

Allergic bronchopulmonary aspergillosis: what's known and what's new

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Abstract Recent investigations concerning ABPA have expanded our understanding of the disease. The diagnostic criteria for ABPA are not standardized. Novel analytic techniques have compared the varied diagnostic criteria even in the absence of a gold standard. Additional analyses have determined the sensitivity and specificity of various parameters for the diagnosis of ABPA, as well as combinations of several parameters that have extremely high specificity and sensitivity. New biomarkers have also been proposed to diagnosis and monitor ABPA. Research concerning specific antigenic triggers of the Th2 response and HLA polymorphisms in ABPA has led to relevant new insights concerning the immunopathogenesis of the disease. Treatment trials have further clarified the optimal corticosteroid dosing regimen and the role of antifungal therapy and anti-IgE therapy for the treatment of ABPA. We suspect that such research efforts will continue to accelerate our understanding of this disease that will benefit ABPA patients.

Keywords Allergic bronchopulmonary aspergillosis · Diagnosis · Pathogenesis · Treatment · Monitoring · Corticosteroids

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease caused by a hypersensitivity response of *Aspergillus fumigatus* (*Af*) colonization of the airways. ABPA develops almost exclusively in atopic patients with asthma who are often corticosteroid dependent or in cystic fibrosis (CF) patients [1]. The symptoms of ABPA include those typically observed with asthma including dyspnea, cough, and wheeze. Additional symptoms include the expectoration of tan to brown plugs, low-grade fever, and symptoms of allergic rhinitis. The common pathologic findings in ABPA consist of mucoid impaction and eosinophilic pneumonia that are most prominent in the posterior segments of the upper lobe. The mucus of ABPA contains aspergillus antigens, inflammatory cells, and eosinophilic inflammatory mediators, which may cause airway and parenchymal lung destruction leading to bronchiectasis and pulmonary fibrosis [1]. Typical laboratory findings include peripheral eosinophilia, markedly elevated serum IgE, immediate cutaneous reactivity to *Af*, serum precipitin reactions to *Af*, elevated specific serum levels of IgE and IgG to *Af*, as well as the following radiographic findings: recurrent lung opacities, central bronchiectasis, and mucoid impaction of dilated bronchi that may appear as toothpaste shadows and finger-in-glove opacities [2]. As mentioned, the constituents of the mucus of ABPA are dissimilar from other pulmonary conditions, and this results in ABPA mucus demonstrating high attenuation on chest computed tomography (CT) imaging [3].

This manuscript will focus on the diagnosis, immunopathogenesis, treatment, and approach to monitoring of ABPA. In each of these areas, established concepts will be briefly reviewed (what's known) and then immediately followed by recent insights in these areas (what's new).

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Diagnosis of ABPA: what's known

The diagnosis of ABPA is problematic because it shares several clinical features with asthma and CF. The diagnostic criteria for ABPA have not been standardized. Several diagnostic criteria are shown in Table 1 [4, 5, 6•, 7]. However, in clinical practice, many patients with presumed ABPA fail to meet any of these diagnostic criteria sets [8]. Although the diagnosis ABPA usually requires the presence of pulmonary opacities or central bronchiectasis, a patient may be classified as having ABPA serologically (ABPA-S) who either never or rarely has demonstrated pulmonary opacities radiographically [1]. It is thought that ABPA-S is an early stage of the disease where the destructive mucus has not yet developed to a significant degree to cause bronchiectasis (ABPA-CB) and/or pulmonary fibrosis to result in permanent lung injury.

Diagnosis of ABPA: what's new

Recently, various diagnostic criteria for ABPA have been directly compared in terms of their ability to identify ABPA in an asthma cohort [6•]. Such analyses are hampered by the lack of a gold standard for the diagnosis of ABPA. The authors attempted to circumvent this limitation using latent-class analysis, based on the concept that although the true disease status of an individual is unknown, certain probabilistic estimates of disease can be made [9]. These latent-class models can obtain direct estimates of disease sensitivity and specificity in the absence of a gold standard [10]. The authors compared the Rosenberg criteria [7] with the Agrawal criteria [6•] for ABPA (see Table 1) in 372 asthmatic subjects [6•]. They found that the Rosenberg criteria using at least six

