AAAAI Committee Report

Allergic Bronchopulmonary Aspergillosis

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There remains a lack of agreement on diagnostic criteria and approaches to treatment of patients with allergic bronchopulmonary aspergillosis (ABPA). The results of a survey of American Academy of Allergy, Asthma, & Immunology members regarding these 2 issues are presented and compared for concordance with published recommendations. The literature was reviewed for pertinent reports, and an electronic survey was conducted of American Academy of Allergy, Asthma, & Immunology members and fellows regarding diagnostic criteria, numbers of patients evaluated for ABPA, and treatment approaches. From 508 respondents to the survey sent to 5155 US physicians in the American Academy of Allergy, Asthma, & Immunology database of members and fellows, 245 health professionals (48%) had treated at least 1 patient with ABPA in the previous year. For the diagnosis of ABPA, there was a difference in the threshold concentration of total serum IgE because 44.9% used ≥417 kU/L, whereas 42.0% used ≥1000 kU/L. Analysis of these findings suggests that ABPA might be underdiagnosed. With regard to pharmacotherapy, oral steroids were recommended for 97.1% of patients and oral steroids plus inhaled corticosteroids plus antifungal agent were used with 41.2% of patients. The armamentarium for treatment of ABPA includes oral corticosteroids as the initial treatment with inhaled corticosteroids used for management of persistent asthma. Azoles remain adjunctive. Published experience with omalizumab has been limited. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:703-8)

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The global prevalence of allergic bronchopulmonary aspergillosis (ABPA) has been estimated to be as high as 2.5%,[1] yet, delays in diagnosis or undertreatment may lead to pulmonary fibrosis, bronchiectasis with chronic sputum production, and increasingly severe persistent asthma with loss of lung function. There are differences of opinion over the criteria for diagnosis, screening tests of patients with asthma, and how best to manage and treat the patient.[2] ABPA is almost always caused by *Aspergillus fumigatus*, which has intrinsic virulence, survival characteristics, proinflammatory actions, and enzymatic properties in susceptible hosts. The purpose of this review is to consider fungi implicated in allergic bronchopulmonary mycoses (ABPM), give a brief discussion of the immunopathology and approaches to management and treatment, and to report findings from a survey of allergist/immunologists in the American Academy of Allergy, Asthma, & Immunology (AAAAI) that explored the diagnostic criteria and treatments of ABPA.

ABPM

Since the original description of APBA in 1952,[3] a number of other fungi or yeasts have been implicated as causing a similar clinical syndrome. Examples are listed in Table I. *A fumigatus* is by far responsible for the majority of these cases, but other fungi or yeasts have been identified when patients presented with features of ABPA (eg, pulmonary infiltrates with peripheral blood eosinophils, with or without bronchiectasis; underlying asthma) but lacked evidence of sensitization or recovery of *A fumigatus*. The culprit fungus was identified in sputum or airway samples, along with evidence of sensitization to the fungus by skin test or *in vitro* measurement. The diagnosis of ABPM, therefore, is predicated on the identification of fungi, other than *A fumigatus*, by appropriate culture or molecular biology techniques of patients with clinical features of ABPA. Often there is repeated recovery of the rare fungus or yeast that leads to the diagnosis. Because commercially available reagents for skin testing and for *in vitro* methods to detect

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Abbreviations used
AAAAI- American Academy of Allergy, Asthma, & Immunology
ABPA- Allergic bronchopulmonary aspergillosis
ABPM- Allergic bronchopulmonary mycosis
CF- Cystic fibrosis
TLR- Toll-like receptor

specific IgE antibodies are lacking for many of these fungi involved in ABPM, investigators need to prepare their own reagents or refer patients and/or samples to specialized centers for evaluation. It is likely that additional case reports of ABPM will appear due to the spectrum of fungi in the environment and the increasing prevalence of asthma.

