

## Allergic bronchopulmonary aspergillosis

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Allergic bronchopulmonary aspergillosis (ABPA) complicates asthma and cystic fibrosis. The survival factors in *Aspergillus fumigatus* that support saprophytic growth in bronchial mucus are not understood. Prednisone remains the most definitive treatment but need not be administered indefinitely. MHC II-restricted CD4<sup>+</sup> T<sub>H</sub>2 clones have been derived from patients with ABPA. The total serum IgE concentration is elevated sharply but is "nonspecific." IgE serum isotypic antibodies to *A fumigatus* are useful in diagnosis; this is in contrast to the situation for patients with asthma without ABPA. High-resolution computed tomography of the chest demonstrates multiple areas of bronchiectasis in most patients with ABPA and is a useful radiologic tool. Some asthma control patients might have a few bronchiectatic airways, but not to the extent seen in or of the same character as those in ABPA. This review discusses clinical, radiologic, investigational, pathogenetic, and treatment issues of ABPA. (*J Allergy Clin Immunol* 2002;110:685-92.)

**Key words:** *Aspergillosis, bronchiectasis, Aspergillus fumigatus, end-stage, sinusitis, prednisone, IgE antibody, lymphocytes, eosinophils*

The first cases of allergic bronchopulmonary aspergillosis (ABPA) in the United States were identified more than 30 years ago,<sup>1,2</sup> whereas the initial literature report in the United Kingdom was in 1952.<sup>3</sup> The prevalence of ABPA is as high as 1% to 2% of patients with persistent asthma if screening is carried out,<sup>4</sup> though even higher rates have been reported.<sup>5</sup> In cystic fibrosis, the prevalence of ABPA ranges from 2% to 15%.<sup>6-21</sup> ABPA is sometimes recognized in patients with allergic fungal sinusitis,<sup>22,23</sup> though such an association is unusual. ABPA has been identified in patients with hyper-IgE syndrome and chronic granulomatous disease, which might create management dilemmas because of concerns about administration of prednisone.<sup>24</sup> In patients with asthma, ABPA is sometimes diagnosed in the absence of the typical proximal bronchiectasis; in such cases, it is

### Abbreviations used

AAS: Allergic *Aspergillus* sinusitis

ABPA: Allergic bronchopulmonary aspergillosis

BAL: Bronchoalveolar lavage

CT: Computed tomograph(y)

designated *ABPA-seropositive*.<sup>25</sup> Often, ABPA is suspected (1) because of an episode of "pulmonary eosinophilia" or tenacious mucus plugging, (2) when a chest roentgenogram and an unexpected infiltrate is obtained, or (3) after skin testing and serologic testing.

### THE DIAGNOSIS OF ABPA IN ASTHMA AND CYSTIC FIBROSIS

For a diagnosis of ABPA in a patient with asthma, there should be a minimum of 5 criteria: (1) asthma, (2) proximal bronchiectasis (dilated bronchi in the inner two thirds of the chest field on a computed tomograph [CT]), (3) immediate cutaneous reactivity to *Aspergillus* species or *Aspergillus fumigatus*, (4) a total serum IgE that is elevated (>417 kU/L or 1000 ng/mL), and (5) elevated serum IgE-*A fumigatus* and/or serum IgG-*A fumigatus* in comparison with what is seen in sera from skin test-positive patients with asthma who do not have ABPA. Such patients can be designated *ABPA-central bronchiectasis*.<sup>25</sup> Most newly diagnosed patients will have the classic criteria, which are presented in Table I. Classic cases will have other features as well, including chest roentgenographic infiltrates, peripheral blood eosinophilia in the absence of oral corticosteroids, precipitating antibodies to *A fumigatus*, and production of mucus plugs containing *A fumigatus*. In such cases, the allergist-immunologist or pulmonologist should have little difficulty with the diagnosis. Failure of the chest roentgenographic or chest CT infiltrates to clear over a 2-month period of prednisone therapy suggests noncompliance, another ABPA exacerbation, or possibly other diagnoses, such as cystic fibrosis.<sup>26</sup> At least 1 case of an allergic bronchopulmonary mycosis from *Fusarium* species was followed by emergence of Churg-Strauss syndrome.<sup>27</sup>