positive parameters was 100 % sensitive and specific, whereas the Agrawal criteria were also 100 % specific and more than 96 % sensitive. In terms of the individual clinical parameters incorporated into these criteria, type 1 *Aspergillus* skin test positivity was nearly 90 % sensitive, and serum IgE levels >1000 IU/ml were over 90 % sensitive. The following clinical parameters were greater than 95 % specific for the diagnosis of ABPA in their asthma cohort: *A. fumigatus* precipitins positivity, chest radiographic transient opacities, high attenuation mucus on high resolution chest CT scanning. The total eosinophil count >1000 cells/ μ L was between 90 and 95 % specific for the diagnosis of ABPA. In a reanalysis of these data, cutoff values of 2347 for serum IgE, 1.91 kUA/L for *A. fumigatus*-specific IgE, and eosinophils count of 507 cells/ μ L were the optimal cutoff values for separating ABPA from non-ABPA asthma [11]. No single test was highly specific for the diagnosis of ABPA; however, the combination of all these tests being positive had 100 % specificity. The negative predictive value for each of these tests was greater than 90 %. It should be noted that the performance of commercial antibody testing with enzyme immunoassays (EIA) is not identical, and various EIA for *A. fumigatus*-specific IgG have demonstrated different sensitivities and specificities for ABPA [12].

It has been proposed that the presence of high attenuation mucus on chest CT scanning is specific enough to be considered as a diagnostic test for ABPA (Fig. 1) [13•]. To our knowledge, only one study examined the specificity of this parameter to differentiate non-ABPA asthma from ABPA and found that it was 100 % specific [6•]. Two cohorts of at least 100 ABPA patients were found to have a rate of high attenuation mucus on chest CT of 28 and 36 %, respectively [13•, 14]. In one of these cohorts, 60 % (28/47) of the patients demonstrating mucoid impaction had high attenuation mucus [14]. In keeping with aforementioned concept that a clinical

Table 1 Various diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA)

Condition	Ref#	Asthma/ PFT↓	+ASP skin test	Total IgE >1000*	↑ASP spec IgE	↑ASP spec IgG	CXR/ CT opacities	Eosinophilia	+ASP PPTs	CB	ASP in mucus	Criteria for diagnosis
ABPA ± CF	4	+	+	+	+	+	+	A	A	A	A	All +
ABPA	7	+	+	+	+	0	+	+	+	+	0	5 to 8 +
ABPA	6	+	A	+	+	0	A	A	A	A	0	All +, AND ≥3A
ABPA + CF	5	+	+	+**	0	0	A	0	A	A	0	All +, AND ≥1A

CF, cystic fibrosis, + required for diagnosis, 0 not required for diagnosis, A adjunctive test for the diagnosis (see “Criteria for dx” column to determine how many adjunctive parameters are required), ≥3A at least three of the adjunctive criteria present, ≥1A at least one of the adjunctive criteria present, REF# reference number, PFT↓ reduction in pulmonary function tests, +ASP positive *Aspergillus*, spec specific, CXR/CT opacities chest radiograph or chest computed tomography scan lung parenchymal opacities, PPT precipitins, CB central bronchiectasis on lung imaging, * >416 IU/mL, ** >500 IU/mL



Fig. 1 Chest CT scan slice of an ABPA patient that demonstrates impacted high attenuation mucus in branches of the right upper lobe (courtesy of Dr. James G. Ravenel, Medical University of South Carolina)

diagnosis of ABPA can be established without radiographic criteria, one of these reports noted that 22 % of their cohort demonstrated a normal lung parenchyma on chest CT scanning [13•].

Novel biomarkers have recently been investigated for the diagnosis of ABPA. Traditional serologic criteria for the diagnosis of ABPA have been based on the patient's immunological reactivity to crude *Af* extracts. These extracts may not indicate genuine *Af*-sensitization. A study of 53 ABPA patients and 253 non-ABPA asthmatics measured the *A. fumigatus*-specific IgE and IgG responses to crude *Af* extracts and purified recombinant *Af*1 through *Af*6 [15]. ABPA patients demonstrated significantly higher levels of IgE antibodies to *Af*1 and *Af*2 than the non-ABPA asthmatics. A limitation of this study was that patients with atopic dermatitis also strongly reacted to these antigens. However, antibody testing against purified recombinant *Af* antigens shows promise as a future diagnostic test for ABPA pending further refinement.

ABPA and CF are both associated with pulmonary symptoms, airflow obstruction, and bronchiectasis and, therefore, are problematic to distinguish. Previous research has shown that basophils are primed and hyper-responsive to *Af* allergen stimulation in CF patients with ABPA compared to CF patients with *A. fumigatus* colonization and CF patients without ABPA or *A. fumigatus* colonization [16•]. Recently, these three groups of CF patients underwent serial measurements of blood basophil activation surface markers such as CD203c [17]. Basophil CD203c surface expression reliably differentiated CF patients with ABPA from those who did not have ABPA, including those colonized with *A. fumigatus*. A similar recent study found that both basophil CD203c and CD68 expression reliably distinguished patients with CF and concomitant ABPA from CF patients without ABPA [18].