CRITERIA FOR DIAGNOSIS OF ABPA

In a 2012 review in *The Journal of Allergy and Clinical Immunology*, the criteria for diagnosis were presented as follows: "The minimal criteria required for the diagnosis of ABPA are as follows: (1) asthma or [cystic fibrosis] with deterioration of lung function, (2) immediate *Aspergillus* species skin test reactivity, (3) total serum IgE level of 1000 ng/mL (416 IU/mL) or greater, (4) increased *Aspergillus* species−specific IgE and IgG antibodies, and (5) chest radiographic infiltrates. (See Table 2) Additional criteria might include peripheral blood eosinophilia, *Aspergillus* species serum precipitating antibodies, central bronchiectasis, and *Aspergillus* species−containing mucus plugs."[18]

In 2003, the ABPA Consensus Conference of the Cystic Fibrosis Foundation[19] proposed that ABPA be diagnosed for a classic case as follows: (1) acute or subacute clinical deterioration (increased cough, wheezing, exercise induced asthma, increased sputum, decrease in pulmonary function), (2) serum total IgE concentration >1000 kU/L unless the patient is receiving systemic corticosteroids, (3) immediate cutaneous reactivity (skin prick test) to *Aspergillus* or the presence of serum IgE−*A fumigatus*, and (4) precipitating antibodies to *A fumigatus* or serum IgG−*A fumigatus*. The minimal diagnostic criteria are (1) acute or subacute clinical deterioration (increased cough, wheezing, exercise induced asthma, increased sputum, decrease in pulmonary function); (2) serum total IgE concentration >500 kU/L (If ABPA is suspected and the total serum IgE level is 200 to 500 kU/L, repeat the total serum IgE in 1 to 3 months. If the patient is using oral corticosteroids, repeat the total serum IgE when steroid treatment has been discontinued[19]); (3) immediate cutaneous reactivity (skin prick test) or the presence of serum IgE−*A fumigatus;* (4) one of the following: (a) precipitins to *A fumigatus* or demonstration of IgG−*A fumigatus* or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or computed tomography of the chest (bronchiectasis) that has not cleared with antibiotics and standard physiotherapy.[19] Potential diagnostic tools related to detection of fungal infection or colonization include findings from studies of invasive aspergillosis[20] and cystic fibrosis (CF),[21] which consist of enzyme assays for detection of antigenic side chains of *Aspergillus* galactomannan,[20] 1,3-β-D-glucan, which is the cell wall component of *A fumigatus* and other fungi,[20] and *A fumigatus* DNA by PCR.[20] The latter methodology detects viable and dead fungal organisms and inert spores.[21]

GENETIC RISK FACTORS

Genetic studies may provide potential aids in diagnosis and pathogenesis. For example, HLA-DR restriction has been shown to be a risk factor for the development of ABPA. Chauhan et al[22-24] observed that patients with asthma and patients with CF who expressed HLA-DR2 and/or HLA-DR5 but lacked HLA-DQ2 were at increased risk for ABPA after exposure to *A fumigatus*. In particular, HLA-DR2, HLA-DRB1*1501, and HLA-DRB1*1503 genotypes were reported to provide high relative risk. Further studies indicated that the presence of HLA-DQ2, especially DQB1*0201, provided protection from the development of ABPA. Brouard et al[25] reported that the *-1082GG* genotype of the IL-10 promoter was associated with colonization of *A fumigatus* and the development of ABPA in CF. The *-1082GG*

TABLE I. Fungi associated with ABPM

Organism	Study
Aspergillus fumigatus	Hinson et al, 1952[3]
Aspergillus ochraceus	Greenberger, 1988[4]
Aspergillus oryzae	Akiyama at al. 1987[5]
Aspergillus terreus	Elliott and Newman-Taylor, 1997[6]
Alternaria alternata	Chowdhary et al, 2012[7]
Bipolaris (Dreschleria) hawaiiensis	McAleer et al, 1981[8]
Candida albicans	Akiyama et al, 1984[9]
Cryptococcus neoformans	Arora and Huffnagle, 2005[10]
Curvularia lunata	Halwig et al, 1985[11]
Fusarium vasinfectum	Backman et al, 1995[12]
Geotricum candidum	Elliott and Newman-Taylor, 1997[6]
Helminthosporium species	Hendrich et al 1982[13]
Penicillium species	Elliott and Newman-Taylor, 1997[6]
Peudoallescheria boydii	Elliott and Newman-Taylor, 1997[6]
Sacchromycetes cerevisiae	Ogawa et al, 2004[14]
Schizophyllum commune	Kamei et al, 1994[15]
Stemphyllium lanuginosum	Benatar et al, 1980[16]
Torulopsus glabrata (now designated *Candida glabrata*)	Patterson et al, 1982[17]