Proposed criteria for the diagnosis of ABPA in patients with cystic fibrosis are presented in Table II, which is based on the work of a Consensus Conference of the Cystic Fibrosis Foundation.<sup>26</sup> There is disagreement in the literature regarding criteria for the diagnosis of ABPA in

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**TABLE I.** Criteria for the diagnosis of ABPA in patients with asthma

	Minimal essential criteria
Criteria for ABPA-central bronchiectasis	
1. Asthma	Yes
2. Central bronchiectasis (inner two thirds of chest CT field)	Yes
3. Immediate cutaneous reactivity to <i>Aspergillus</i> species or <i>A fumigatus</i>	Yes
4. Total serum IgE concentration >417 kU/L (1000 ng/mL)	Yes
5. Elevated serum IgE- <i>A fumigatus</i> and or IgG- <i>A fumigatus</i>	Yes
6. Chest roentgenographic infiltrates	No
7. Serum precipitating antibodies to <i>A fumigatus</i>	No
Criteria for the diagnosis of ABPA-seropositive	
1. Asthma	Yes
2. Immediate cutaneous reactivity to <i>Aspergillus</i> species or <i>A fumigatus</i>	Yes
3. Total serum IgE concentration >417 kU/L (1000 ng/mL)	Yes
4. Elevated serum IgE- <i>A fumigatus</i> and or IgG- <i>A fumigatus</i>	Yes
5. Chest roentgenographic infiltrates	No

CT, Computed tomograph.

cystic fibrosis and even regarding whether ABPA worsens the natural history of patients with cystic fibrosis.<sup>28</sup> Of note, the prevalence of ABPA is higher in patients with cystic fibrosis than in patients with persistent asthma.

Some patients who seem to have had no history of asthma or cystic fibrosis and then present with chest roentgenographic infiltrates and lobar collapse are found to have ABPA.<sup>29</sup> Some patients with ABPA have had histories of intermittent mild asthma (exercise-induced bronchospasm) before their ABPA was diagnosed. Conversely, the asthma might have been persistent moderate or severe (corticosteroid-dependent).<sup>30</sup>

## DEFENSES AGAINST INVASIVE ASPERGILLOSIS

In ABPA and allergic *Aspergillus* sinusitis (AAS),<sup>31-33</sup> there is no systemic invasive aspergillosis. The patients are not immunocompromised. There is saprophytic growth of *A fumigatus* (or other fungi) in bronchial mucus or sinuses. In AAS, there can be expansile effects of the mucoid impactions in closed spaces that thin bones or deviate them outright. It is possible to demonstrate localized bony invasion if adequate surgical debridement and marsupialization have not been performed. For practical purposes, in ABPA, after inhalation of spores from the environment, there is growth of *A fumigatus* hyphae in bronchial mucus but no invasive disease. Defenses against *A fumigatus* spores include both polymorphonuclear leukocytes and alveolar macrophages.<sup>34</sup> Certainly, invasive aspergillosis is a too-frequent complication of cancer treatment when there is leukopenia and possible

**TABLE II.** Criteria for the diagnosis of ABPA in patients with cystic fibrosis

Classic case criteria	
Clinical deterioration (increased cough, wheezing, exercise intolerance, increased sputum, decrease in pulmonary function)	
Immediate cutaneous reactivity to <i>Aspergillus</i> or presence of serum IgE- <i>A fumigatus</i>	
Total serum IgE concentration >1000 kU/L	
Precipitating antibodies to <i>A fumigatus</i> or serum IgG- <i>A fumigatus</i>	
Abnormal chest roentgenogram (infiltrates, mucus plugging, or a change from earlier films)	
Suggestions for screening on annual phlebotomy for ABPA	
Maintain clinical suspicion for ABPA.	
Annual total serum IgE determination: If it is >500 kU/L, test for immediate cutaneous reactivity to <i>Aspergillus</i> or by an in vitro test for serum IgE- <i>A fumigatus</i> .	
If the total serum IgE is <500 kU/L, repeat if clinical suspicion is high.	

From the ABPA Consensus Conference of the Cystic Fibrosis Foundation.<sup>26</sup>

damage to the pulmonary epithelium from chemotherapy. The latter would become a less formidable barrier. In addition, it is thought that chemotherapy can injure pulmonary epithelial cells.<sup>34</sup> The doses of prednisone used to treat ABPA include 1 to 2 weeks of daily therapy for pulmonary infiltrates followed by alternate-day therapy for 2 months. At 0.5 mg/kg, this treatment does not interfere with delayed hypersensitivity responses, cause supra-infections, or result in invasive aspergillosis.

