

Diagnosis of Allergic Bronchopulmonary Aspergillosis Exacerbations



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Allergic bronchopulmonary aspergillosis (ABPA) is a complex disease induced by an allergic immune response to the fungus *Aspergillus fumigatus* (*Asp f*). ABPA is associated with asthma and cystic fibrosis, in which there are structural changes of the lower airways, including mucus accumulation, as well as dysfunction in innate and specific immune responses. *Asp f* colonizes and proliferates in these impaired lower airways, inducing an exacerbated T helper type 2 immune response in predisposed patients who may develop ABPA.¹

The study of the human microbiome and its importance in health and disease is a growing field. Disturbance in the interaction between human and fungus may lead to several pulmonary disorders (Table I). ABPA is a disease at the allergic spectrum of the pulmonary disorders induced by fungus. Although the disease affects less than 1% of all patients with asthma, its prevalence may be greater than 5% in severe asthma.^{2,3} Regarding cystic fibrosis, ABPA prevalence ranges from 7% to 15% of patients.^{1,4}

Early recognition and treatment of ABPA are fundamental to prevent the progression of the disease, with the development of bronchiectasis, pulmonary fibrosis, and end-stage lung disease. ABPA in its initial stages, when only the serological markers are present, is designated serologic ABPA, but, unfortunately, ABPA is often diagnosed only after years of disease monitoring, when the process of healing/fibrosis/remodeling is evident (ABPA with central bronchiectasis). ABPA diagnosis is a challenge for a number of reasons:⁵

- (1) There is no unique biomarker for disease diagnosis and follow-up. Some criteria have been proposed based on clinical, immune-laboratory, and radiological parameters (Table II).⁶⁻⁹ The criteria are not specific for ABPA and it is uncommon for all of them to be present at once.
- (2) The clinical presentation of ABPA is characterized by periods of remission and exacerbation.
- (3) The lack of standardization of the allergens used in the diagnosis of ABPA affects the reproducibility of results.

- (4) Treatment of asthmatic patients with corticosteroids and other anti-inflammatory drugs may mask several criteria.
- (5) Other fungi may colonize the lower airways and induce an ABPA-like disease, which is designated allergic bronchopulmonary mycosis.

There is no unique criterion with good positive and negative predictive values to diagnose ABPA. The immediate intradermal test, as well as the specific and serum total IgE (these last 2 depending of the cutoff value used), may present acceptable sensitivity and could be used as screening tests. The cutoff value for total IgE is controversial and ranges from 417 to 1000 IU/mL. On the other hand, a serum specific IgG of 27 mgA/L and some radiographic findings such as hyperattenuating mucoid impaction may present acceptable specificity and could be used as “rule-in” tests.⁶⁻⁹ The serum total IgE may also be useful during patients’ follow-up. A serum total IgE increase greater than 50% along with clinical worsening and appearance of new radiologic findings suggests an exacerbation of ABPA.¹ In recent years, component-resolved diagnosis has been introduced for the purpose of determining the clinical relevance of any given sensitization. However, regarding ABPA, this technology needs further development before it can be routinely used in the disease diagnosis.⁵

In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Gothe et al⁴ provide further evidence that total-IgE levels may be a reliable biomarker of ABPA activity in patients with cystic fibrosis and sensitized to *Asp f*.⁴ Doubling of total-IgE levels within 3 months exceeding the normal range may indicate ABPA requiring treatment in these patients. The authors demonstrated that episodes of increasing total IgE were accompanied by forced expiratory volume in 1 second declines, and the treatment of these episodes with steroids resulted in improved long-term pulmonary outcomes.⁴

The pathogenesis of ABPA remains controversial, and its diagnosis and treatment a challenge that relies on a combination of clinical, radiological, and immunological criteria. Serial measurements of serum total IgE may aid in the follow-up of patients with ABPA until better biomarkers are identified.

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TABLE I. Pulmonary disorders induced by fungus

Type of interaction	Disorder
Saprophytic	Fungus ball
Allergic	Asthma
	Allergic bronchopulmonary mycosis
	Hypersensitivity pneumonitis
Infection (invasive)	Chronic pulmonary mycosis
	Invasive pulmonary mycosis

TABLE II. Criteria for ABPA diagnosis

Criteria	Parameters
International Society for Human and Animal Mycology, 2013 ⁶	A. Predisposing conditions: asthma, cystic fibrosis B. Essential criteria (both must be met) 1. Positive serum specific IgE (>0.35 kUA/L) or immediate skin test 2. Serum total IgE > 1000 IU/mL C. Additional criteria (at least 2 of 3) 1. Presence of serum specific IgG 2. Thoracic imaging findings consistent with ABPA 3. Peripheral blood eosinophil count >500 cells/μL (may be historical)
Diagnostic Criteria in Asthma ⁷	1. Asthma 2. Positive immediate skin test 3. Serum total IgE ≥ 1000 ng/mL (417 IU/mL) 4. Serum specific IgE and IgG 5. Thoracic imaging findings consistent with ABPA Additional criteria: 1. Peripheral blood eosinophilia 2. Aspergillus species serum precipitating antibodies 3. Central bronchiectasis 4. Aspergillus species-containing mucus plugs
Cystic Fibrosis Foundation Consensus Conference, 2003 ⁸	1. Cystic fibrosis with acute or subacute clinical deterioration 2. Serum total IgE concentration >1000 IU/mL unless the patient is receiving systemic corticosteroids 3. Positive serum specific IgE (>0.35 kUA/L) or immediate skin test 4. Presence of serum specific IgG

ABPA, Allergic bronchopulmonary aspergillosis.

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