TABLE II. Diagnostic criteria for ABPA in patients with asthma or CF

Patients with asthma or CF (2012 Criteria in Ref 18)
Asthma or, if CF, with deterioration of lung function
Immediate skin reactivity to *Aspergillus* species
Total serum IgE ≥ 1000 ng/mL (416 IU/mL)*
Increased *Aspergillus* species-specific IgE and IgG antibodies
Chest roentgenographic infiltrates
"Additional criteria might include peripheral blood eosinophilia, *Aspergillus* species serum precipitating antibodies, central bronchiectasis, and *Aspergillus* species-containing mucus plugs"[18]
ABPA Consensus Conference of the Cystic Fibrosis Foundation (Ref 19)
Acute or subacute clinical deterioration (increased cough, wheezing, exercise-induced asthma, increased sputum, decrease in pulmonary function)
Total serum IgE concentration >1000 kU/L unless the patient is receiving systemic corticosteroids
Immediate cutaneous reactivity (skin prick test) to *Aspergillus* or presence of serum IgE−*A fumigatus*
Precipitating antibodies to *A fumigatus* or serum IgG−*A fumigatus*
If the total serum IgE concentration is >500 but ≤1000 kU/L, then repeat it, especially if the patient no longer requires oral corticosteroids. See text for criteria when the total IgE is 200-500 kU/L

*1 IU/mL = 1 kU/L = 2.4 ng/mL.

TABLE III. Patients and practice settings of 508 allergist/immunologists who completed a survey about their patients with ABPA

Patients	Results, no. (%)
Patients with ABPA in the past year	
No	263 (51.8)
Yes	245 (48.2)
1-5 patients	214 (87.3)
6-10 patients	23 (9.4)
>11 patients	8 (3.3)
Patients with CF and with ABPA	40 (16.3)
1-5 patients	36 (14.7)
6-10 patients	3 (1.2)
>11 patients	1 (0.4)
Practice setting of physicians with patients with ABPA	
Rural area	9 (3.7)
Metropolitan area population	
<100,000	33 (13.5)
100-999,000	84 (34.3)
>1,000,000	116 (47.3)
Missing	3 (1.2)

TABLE IV. Diagnostic criteria used by 245 allergist/immunologists who diagnosed ABPA in the past year

Study	No. (%) of allergist/immunologists treated previously
Patients with asthma and with ABPA	205 (83.7)
Patients with CF and with ABPA	40 (16.3)
A fumigatus SPT	188 (76.7)
A fumigatus IDST	104 (42.4)
Anti–*A fumigatus* IgE	157 (64.1)
PST and/or IDST, anti *A fumigatus* IgE	231 (94.3)
A fumigatus precipitins	127 (51.8)
Anti–*A fumigatus* IgG	99 (40.4)
Af precipitins antibodies/anti–*A fumigatus* IgG	175 (71.4)
Total IgE ≥ 417 IU/mL	110 (44.9)
Total IgE ≥ 1000 IU/mL	103 (42.0)
Peripheral blood eosinophils ≥400/μL	54 (22.0)
Bronchiectasis	122 (49.8)

IDST, Intradermal skin test; *SPT*, skin prick test.

polymorphism has been associated with increased IL-10 synthesis; whereas, the *−1082A* allele has lower IL-10 synthesis. Saxena et al[26] reported that patients with ABPA and with polymorphisms (ala91pro, arg94arg) in the collagen region of pulmonary surfactant protein A2 had elevated total IgE concentrations and higher percentages of eosinophilia than observed in those patients who lacked the single nucleotide polymorphisms. They also found that 80% of patients carrying both alleles had ABPA (odds ratio 10.4; $P = .0079$), whereas only 50% and 60% of patients carrying each allele, individually, were subjects with ABPA, which suggests an additive effect.[26] It is theorized that changes in conformation or affinity of surfactant protein A2 may decrease these interactions and compromise host defense.