## CHARACTERISTICS OF ASPERGILLUS SPECIES

Most human disease attributable to the genus *Aspergillus* is caused by *A fumigatus*. The spores are remarkably thermotolerant; they grow at temperatures from 15° to 53°C. They can be recovered in outdoor winter air and from warm compost piles. The spores are readily grown on Sabouraud dextrose agar slants. The hyphae are 7 to 10 µm long and septate, and they branch at 45°. Hyphae present in a mucus plug from sputum or sinus debris can be identified through use of a Gomori methenamine silver stain or a periodic acid-Schiff stain. The spores measure only 2 to 3.5 µm in diameter, so they easily pass the carina, which excludes many particles larger than 7 µm. The spores are typically green, but they can be white. The substrates for *Aspergillus* species include decomposing organic matter, such as decaying vegetation in soil or in crawl spaces, mulches, wood chips, freshly mown grass, and sewage treatment debris. *A fumigatus* can be present in fungal cultures from basements, in indoor (and outdoor) air, and on walls or ceilings where water damage has occurred. *Aspergillus* spores and deep fungi, *Histoplasma* and *Cryptococcus*, grow in bird excreta. Workers who remove bird excreta from rooftops can be exposed to thousands of fungal spores. *Aspergillus* spores

**TABLE III.** Stages of ABPA

Stage	Description	Radiographic infiltrates	Total serum IgE
I	Acute	Upper lobes or middle lobe	Sharply elevated
II	Remission	No infiltrate and patient off prednisone for >6 mo	Elevated or normal
III	Exacerbation	Upper lobes or middle lobe	Sharply elevated
IV	Corticosteroid- dependent asthma	Often without infiltrates, but intermittent infiltrates might occur	Elevated or normal
V	End stage	Fibrotic, bullous, or cavitary lesions	Might be normal

are ubiquitous, and their recovery on a culture does not necessarily implicate them in disease. Nevertheless, the requirements of *Aspergillus* species for moisture and organic material or some other substrate allow for growth in many places. In some cases, the mold-allergic patient with asthma or ABPA will experience acute respiratory symptoms of asthma or develop an episode of ABPA pulmonary eosinophilia after exposure to an especially moldy environment. In the Chicago area, over a period of 5 years, 75% of ABPA exacerbations occurred during the period June through November, when the total outdoor mold counts were highest, though there were no major changes in outdoor *Aspergillus* counts.<sup>35</sup>

### ASPERGILLUS-RELATED CONDITIONS

*Aspergillus* species can cause allergic asthma and acute respiratory responses with experimental challenges. In ABPA, bronchoprovocation challenges are not required for the diagnosis and can result in very large reductions in FEV<sub>1</sub>. In 1971, McCarthy and Pepys<sup>36</sup> reported declines of as much as 40% to 50% in FEV<sub>1</sub> during the immediate response with reversal by a β-adrenergic agonist.<sup>36</sup> Late reactions began within 4 to 10 hours and lasted from 30 to 70 hours; there were declines in FEV<sub>1</sub> from 50% to 79%.<sup>36</sup> Some patients experienced mild to moderately severe malaise and myalgias. Their temperatures increased to 37° to 38°C, with a peak at 8 to 12 hours. The inhalation challenges resulted in increases in peripheral blood eosinophilia at 15 minutes and 6 and 24 hours after bronchoprovocation.<sup>36</sup> These challenges were carried out with a diluted extract based on the skin test titration, yet they produced very severe dual responses. Patients with ABPA are especially responsive to inhalation of *A fumigatus* spores or extracts. Their immune responses are increased vastly in comparison with those of patients with asthma and immediate cutaneous reactivity to *Aspergillus* species or *A fumigatus* in whom sufficient criteria for a diagnosis of ABPA do not exist.

