questions in the management of ABPA.[11] One randomized trial is comparing the efficacy of oral glucocorticoids to oral itraconazole monotherapy (NCT01321827), another comparing oral glucocorticoids to oral voriconazole (NCT01621321), and a third one comparing oral glucocorticoids to combined oral glucocorticoid–itraconazole therapy (NCT0244009). Moreover, as steroid therapy is often complicated by systemic toxicity,[96] alternative treatment options for ABPA are being actively explored.[11] Omalizumab appears to be an effective steroid-sparing drug that reduces the frequency of relapse and exacerbations in patients with ABPA.[85-89] More evidence from larger randomized clinical trials will further substantiate its role in the management of ABPA.[92] Some other studies are currently underway to evaluate the efficacy of amphotericin B for the management of ABPA. One randomized controlled trial is exploring the role of nebulized liposomal amphotericin B in maintaining remission in patients with asthma and ABPA (NCT00787917). Another randomized trial aims to compare inhaled glucocorticoid monotherapy to nebulized amphotericin B deoxycholate combined with inhaled glucocorticoids in reducing the frequency of exacerbations (NCT01857479). The results of these clinical trials will provide an evidence base to rationalize the management of ABPA over the next decade.

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Conflicts of interest
There are no conflicts of interest.

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