Miller et al[27] examined mutations in the CF transmembrane conductance regulator gene in subjects with asthma who did not have a diagnosis of CF. Mutations were present at a higher frequency in patients with asthma who developed ABPA, 6 of 21 (28.5%), versus control patients with asthma, 2 of 43 (4.6%). These patients with ABPA were heterozygous for the mutations. It is unclear what effect heterozygous cystic fibrosis transmembrane conductance regulator mutations may have on mucus quality in airways of patients with asthma. Carvalho et al[28] examined Toll-like receptor (*TLR*) polymorphisms of *TLR2*, *TLR4*, and *TLR9* in cavitary pulmonary aspergillosis, severe asthma associated with fungal sensitization, and patients with ABPA. Patients with ABPA had increased frequency of allele C for the *TLR9* T-1237C polymorphism compared with control patients. TLR-9 is a receptor that recognizes CpG motifs prevalent in bacterial and viral DNA. Novak et al[29] reported that the *TLR9* C allele of T-1237C decreases expression. Thus, decreased TLR-9 protective function may be an underlying susceptibility in the development of ABPA.

TABLE V. Medications and/or testing by 245 allergist/immunologists for patients with ABPA in the past year

Treatment or test	Patients, no. (%)
OCS	238 (97.1)
OCS + ICS	124 (50.6)
OCS, no ICS	26 (10.6)
Antifungal alone	3 (1.2)
OCS-ICS + antifungal	101 (41.2)
Voriconazole and/or posaconazole	65 (26.5)
Omalizumab	23 (9.4)
ACTH stimulation test	
1 mo	13 (5.3)
3-6 mo	36 (14.7)

ICS, Inhaled corticosteroid; *OCS*, oral corticosteroid.

DIAGNOSTIC CRITERIA BY ALLERGIST/IMMUNOLOGISTS

The results from a survey carried out by the AAAAI in 2012 are presented in Tables III to V. By using the AAAAI's database of 5155 US physicians, members and fellows were contacted on multiple occasions. (see Appendix E1 in this article's Online Repository at www.jaci-inpractice.org for the questionnaire). The response rate was 9.8% (508 physicians). Of these, 245 allergist/immunologists answered affirmatively to question 1 (Appendix E1) that they had seen a patient with ABPA in the past year and provided demographic information about their practice locations and range of patients with ABPA seen in the past year (Table III). The range of diagnostic criteria used are presented in Table IV. There is an evenly divided difference between using the total IgE concentration of ≥417 IU/mL (kU/L) by 44.9% respondents and ≥1000 IU/mL (kU/L) by 42% respondents. In retrospect, some results may be attributable to the order of questions in the survey (Appendix E1, question 3 comes after both 1 and 2 and should have come after 1 to focus on ABPA and the same question coming after question 2 to focus on CF). Alternatively, because 83.7% of respondents referred to patients with ABPA, it is suspected that some of the difference in concentration of total IgE as a criterion does apply to ABPA. Bronchiectasis was a diagnostic criteria by 49.8% of the respondents. These data emphasize the need to clarify diagnostic criteria to increase (enhance) uniform application.

TABLE VI. Stages of ABPA of patients with asthma

Stage	Radiography on chest roentgenogram or computed tomography of lungs (examples)	Total IgE concentration
I (acute)	Homogeneous infiltrates, mucus plugging, consolidation or lobar collapse, "tree-in-bud" findings, bronchiectasis	Elevated
II (remission)	No infiltrates	Normal or elevated but less than in stage I
III (exacerbation)	As in stage 1	Elevated (double that of stage 2)
IV (steroid-dependent asthma)	No infiltrates, can have atelectasis or hyperinflation from asthma (if an exacerbation occurs, then pulmonary infiltrates such as in stage 1 can be present)	Elevated or normal
V (end-stage fibrotic)	Scarring, hyperinflation, chronic infiltrates, fibrosis or cavities or fibrocavitary findings	Normal or elevated

