

Allergic bronchopulmonary aspergillosis

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with asthma or cystic fibrosis, and results in pulmonary infiltrates, tenacious mucus plugs that harbor hyphae of *Aspergillus fumigatus*, elevations of total serum immunoglobulin E concentration and peripheral blood and sputum eosinophilia. Bronchiectasis is an irreversible complication of ABPA. The key to early diagnosis is to consider ABPA in anyone with asthma or cystic fibrosis and with a positive skin test result for *Aspergillus*, and/or recurrent infiltrates on radiographs. The differential diagnosis for ABPA in patients with asthma includes diseases in which there is an overlap of asthma, peripheral blood eosinophilia, and radiographic infiltrates. Examples include chronic eosinophilic pneumonia, Churg-Strauss syndrome, drug-induced pulmonary infiltrates, infection with a parasite, asthma with atelectasis, and lymphoma. Mucus plugging that causes a “tree in bud” pattern on computerized tomography examination of the lungs may be from ABPA or other conditions, such as nontuberculous (atypical) mycobacteria (*Mycobacterium avium*–*Mycobacterium intracellulare* complex). Prednisone is indicated to clear pulmonary infiltrates, and a usual course is for 3 months. Itraconazole and voriconazole are adjunctive, and drug-drug interactions must be considered because azoles decrease elimination of various medications. Although not familial in most patients, presentation of *Aspergillus fumigatus* fl (Asp fl) antigen is restricted to specific major histocompatibility complex (MHC) class II molecules, Human Leukocyte Antigen-DR2 (HLA-DR2), and HLA-DR5. There is an increased number of CD4⁺ T-helper type 2 lymphocytes in bronchoalveolar lavage, and *A. fumigatus* can serve as a growth factor of eosinophils potentiating the effects of interleukin (IL) 3, IL-5, and Granulocyte-colony stimulating factor (G-CSF). Eosinophils interact directly with *A. fumigatus* spores and generate extracellular traps, which can injure the bronchial epithelium.

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Allergic bronchopulmonary aspergillosis (ABPA) is a disease that occurs when the pulmonary immune system reacts to antigens of *Aspergillus fumigatus*, a ubiquitous thermophilic fungus that colonizes bronchial mucosa. It is thought that *A. fumigatus* spores within the bronchial tree activate the immune system to cause tissue damage, including proximal bronchiectasis and bronchiolitis obliterans distally. Patients at risk for ABPA are typically those with asthma or cystic fibrosis.

This disease occurs in 1–2.5% of patients with persistent asthma and occurs in an estimated 10.1% versus 8.9% in adults versus children with cystic fibrosis.^{1–3} ABPA should be suspected in any patient with asthma and a positive result of an immediate skin test or *in vitro* test for immunoglobulin E (IgE) to *A. fumigatus*, with any of the following characteristics: worsening asthma; recurrent infiltrates; expectoration of golden brown mucous plugs; or, in cystic fibrosis, patients who begin to wheeze regularly or have an elevated IgE

concentration > 500 IU/mL. The severity of asthma in patients with ABPA ranges from mild intermittent asthma to corticosteroid-dependent asthma. In general, exacerbations of ABPA are associated with increased external fungal spore recoveries; therefore, in Chicago, exacerbations predominantly occur from June to November, and, in Great Britain, occur from October to February.

The differential diagnosis for ABPA includes diseases in which there is an overlap of asthma, peripheral blood eosinophilia, and radiographic pulmonary infiltrates; and in patients with asthma and sensitization to fungal antigens. The former may include chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis (formerly called Churg-Strauss syndrome), drug-induced pulmonary infiltrates, infection with a parasite, asthma with atelectasis, and lymphoma. Mucus plugging that causes a “tree in bud” pattern on computerized tomography (CT) examination of the lungs may be from ABPA or other conditions, such as nontuberculous (atypical) mycobacteria (*Mycobacterium avium*–*Mycobacterium intracellulare* complex) and may occur in patients with asthma, especially during exacerbations. The latter refers to one of two populations, either the ≥25% of patients with persistent asthma who have immediate skin test reactivity to *Aspergillus* species, or other fungal antigens or patients with severe asthma with fungal sensitization.⁴ Patients with severe asthma with fun-

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Table 1 Acceptable criteria for identifying and diagnosing ABPA

AAAAI Committee Report*

Minimum essential criteria

- Asthma or cystic fibrosis
- Immediate cutaneous reactivity on skin-prick testing
- Elevated total serum IgE level (>417 IU/mL or >1000 ng/mL)

Plus one or both of the following:

