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To cite this article: Alan P. Knutsen (2017) Allergic bronchopulmonary aspergillosis in asthma, Expert Review of Clinical Immunology, 13:1, 11-14, DOI: [10.1080/1744666X.2017.1232620](https://doi.org/10.1080/1744666X.2017.1232620)

To link to this article: <http://dx.doi.org/10.1080/1744666X.2017.1232620>



Accepted author version posted online: 07 Sep 2016.
Published online: 22 Sep 2016.



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EDITORIAL

Allergic bronchopulmonary aspergillosis in asthma

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ARTICLE HISTORY Received 2 August 2016; accepted 1 September 2016; published online 22 September 2016

KEYWORDS ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycoses; *Aspergillus fumigatus*; asthma; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; HLA-DR; HLA-DQ; IL4RA, Interleukin 4 receptor alpha chain; SAFS, severe asthma associated with fungal sensitivity

Hinson et al. [1] first described allergic bronchopulmonary aspergillosis (ABPA) in three adult asthmatics in 1952 in England, and subsequently Slavin et al. [2] described the first case of ABPA in a child in 1970 in the United States. Initially thought to be rare, the prevalence of ABPA is estimated to be 1–2% in asthmatic patients and 7–9% in patients with cystic fibrosis (CF) [3–5]. Furthermore, Denning et al. [6] have estimated that global prevalence of ABPA may be 0.7–3.5% of patients with asthma.

ABPA is a TH2 hypersensitivity lung disease caused by bronchial colonization with *Aspergillus fumigatus* that affects asthmatic and/or CF patients (Table 1) [3–5]. ABPA is characterized by exacerbations of asthma, worsening of pulmonary function, recurrent transient pulmonary infiltrates, peripheral blood and pulmonary eosinophilia, elevated total IgE level, and elevated *A. fumigatus* specific IgE, IgG, and IgA antibody levels. During episodes of ABPA exacerbations, thick brown mucoid sputum may contain *A. fumigatus* hyphae. Cylindrical bronchiectasis of the central airways, particularly involving the upper lobes may be a consequence of pulmonary infiltrates due to eosinophilic inflammation [3–5]. The large airways may also be occluded by impacted mucus and hyphae. Agarwal et al. [7–10] have also reported this as bronchi-filled hyperdense high attenuation mucus (HAM) resulting in consolidation on chest radiograph. On biopsy, the airways demonstrate bronchial wall inflammation consisting of eosinophils, lymphocytes, and plasma cells. The airway lumen may be occluded by mucus containing *Aspergillus* hyphae and eosinophils. Squamous metaplasia of the bronchial mucosa is common, and granulomas may develop. With long-standing inflammation bronchial fibrosis and bronchiolitis obliterans may develop.

In the pathogenesis of ABPA, *A. fumigatus* spores 3–5 µm in size are inhaled and germinate into hyphae deep within the bronchi [3–5]. In addition, fragments of the hyphae have been demonstrated within the interstitium of the pulmonary parenchyma [12]. The implication is that there is the potential for high concentrations of *A. fumigatus* allergens to be exposed to the respiratory epithelium and immune system. A variety of *Aspergillus* proteins are released, including superoxide dismutases, catalases, proteases, ribotoxin, phospholipases,

hemolysin, gliotoxin, phthioic acid, and other toxins, that have biologic activity in addition to being immunologic. In particular, Kauffman et al. [13] demonstrated that *Aspergillus* proteases induce epithelial cell detachment and induce human bronchial cell lines to produce proinflammatory chemokines and cytokines, such as IL-8, IL-6, and MCP-1. Interestingly *Alternaria* and *Cladosporium* proteases also had this effect. These proteases also stimulate the epithelial protease associated receptor 2 (PAR2), inducing an allergic inflammatory response.