MANAGEMENT OF ABPA

Treatment goals

The overall goals are 4-fold: (1) control of symptoms of asthma or CF, (2) prevent or treat pulmonary exacerbations of ABPA, (3) reduce or remit pulmonary inflammation, and (4) mitigate progression to end-stage fibrotic or cavitary disease (Table VI). Early and aggressive treatment of ABPA has the greatest likelihood of preventing progression to end-stage fibrotic lung disease (stage V).[30-34] After therapy, many patients with stage I (acute stage) and stage III (exacerbation stage) can enter complete remission, stage II, represented by a 35% to 50% reduction in total serum IgE by 6 weeks, clearing of pulmonary infiltrates and symptomatic improvement. Unfortunately this may not be permanent because some patients relapse and have additional pulmonary infiltrates.[33,34] Earlier diagnosis and treatment appears to lower the risk of advancement to stage IV (glucocorticosteroid dependent) or stage V (fibrocavitary disease).[34]

Exposure

Bioaerosols of very large numbers of fungi (with bacteria and endotoxins) occur from disturbing organic waste and have been associated with ABPA in 2 of 28 garden waste collectors.[35] We were unable to find evidence to make a strong recommendation to minimize exposure to fungi through avoidance and mitigation, such as from moldy basements, water damaged buildings, saunas, and indoor areas with improper home ventilation. Although these are prime locations for growth of molds,[36] and can be pertinent for patients with asthma and allergic rhinitis, there is a lack of evidence to make a strong recommendation regarding prevention of pulmonary infiltrates in ABPA.

Therapeutics

Oral corticosteroids. Corticosteroids remain the mainstay in the management of ABPA, by targeting the inflammatory response triggered by *A fumigatus*.[34] Most patients with ABPA require periods of oral steroid treatment, followed by tapering doses. Dosing of oral steroids for ABPA has not been well defined. Lower dose oral steroids have been associated with a higher rate of relapse, whereas higher doses for longer duration have a higher remission rate. A common strategy is 2 weeks of daily prednisone 0.5 mg/kg, followed by 6 to 8 weeks of alternate day therapy and then tapering by 5 to 10 mg every 2 weeks.[34] A more aggressive approach[32,33] is prednisolone 0.75 mg/kg/d for 6 weeks, then 0.5 mg/kg/d for 6 weeks, followed by a tapering dose of 5 mg every 6 weeks to continue for a total duration of 6 to 12 months.

Oral steroids are important in the control of symptoms and reducing the likelihood of relapse. Patients are considered in remission when they remain without pulmonary infiltrates and/or eosinophilia for 6 months after oral steroid withdrawal.[34] A useful marker of disease activity and success of therapy is a total serum IgE concentration. Total serum IgE is monitored every 6 to 8 weeks after the initiation of oral steroids and is continued for 1 year thereafter. The goal is to achieve a 35% to 50% reduction of total serum IgE, which leads to clinical and radiologic improvement. Chest imaging, either by chest radiograph or high-resolution chest computed tomography, after 4 to 8 weeks of initiation of oral steroid therapy, is important to assess resolution of infiltration. Spirometry also is a useful tool to objectively assess response to therapy.[40]

Intravenous corticosteroids. Pulse therapy with monthly intravenous methylprednisolone at a dose of 10 to 20 mg/kg/d for 3 consecutive days, in conjunction with itraconazole, has been demonstrated effective in both reduction in subjective symptoms as well as objective measurements.[37,38] This may be a consideration of patients who demonstrated resistance to oral therapy. A potent inhibitor of CYP3A4, itraconazole increases concentrations of methylprednisolone but not prednisolone and can cause suppression of cortisol secretion.[39]

Inhaled corticosteroids. Inhaled corticosteroids are a central component in the management of persistent asthma; however, in the dosage equivalent of 400 to 800 μg of beclomethasone dipropionate, when combined with a long-acting β-agonist, they have not been shown to be effective in preventing increasing concentrations of total IgE.[40] Although symptoms of asthma were improved, they could not be controlled completely.[40] The researchers concluded that "High doses of [inhaled corticosteroids] alone have no role in the management of ABPA-S and should not be used as first-line therapy."[39]

Antifungals. Antifungals play an important, yet adjunctive role in the management of ABPA. Antifungals may reduce the requirement for prolonged high-dose systemic corticosteroids by decreasing the burden of fungal colonization and attenuating inflammatory responses. The majority of the literature that addressed antifungal therapy focus on the use of amphotericin and the azoles (ketoconazole, itraconazole, voriconazole, and posaconazole). In recent years, the use of amphotericin B and

ketoconazole has been replaced by antifungals with fewer potential adverse effects.