- Elevated serum IgE and IgG levels to *A. fumigatus* (at least twice asthma controls)
- Proximal (central) bronchiectasis on radiograph (inner two-thirds of lung on CT)

ISHAM Working Group#

Predisposing conditions

- Asthma or cystic fibrosis

Obligatory criteria (both must be present)

- Aspergillus* skin test positivity or elevated IgE levels against *A. fumigatus*

- Elevated total IgE concentration (typically > 1000 IU/mL, but if the patient meets other criteria, then an IgE value of <1000 IU/mL is acceptable)

Other criteria (at least 2 must be present)

- Precipitating serum antibodies to *A. fumigatus* or elevated serum *Aspergillus* IgG by immunoassay

- Radiographic pulmonary opacities consistent with ABPA

- Total eosinophil count of >500 cells/ μ L in patients who are steroid naive (may be historical)

ABPA = Allergic bronchopulmonary aspergillosis; AAAAI = American Academy of Allergy, Asthma & Immunology; IgE = immunoglobulin E; *A. fumigatus* = *Aspergillus fumigatus*; CT = Computerized tomography; ISHAM = International Society for Human and Animal Mycology.

*From Ref. 5.

#From Ref. 7.

gal sensitization do not meet criteria for ABPA but should have a total serum IgE value of <1000 IU/mL and immediate skin test reactivity or *in vitro* IgE antibodies to at least one fungal antigen.⁴

Uniform criteria for a diagnosis of ABPA have been lacking but increased efforts have been made to create a standardized approach for testing. One approach to diagnose ABPA is presented in Table 1, which was published in the 2012 AAAAI committee report.^{5,6} In 2013, The International Society for Human and Animal Mycology created a working group to formulate a revised set of diagnostic criteria.⁷ The criteria proposed was based on a systematic review of previous literature on the subject and needs further validation (Table 1). Both sets of criteria highlight key features important for identifying and diagnosing ABPA.^{5,7} There is a separate set of diagnostic criteria for ABPA in cystic fibrosis (CF) that has been published but is not discussed here.

Patients with classic ABPA also may have radiographic infiltrates, peripheral blood eosinophilia (if not treated with prednisone), precipitating antibodies, and mucus plugs with *A. fumigatus*. Radiographs of patients with ABPA can show transient or permanent infiltrates and, when advanced, can show pulmonary fibrosis, cavitation, contracted upper lobes, and lobar collapse.^{1,8} Patients who meet the criteria only for se-

rologic tests are labeled ABPA-seropositive, and, if central bronchiectasis is present, then they are labeled ABPA-central bronchiectasis. The International Society for Human and Animal Mycology working group has recommended ABPA with high-attenuation mucus, and ABPA with chronic pleuropulmonary fibrosis as part of the radiologic classification.⁷

ABPA is classified into five stages.^{1,8} Stage I (acute) is diagnosed when a patient first appears with the essential criteria of ABPA, including increased total IgE concentration and elevated levels of IgE—*A. fumigatus* and IgG—*A. fumigatus*. The chest radiograph or CT (high-resolution) examination may or may not have bronchiectasis but demonstrate infiltrates not explained by other conditions. Stage II (remission) occurs when the total IgE concentration has fallen to 50–75% of the peak IgE value; total IgE concentration may not normalize but the chest radiographic or CT infiltrates have cleared. Stage III (exacerbation) occurs when there are new radiographic infiltrates by chest radiograph or CT examination, and, in most patients, the total serum IgE level doubles over the baseline value. Administration of prednisone helps clear the infiltrates and reduces the total IgE concentration. Stage IV (corticosteroid-dependent asthma) occurs when a patient's oral prednisone cannot be tapered without causing an increase in the IgE level or worsening of the asthma or

recurrent pulmonary infiltrates. Stage V (fibrotic) is the most severe stage of the disease. In this stage, the lungs are fibrotic, cavitary, or both. Radiographic images will show fibrosis or cavitary lesions, and pulmonary function tests will show restrictive physiology with irreversible obstruction. Lung transplantation has been attempted in a few patients, and, in one patient, has been associated with recurrence of ABPA within a year. It should be noted that patients in stage V are never classified as ABPA-seropositive, and, if patients are diagnosed and treated early and aggressively, then few if any will progress to stage V.

