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.