Immunopathogenesis: what's known

A. fumigatus is a ubiquitous fungus, and although some associations between level of fungal exposure and the development of ABPA has been identified [19], specific host susceptibility is more important in the pathogenesis of ABPA than environmental factors [20–22]. ABPA develops in a small subset of individuals who are sensitized to aspergillus mold. Although both allergic asthma and ABPA are characterized by a type 2 helper cell (Th2) immune response to aspergillus, the response is greatly exaggerated with ABPA [1].

Aspergillus mycelia grow in the airways of ABPA patients, and spores and hyphae release proteases that can damage the bronchial epithelium causing discrete areas of airway damage and impairing mucociliary clearance. This airway damage releases several cytokines including thymus-regulated and activation-regulated chemokine (TARC) (CCL17), monocyte chemotactic protein (MCP)-1, eotaxin, RANTES (regulated on activation, normal T-cell expressed and secreted), interleukin-8, and macrophage inhibitory protein (MIP)-1 α [1]. In addition, these mycelia release fungal antigens that are processed by antigen-presenting cells (APCs) bearing HLA-DR markers. These processed antigens are presented by APCs to Th2 lymphocytes that release cytokines resulting in a type 1 hypersensitivity response. The Th2 response is intensified by the aforementioned cytokines as the result of airway damage. These Th2 lymphocytes produce IL-4, IL-5, IL-9, IL-10, and IL-13 that promote eosinophil growth, mast cell proliferation, and IgG and IgE isotype switching. Aspergillus-specific IgE, IgG, and IgA markedly increase in the serum [23] and bronchoalveolar lavage fluid [24]. The total IgE is increased out of proportion to the aspergillus-specific IgE. These fungal organisms and the inflammatory mediators that they induce lead to airway destruction, mucoid impaction, bronchiectasis, pulmonary fibrosis, and permanent lung damage.

Immunopathogenesis: what's new

Recently, the specificity of *Aspergillus* to stimulate the Th2 immune response was examined in healthy controls as well as ABPA patients [25]. Peripheral blood monocytes were stimulated with heat-killed *Aspergillus*, numerous Gram-negative and Gram-positive bacteria, *Candida albicans*, chitin, β -glucan, and Toll-like receptor ligands. Only *Aspergillus* stimulated the Th2 cytokines IL-5 and IL-13. CD4+ lymphocytes were responsible for this stimulation. ABPA patients displayed a significantly increased *Aspergillus*-induced Th2/Th1 ratio (as measured by cytokine production) compared to healthy controls. These data suggest that *Aspergillus* is unique in triggering Th2 responses. These investigators also demonstrated that ABPA patients demonstrate decreased interferon γ

(INF- γ) production compared to healthy controls, suggesting that INF- γ may be a corticosteroid-sparing option in ABPA.

Recently, investigators attempted to isolate the specific *Aspergillus* antigens responsible for Th2 cytokine secretion [26]. IL-4 production in CD4+ lymphocytes was measured after exposure to *Af1*, *Af2*, *Af3*, *Af4*, as well as the *Aspergillus* antigens Crf1 and Catalase 1. ABPA patients demonstrated production of IL-4 to all these *Aspergillus* antigens, whereas healthy controls demonstrated a Th1 response and produced predominantly INF- γ . These data suggest that the Th2 CD4+ lymphocyte response in ABPA is not specific for a particular *Aspergillus* antigen. These data are also consistent with the aforementioned study in demonstrating that the Th1 INF- γ response of healthy controls is blunted in ABPA patients.

A recent study of HLA polymorphisms confirmed that several HLA-DRB1 alleles (DRB1*15:01, DRB1*11:04, DBR1*04, DRB1*11:01, DRB1*07:01) are associated with ABPA in CF patients more so than in CF patients with non-ABPA asthma and without asthma [27]. Furthermore, this analysis also identified that DQB1*06:02, a HLA-DQB1 allele, was also more frequent in CF patients with ABPA than other CF patients. Another HLA-DQB1 allele, HLA-DQB1*02:01, was found to be protective of ABPA in CF patients.