A central question is why only a small percentage of patients develop ABPA. This has prompted the examination of genetic risk factors in the development of ABPA (Table 2). Chauhan et al. [14–16] reported that asthmatic and CF patients who expressed HLA-DR2 and/or DR5 and lacked HLA-DQ2 were at increased risk to develop ABPA after exposure to *A. fumigatus*. Within HLA-DR2 and HLA-DR5, there are restricted genotypes. In particular, HLA-DRB1*1501 and HLA-DRB1*1503 were reported to produce high relative risk. On the other hand, 40%–44% of non-ABPA atopic *Aspergillus*-sensitive individuals have the HLA-DR2 and/or HLA-DR5 genotype. Additional studies indicated that the presence of HLA-DQ2 (especially HLA-DQB1*0201) provided protection from the development of ABPA. Knutsen et al. [3,5,17] reported single-nucleotide polymorphisms (SNP) of the interleukin 4 receptor alpha chain (IL4RA) in 92% of ABPA subjects, principally the IL-4 binding SNP ile75val. This was associated with increased sensitivity to *in vitro* IL-4 stimulation as measured by enhanced expression of the low-affinity IgE receptor (CD23) on B cells seen in ABPA patients. Brouard et al. [18] reported the association of the –1082GG genotype of the IL-10 promoter with colonization with *A. fumigatus* and the development of ABPA in CF. The –1082GG polymorphism has been associated with increased IL-10 synthesis. Thus, dendritic cells expressing HLA-DR2/DR5, increased IL-10 synthesis, and increased sensitivity to IL-4 stimulation due to IL-4RA polymorphisms, may be responsible for skewing *Aspergillus*-specific Th2 responses in ABPA. Pulmonary surfactant protein A2 (SP-A2) polymorphisms (ala91pro, arg94arg) in the collagen region have been reported in ABPA patients [19]. Miller et al. [20] reported that cystic fibrosis transmembrane conductance regulator gene (CFTR) mutations were

Table 1. Features of allergic bronchopulmonary aspergillosis (ABPA) and allergic bronchopulmonary mycosis (ABPM) [4,7,11].

ABPA*	ABPM**
Asthma or cystic fibrosis (CF) Worsening lung function not attributable to another etiology Positive skin prick test with <i>Aspergillus</i> species Elevated IgE ≥1000 ng/mL (416 IU/mL) #In CF, total serum IgE levels: • ≥1000 IU/mL, classic • ≥500 IU/mL, minimum 200 to 500 IU/mL. If ABPA is suspected, repeat in 1–3 months. If patient is taking steroids, repeat when steroid treatment is discontinued	Severe asthma, mucus production, adult, lung disease duration Less reversible/fixed airflow obstruction Elevated IgE
Increased <i>Aspergillus</i> species-specific IgE and IgG antibodies New or recent abnormalities on chest radiography or chest CT that have not cleared with antibiotics and standard physiotherapy Increase blood eosinophilia ≥400 eosinophils/μL when patient is not on corticosteroids <i>Aspergillus</i> species-specific precipitating antibodies Central bronchiectasis Histopathology: eosinophils, neutrophils, bronchocentric granulomatosis	Increased fungal-specific IgE antibody Increased blood eosinophilia Bronchiectasis Histopathology: eosinophils, neutrophils, bronchocentric granulomatosis Fungal colonization of airways
<i>Aspergillus</i> species-specific containing mucus plugs Genetics: HLA association, rare CFTR variants Treatment: glucocorticosteroids, antifungals, possibly omalizumab	Genetics: HLA association, rare CFTR variants Treatment: glucocorticosteroids, antifungals, possibly omalizumab

*Agarwal et al. [7].

**Lotvall et al. [11].

#Adapted from Stevens et al. [4].

Table 2. Genetic risk factor in the development of allergic bronchopulmonary aspergillosis.

HLA-DR restriction and HLA-DQ protection HLA-DR2: HLA-DRB1*1501 and *HLA-DRB1*1503 HLA-DR5: HLA-DRB1*1101 and HLA-DRGB1*1104 HLA-DQ2 protective, decreased in ABPA DQB1*0201 IL-4RA polymorphisms IL-4RA ile75val IL-10 polymorphisms Promoter –1082 GG genotype Surfactant protein A2 (SP-A2) polymorphisms SP-A2 ala91pro Cystic fibrosis transmembrane conductance regulator (CFTR) mutations Heterozygous CFTR mutations in asthmatic patients with ABPA Toll-like receptor (TLR) polymorphisms TLR9T-1237C

HLA: human leukocyte antigen; IL: interleukin.