Patients with ABPA need to have spirometry measured yearly and be treated for current morbidities, such as allergic rhinitis, gastroesophageal reflux, and rhinosinusitis. They should also avoid places that are harbingers for mold, including leaky basements and places with improperly stored mulch, because these exposures can exacerbate their condition. Exacerbations of ABPA should be treated with avoidance measures (remediation of fungal sources in the home or workplace, focusing on intrusion of water or ineffective dehumidification), management of asthma (and comorbidities such as rhinitis or rhinosinusitis), and prednisone.¹ Initially, 0.5 mg/kg of prednisone is administered every morning for 2 weeks. This dose is converted to every other day for 6 to 8 weeks, then tapered and discontinued. The total serum IgE concentration is measured at the time of diagnosis and is repeated at 4 and 8 weeks and then every 8 weeks for 1 year. If the IgE concentration has decreased by one-third and radiographs are clear of infiltrates at 8 weeks, then the prednisone is tapered by 5 mg every 2 weeks. However, if the total serum IgE concentration doubles, then this change may be indicative of an indolent exacerbation or patient nonadherence, and the prednisone is increased. A repeated high-resolution CT of the lung could be helpful in establishing a diagnosis.

The administration of itraconazole, voriconazole, and posaconazole in the management of ABPA is adjunctive and should not be substituted for oral corticosteroid during acute exacerbations. Long-term use may reduce the total duration of systemic corticosteroids by decreasing the burden of pulmonary fungal colonization and associated inflammation.⁵ A short-term study with itraconazole reported significant reductions in symptoms but not prevention of infiltrates or preservation of lung function.⁹ Also, itraconazole and voriconazole have adverse effects, including inhibition of hepatic metabolism of medications *via* effects on Cytochrome P450 3A4 (CYP3A4). Voriconazole can cause reversible photosensitivity or unpleasant alterations in perception of colors and can reduce metabolism of prednisolone. There is limited experience with posaconazole in ABPA but posaconazole can be considered if itraconazole and voriconazole fail or to their

continued demonstration.⁵ Long-term azithromycin, either daily or three times weekly, can be considered for patients with ABPA–central bronchiectasis who are highly symptomatic because it may provide anti-inflammatory effects to the airways.⁵ If it does not improve cough frequency or reduce sputum production after 2–3 weeks, then azithromycin should be discontinued.

Omalizumab and mepolizumab have not been found to be harmful, and, occasionally, patients are described who have improved, at least in terms of management of persistent asthma.¹⁰ An intriguing report described the synergistic administration of mepolizumab being added to high-dose omalizumab.¹¹ Formal studies are lacking that evaluate the role of any of the currently approved biologic monoclonal antibody therapies for persistent asthma, including anti-IgE (omalizumab), anti-IL5 (mepolizumab, reslizumab), anti-IL5R α (benralizumab), or anti-4R α (dupilumab) in patients with ABPA. Allergen immunotherapy can be administered, but extracts that contain *Aspergillus* species should be avoided on a theoretical basis.

IMMUNOLOGY

- Presentation of the *Asp f1* antigen is restricted to specific major histocompatibility complex (MHC) class II molecules, Human Leukocyte Antigen-DR2 (HLA-DR2), and HLA-DR5.¹
- In ABPA, there is an increased number of CD4 (T-helper type 2 phenotype) T cells in the bronchoalveolar lavage.¹
- There is gain of function of interleukin (IL) 4, which causes activation of CD20 B cells and upregulation of CD23 (the low affinity IgE receptor, Fc ϵ RII).¹²
- *A. fumigatus* can serve as a growth factor of eosinophils, which potentiates the effects of IL-3, IL-5, and Granulocyte colony-stimulating factor (G-CSF).
- Luminal eosinophils interact directly with *A. fumigatus* spores and generate extracellular traps; extracellular traps are made up of a sticky chromatin structure and likely contribute to the viscosity of mucus plugs in patients with ABPA. The eosinophil granules that remain in a trap are not able to kill the spore and are thought to injure the bronchial epithelium and may explain why the mucus remains colonized with spores of *A. fumigatus*.¹³

CLINICAL PEARLS

- Early diagnosis and treatment of ABPA prevent the progression of disease to cavitary or fibrotic lung disease.
- The key to an early diagnosis is in considering this disease in anyone with asthma and a positive skin test result to *Aspergillus*, and/or otherwise unexplained peripheral blood eosinophilia and compati-

ble infiltrates on radiographs or CT examination of the lungs.

- Peripheral blood eosinophilia (in the absence of systemic corticosteroids) is often from 10–25% (in contrast to 40–90% that occurs with parasitism).
- Prednisone is indicated to clear pulmonary infiltrates, and a usual course is for 3 months, not indefinitely, because the total serum IgE concentration remains > 417 IU/mL after 3 months of treatment with prednisone. Avoid prednisone for ABPA when there are no pulmonary infiltrates (consolidations, significant mucus plugging), corticosteroid-dependent asthma or end-stage fibrocavitary ABPA.

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