Itraconazole. Among the antifungals used to treat ABPA, itraconazole is the most commonly recommended. Itraconazole has been demonstrated to significantly reduce total serum IgE, sputum eosinophils, and, most importantly, decrease symptoms and the oral steroid requirement.[41,42] Itraconazole is recommended for those patients who are steroid dependent and for those who have relapse after a course of steroids. The recommended adult dose for itraconazole is 200 mg twice daily for 4 to 6 months and then tapered over the next 4 to 6 months. As mentioned earlier, it is important to note that itraconazole can inhibit the metabolism of methylprednisolone. Renal function and concurrent medication usage also should be monitored. As with most azoles, adverse drug reactions are not uncommon and include nausea and vomiting, diarrhea, flatulence, hyperlipidemia, hypokalemia, and elevated liver enzymes. Phototoxicity and photosensitivity (UVA) have been reported.[43] An alternative approach is for courses of 4 to 6 months.[44-45] As with any antimicrobial agent, resistance to azoles is well known, and fungal sensitivities may need to be obtained with some patients (University of Texas Health Sciences Center at San Antonio, Department of Pathology, 7703 Floyd Curl Drive, MC 7750, Room 329E, San Antonio, TX 78229-3900. Ph: 210 567 4131, Fax: 210 567 4076).

Other azoles. Voriconazole and posaconazole are reported to be an effective adjunct therapy in the management of ABPA, with clinical improvement in 70% of patients with ABPA treated with voriconazole and 78% of patients with ABPA treated with posaconazole.[46,47] Adverse effect profiles were similar to itraconazole in 40% of those treated with voriconazole and 22% of those treated with posaconazole.[46] Dosing of voriconazole in adult patients is 300 to 600 mg/d and posaconazole 880 mg/d, adjusted by plasma monitoring. The target predose voriconazole plasma level was 1.3 to 5.7 mg/mL. The target posaconazole random plasma level was >0.7 mg/L. For patients who did not improve when on itraconazole, at least 70%, who tolerated either voriconazole or posaconazole, responded favorably.[47]

mAb therapy. There have been a few case reports that demonstrated benefit of omalizumab in the management of ABPA, in which some patients had concurrent CF.[48-50] A trial of omalizumab with 16 patients with asthma and ABPA demonstrated significant reductions in exacerbations and steroid requirement, although it did not demonstrate improvement in spirometry.[51] Reduction in exacerbations of asthma and oral steroid requirements has been reported.[52] This potential adjunct in ABPA management, with a low adverse effect profile, warrants double-blinded, randomized, controlled trials. The role of treatment with antibodies to IL-4Rα (dupilumab), IL-5 (mepolizumab), IL-13 (lebrikizumab), or other targets in ABPA remains speculative.

Treatments and tests by allergist/immunologists

The AAAAI survey results regarding treatment and testing approaches are presented in Table V. Oral corticosteroids with or without inhaled corticosteroids were administered by 97% of the respondents. Antifungals plus corticosteroids were used by 41% of respondents. The distribution of medications or their combinations could reflect varying stages of ABPA (pulmonary infiltrates or none), repetitive expectoration of sputum plugs or none, ease or difficulty of treatment of concomitant asthma or ABPA, and physician and patient preferences among other explanations.

SUMMARY

As the worldwide prevalence of asthma has increased, it appears that the prevalence of ABPA also has increased. Thus, ABPA is no longer a rare condition and has been recognized as a specific subtype (endotype) of asthma.[53] The results of the study of allergist/immunologists in the AAAAI suggest that uniform criteria for diagnosis are needed, especially as to the cutoff of total IgE concentration (and the appropriate units, eg, kU/L or IU/mL, in which it is expressed), and that controlled trials would be informative to understand the place in therapy of all of the therapies that are used. Establishing separate registries of patients with ABPA with asthma and with CF in terms of risk factors, exposures, and diagnostic criteria and treatment, would provide valuable information in better understanding and treating ABPA.

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