Treatment: what's known

Timely and aggressive treatment of ABPA has been demonstrated to prevent disease progression and the development of fibrosis [28]. The goal of treatment is not only to treat asthma exacerbations associated with ABPA but inhibit the *Af*-induced inflammatory response to prevent bronchiectasis, lung destruction, and fibrosis [1]. Corticosteroids are the cornerstone of treatment of ABPA exacerbations. There is no consensus on the optimum corticosteroid dosing regimen, but the range of expert opinion has encompassed 0.5–0.75 mg/kg/day of prednisone equivalent for the first 1 to 6 weeks followed by a taper by 5 to 10 mg in the daily dose with discontinuation of corticosteroids, if tolerated, in 3 to 12 months [29, 30]. A large percentage of ABPA patients have corticosteroid-dependent asthma, and efforts should be made to taper patients to the lowest effective corticosteroid dose as well as minimize corticosteroid side effects [1]. Monthly pulse intravenous methylprednisolone may have long-lasting effects in autoimmune diseases with fewer long-term side effects than chronic oral corticosteroids. Two case series of patients with concomitant CF and ABPA showed that 10–20 mg/kg of intravenous methylprednisolone for 3 days at 1-month and 2-month intervals for up to 4 years was efficacious and associated with few side effects [31–33]. However, some patients had to discontinue therapy because of corticosteroid side effects. In addition to systemic corticosteroids, standard asthmatic therapy should also be administered including inhaled corticosteroids, inhaled

short- and long-acting β -agonists, and asthma self-management education.

Antifungal agents have been used in ABPA to reduce the burden of fungal colonization in the lung, thereby attenuating the inflammatory response and subsequent asthma and lung destruction. Two double blind placebo-controlled trials have assessed the efficacy of itraconazole for the treatment of ABPA. Stevens and colleagues demonstrated that the addition of itraconazole at a dose of 200 mg twice daily for 16 weeks to the usual management of corticosteroid-dependent ABPA resulted in a 50 % reduction in the maintenance corticosteroid dose and a 25 % reduction in serum IgE levels compared to placebo [34]. However, these differences were not statistically significant and there was no difference in remission rates between the two groups. Wark and associates reported that itraconazole 400 mg daily for 16 weeks resulted in statistically fewer exacerbations [35]. Because itraconazole may aggravate adrenal suppression induced by regular corticosteroid use, is costly, and has significant toxicity, it is not recommended as primary therapy for ABPA but rather as adjunctive therapy in corticosteroid-dependent patients [29]. Open label and retrospective analyses have suggested that voriconazole and posaconazole may also be efficacious for ABPA [36–38].

Treatment: what's new

Recently, investigators compared two recommended corticosteroid dosing regimens for the initial treatment of ABPA [39]. Ninety-two treatment-naïve ABPA subjects received either a high dose corticosteroid regimen (prednisone 0.75 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 6 weeks, followed by 5 mg of the daily dose every 6 weeks to complete a total duration of 6–12 months) or a medium dose regimen (prednisone 0.5 mg/kg for 1–2 weeks, then on alternate days for 6–8 weeks, followed by 5–10 mg tapering of the daily dose every 2 weeks until discontinuation). This was a prospective open label trial. The number of subjects with exacerbations was similar at 1 and 2 years, as was improvement in lung function and time to first exacerbation. Although composite endpoints were significantly better in the high dose group, corticosteroid side effects were worse. The investigators concluded that the medium dose corticosteroid regimen was as effective as and safer than the high dose treatment.

Recently, two systemic reviews of the literature have examined the evidence for antifungal treatment in the management of ABPA. One such analysis examined the evidence supporting the use of antifungal treatment for ABPA with and without CF by using GRADE methodology [40] in three biomedical databases [41]. This analysis found that the quality of evidence was weak because of shortage of controlled studies, heterogeneity between studies, and potential bias. Although antifungal treatment of ABPA improved patient and disease outcomes, the

recommendation for its use was weak and clinicians were cautioned to individualize the decision to use antifungals based on the risk of adverse side effects. A Cochrane database systemic review of the literature found that there were no published data available to recommend the use of antifungal therapies in patients with concomitant CF and ABPA [42•]. They advocated the performance of randomized double blind trials in this patient population, as none have yet been published.