Adapted with permission from Knutsen and Slavin [17].

increased in asthmatic patients who developed ABPA. In a meta-analysis, Agarwal et al. [21] also reported a higher incidence of CFTR mutations in asthmatic ABPA patients. Carvalho et al. [22] reported increased frequency of the Toll-like receptor 9T-1237C polymorphism (TLR9T-1237C) in ABPA patients. The TLR9C allele of T-1237C results in decreased expression [23]. TLR-9 recognizes *Aspergillus* hyphae and conidia on murine neutrophils [24]. Thus, decreased TLR-9 protective function may be an underlying susceptibility in the development of ABPA. However, in patients with severe asthma associated with fungal sensitivity (SAFS) who are predominantly *Aspergillus* sensitive, there was no association of polymorphisms of TLR2, TLR4, or TLR9 [22].

Perhaps, ABPA should be examined in the larger context of the asthmatic endotype of allergic bronchopulmonary mycosis (ABPM), as described by Lotvall et al. (Table 1) [11]. One feature of *A. fumigatus* compared to other fungi is that *Aspergillus* spores inhaled into the bronchi germinate into hyphae [3–5,17]. In addition, fragments of hyphae have been identified within the interstitium of the pulmonary parenchyma of

patients with ABPA. Thus, the airways are exposed to high levels of *Aspergillus* allergens and enzymes, such as proteases, in ABPA. ABPA then is perhaps the most prevalent form of ABPM. The clinical features of ABPM are similar to those of ABPA: severe asthma, airflow obstruction, bronchial colonization of fungi, elevated total IgE and mold-specific IgE titers, eosinophilia, and bronchiectasis (Table 1). The bronchial pulmonary inflammatory response is similar to ABPA, namely eosinophilic, neutrophilic and bronchocentric granulomatosis. Underlying genetic risks, though, are not well defined. The fungi associated with ABPM are listed in Table 3. These include predominantly *Candida*, *Bipolaris*, *Curvularia*, *Schizophyllum*, and *Pseudallescheriasis*; however, *Alternaria*, *Cladosporium* and *Penicillium* as well as other common fungi have also been identified. *Alternaria*, *Cladosporium*, and *Aspergillus* have all been associated with development of severe asthma [25–28]. In particular, Denning's group coined the termed SAFS [30]. Fungal sensitivities of SAFS included *Aspergillus* (66%), *Cladosporium* (52%), *Alternaria* (34%), *Penicillium* (48%), *Candida* (66%), *Trichophyton* (31%), and *Botrytis* (28%). These fungi are also seen in ABPA and ABPM. In SAFS, antifungal therapy with itraconazole improved quality of life and pulmonary function tests [30]. However, in a similar group of *Aspergillus*-sensitive severe adult asthmatics, Agbetile et al. [31] reported in the EVITA3 study that voriconazole was ineffective.

Examining genetic risk factors, Carvalho et al. [22] found no association with TLR2, TLR4 and TLR9 polymorphisms in SAFS. Knutsen et al. [34,35] reported that children with moderate–severe asthma had significantly increased sensitivities to *A. fumigatus* while sensitivities to *Alternaria* were similar in both moderate–severe and mild asthmatics. The frequency of HLA-DRB1*13 and HLA-DRB1*03 alleles tended to be increased in these mold-sensitive moderate–severe asthmatics. However, the frequency of HLA-DQB1*03 alleles was significantly decreased in mold and *Alternaria*-sensitive moderate–severe asthma and was associated with increased *in vitro* Th2 IL-5 and

Table 3. Fungi associated with allergic bronchopulmonary mycosis (ABPM) [32,33].

Fungi* (literature)	Fungi ** (n = 143)	Percent (%)**
<i>Alternaria alternata</i>	<i>Alternaria alternata</i>	Rarely
<i>Bipolaris</i> spp.	<i>Bipolaris</i> spp.	13%
<i>Candida</i> spp.	<i>Candida albicans</i>	60%
	<i>Candida glabrata</i>	Rarely
<i>Cladosporium</i> spp.	<i>Cladosporium cladosporioides</i>	Rarely
<i>Curvularia</i> spp.	<i>Curvularia</i> spp.	8%
<i>Drechslera</i> spp.		
<i>Fusarium</i> spp.	<i>Fusarium vasinfectum</i>	Rarely
<i>Geotrichum</i> spp.		
<i>Helminthosporium</i> spp.		
<i>Mucor</i> -like spp.		
<i>Paecilomyces</i> spp.		
<i>Penicillium</i> spp.	<i>Penicillium</i> spp.	Rarely
<i>Pseudallescheria</i> spp.	<i>Pseudallescheria boydii</i> spp. complex	3%
<i>Rhizopus oryzae</i>	<i>Rhizopus oryzae</i>	Rarely
<i>Saccharomyces</i> spp.	<i>Saccharomyces cerevisiae</i>	Rarely
<i>Schizophyllum</i> spp.	<i>Schizophyllum commune</i>	11%
<i>Stemphylium</i> spp.	<i>Stemphylium languinosum</i>	Rarely
<i>Torulopsis</i> spp.		
<i>Trichosporon</i> spp.	<i>Trichosporon beigeli</i>	Rarely