There has been a recent interest in the potential of inhaled antifungals for the treatment of ABPA. A case has been reported of a patient with concomitant CF and ABPA who had failed to respond to oral corticosteroids and azoles who subsequently improved while receiving nebulized liposomal amphotericin B. In contrast, a case series of 21 adult asthmatics with fungal sensitization, 11 of whom had ABPA and had failed or developed side effects to azoles, were treated with 10 mg of nebulized amphotericin B daily and only 3 (14 %) patients responded [43]. More than half of them discontinued therapy within 12 months because of bronchospasm, equipment problems, or lack of benefit. Ram and colleagues reported of 21 consecutive patients with ABPA who were randomized to receive either inhaled amphotericin B plus budesonide or inhaled budesonide alone for 1 year [44]. The primary endpoint, time to first exacerbation, was similar in both groups. Only one of five secondary endpoints (percentage of each group that had a least one exacerbation over 1 year) was statistically different and less in the group that received both inhaled medications. A novel inhalable concentrated itraconazole nanosuspension was recently developed and tested in rats [45]. This nanosuspension was well tolerated and achieved adequate serum itraconazole levels. The authors postulated that this could be a potentially beneficial treatment for ABPA.

Several case reports and case series have suggested that omalizumab, a humanized monoclonal antibody to IgE, may be a useful treatment for ABPA [46–53]. These reports demonstrated the following benefits in ABPA with or without concomitant CF: improvement in symptoms, improvement in pulmonary function, weaning from corticosteroids, reduction in serum IgE and other biomarkers of ABPA-related inflammation, reductions in exhaled nitric oxide, and reductions in exacerbation rates and hospitalization rates. However, there are no published double blind, randomized, placebo-control trials, and a Cochrane database systemic review determined that there was a lack of evidence for the efficacy and safety of anti-IgE therapy for ABPA in CF patients [54•].

Vitamin D deficiency is prevalent in CF patients because of inadequate absorption [55]. Patients with ABPA and CF have lower vitamin D levels than patients with CF alone [56]. Furthermore, in vitro treatment with 1,25 di-hydroxy vitamin D decreased *Aspergillus*-induced IL-13 responses of CD4+ lymphocytes obtained from ABPA patients [56]. These facts prompted investigators to administer 4000 IU of vitamin D₃ to seven patients with ABPA and CF in an open label fashion and

examine the *Aspergillus*-induced IL-13 response of their CD4+ lymphocytes [57]. They found that vitamin D supplementation significantly reduced this IL-13 response as well as lowered *Aspergillus*-specific IgE levels.

Monitoring: what's known

There are little evidenced-based data concerning monitoring ABPA patients. It has been recommended that ABPA patients be re-evaluated at 6-week to 8-week intervals over the first year, and at 3-month intervals when they achieve remission [1]. During each monitoring visit, patients should be evaluated for the following: (1) the response to therapy; (2) a possible ABPA exacerbation; (3) the level of asthma control; (4) allergen avoidance; and (5) adverse effects of medication and drug-drug interactions [1]. An analysis of ABPA patients suggested that remission of ABPA was associated with at least a 35 % decline in serum IgE levels [58]. It is recommended to perform a serum IgE level, spirometry, and a chest radiograph at 6-month intervals [59]. Doubling of serum IgE levels and worsening chest radiographic findings suggest an ABPA exacerbation [1].

Monitoring: what's new?

Recently, two studies have examined the timing and rate of decline in the serum IgE level after treatment of ABPA. Agarwal and coworkers noted that a decline at least 20 % in the IgE level, rather than the traditional 35 %, was more sensitive to detect remission of ABPA [60]. Radiographic improvement was also the norm with ABPA remission. ABPA exacerbations were associated with at least a doubling of the serum IgE in more than 90 % of cases. However, *Aspergillus*-specific IgE was vastly inferior to the serum IgE in confirming an exacerbation. Natarajan and Subramanian followed the rate of IgE decline in 24 ABPA patients [61]. They found that IgE level at 1 month declined (26 %), but they declined less than half as much as the 2-month decline (59 %). The decline in IgE levels at 2 months (59 %) was almost identical to the 6-month decline (61 %). These authors concluded that IgE monitoring for immunological control should occur at 2 months after treatment, and to detect treatment failures at 6 months.

Conclusions

Recent insights concerning ABPA have improved the management of this destructive lung disease. Investigators have developed techniques to distinguish ABPA from other lung diseases, specifically non-ABPA asthma and CF. This distinction is important because the early detection of ABPA may

allow for interventions that may avoid serious complications. Our understanding of the immunopathogenesis of ABPA has broadened, enabling consideration of novel treatments and biomarkers. Recent treatment trials of novel agents and critical comparison of standard ABPA treatment regimens and monitoring algorithms have the potential to improve ABPA patient outcomes and minimize treatment side effects. We suspect that such research efforts will continue to accelerate our understanding of this disease and benefit ABPA patients.

Compliance with Ethical Standards

Conflict of Interest Marc Judson is a consultant for Biogen and Mallinckrodt. He has received institutional grant support from Mallinckrodt and the Foundation for Sarcoidosis Research.

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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