*Adapted from Singh and Denning [32].

**Adapted from Chowdhary et al. [33].

IL-13 synthesis in *Alternaria*- and Asp f3-stimulated cultures. This suggests that HLA-DQB1*03 may be protective against the development of *Alternaria*-sensitive severe asthma. Knutsen et al. [35] also reported increased frequency of the IL4RA ile75val SNPs increased sensitivity to IL-4 stimulation and increased Th2 response to *Alternaria* stimulation in children with *Alternaria*-sensitive moderate-severe asthma. Thus, there were similar genetic risk factors in *Alternaria/Aspergillus* sensitive moderate-severe asthma in children as observed in ABPA.

In ABPA, ABPM, and SAFS standard medication used to treat asthma, such as inhaled corticosteroids, long-acting beta agonists and leukotriene receptor antagonists, are not adequate to manage the symptoms and allergic pulmonary inflammation. Systemic corticosteroids are frequently necessary. Recently, Agarwal et al. [36] compared medium-dose oral corticosteroid (OCS) versus high-dose OCS in the treatment of acute stage ABPA. Medium-dose OCS was defined as oral prednisolone 0.5 mg/kg/day for 2 weeks followed by 0.5 mg/kg/day on alternate days for 8 weeks, then taper by 5 mg every 2 weeks, and discontinue after 3–5 months, and high-dose OCS as oral prednisolone 0.75 mg/kg/day for 6 weeks followed by 0.5 mg/kg/day for 6 weeks, then taper by 5 mg every 6 weeks, and discontinue after 8–10 months. In comparison of 48 subjects treated with medium-dose OCS versus 44 subjects treated with high-dose OCS, there were no significant differences in ABPA exacerbation rates after 1 year (50% vs. 40.9%) or OCS dependence diagnosed after 2 years (14.6% vs. 11.4%). However, there were significantly greater side effects in the high-dose OCS-treated ABPA patients. These findings also suggest that medium-dose OCS is effective in the treatment of acute ABPA exacerbations, but not sufficient along with standard asthma therapy in the treatment of ABPA.

Anti-fungal medications are beneficial in ABPA; however, it is not clearly beneficial in ABPM and SAFS. This then leads to the use of biological modifiers. In ABPA, Tillie-Leblond et al. [29] evaluated 16 patients with ABPA who received omalizumab for one year. This group of patients had decreased

exacerbations and need for oral steroids during this time. In 2016, Voskamp et al. [37] reported a randomized, double-blind, placebo-controlled, cross-over trial with two treatment phases of 4-month duration. Thirteen patients with asthma and ABPA were identified and underwent the active treatment phase with omalizumab 375 mg every 2 weeks for 4 months with a washout period of 3 months, and cross-over arm. ABPA exacerbations occurred less frequently during omalizumab treatment compared with the placebo period, 2 versus 12 events. Mean fractional exhaled nitric oxide (FeNO) decreased from 30.5 to 17.1 ppb during omalizumab treatment. In addition, omalizumab treatment resulted in decreased basophil reactivity to *A. fumigatus* and decreased FcεR1 and surface-bound IgE levels. These studies and many case reports show the benefit this additional treatment option offers patients with ABPA.

In summary, ABPA, ABPM, and SAFS do not respond clinically to conventional asthma therapy. Understanding the genetic risks and allergic inflammatory pathways will be beneficial in designing better treatments probably with biologic modifiers to block IgE (omalizumab), IL-5 (mepolizumab), IL-13 and/or IL-4 (lebrikizumab, tralokinumab), IL4Ra (dupilumab, pitrakinra), and/or thymic stromal lymphopoietin (TSLP) antagonist (AMG157) [38].

Funding

This paper was not funded.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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