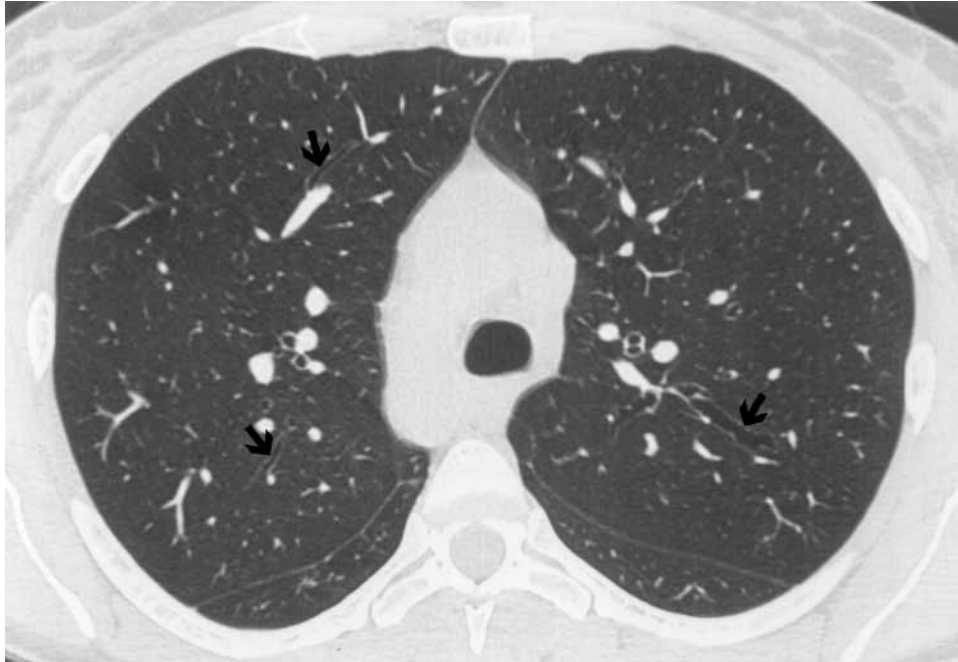
*Aspergillus* species, primarily *A fumigatus* in human beings, can cause AAS or be a manifestation of its presence; they can also cause invasive aspergillosis, chronic necrotizing pneumonia, hypersensitivity pneumonitis, pulmonary aspergillomas (mycetomas), and ulcerative tracheitis. Animals can be infected by *Aspergillus* species, with serious economic consequences; examples include abortions in sheep, avian aspergillosis in turkeys (which causes the turkeys to cough and lose weight),

ulcerative tracheitis in prized racing camels, and invasive aspergillosis in horses, cattle, calves, and lambs.

### STAGING OF ABPA

The 5 stages proposed by Patterson et al<sup>37</sup> remain useful. These stages are not phases of a disease, and in each case the physician should attempt to determine the stage that is present. The stages are presented in Table III. Most patients who have classic findings and current chest roentgenographic or CT infiltrates are in stage III (recurrent exacerbation). Other patients with current infiltrates are in stage IV (corticosteroid-dependent asthma) or possibly stage I (acute) for first-time recognized infiltrates. High doses of inhaled corticosteroids have not prevented the emergence of infiltrates. Similarly, despite its widespread administration, the antifungal agent itraconazole has not prevented new infiltrates consistently. Patients who are in stage I or stage III with acute infiltrates should respond to prednisone administration, with clearing of the chest roentgenographic or CT infiltrates over 1 to 2 months, and they should become less symptomatic (reduced dyspnea and cough and improved spirometry results). Total serum IgE, if obtained serially, will decline by at least 35% over 6 weeks.<sup>38</sup> One should not attempt to administer prednisone indefinitely in an attempt to reduce the total serum IgE concentration into the normal range. Unless the patient enters stage II (remission) or stage V (end stage), it is doubtful that the total serum IgE concentration will return to normal ranges. Conversely, knowing the ranges of total serum IgE when there are no chest roentgenographic infiltrates will establish a baseline from which increases of 100% or greater can alert one to an exacerbation.

Patients with fibrocavitary ABPA (stage V) can have extensive bronchiectasis resembling end-stage cystic fibrosis. Infiltrates can be from *Pseudomonas aeruginosa* or *Staphylococcus aureus* pneumonias or from rare species that have colonized the bronchi. Response to prednisone is limited, and additional modalities, such as bronchial hygiene, coughing- or sputum-assist devices, inhaled RNAase, and anti-pseudomonal antibiotic coverage might be required. An earlier diagnosis of ABPA will result in fewer stage V patients. Noncompliant patients who refuse to take prednisone for infiltrates might develop a greater number of bronchiectatic areas that can eventually lead to stage V ABPA with a poor prognosis. Similarly, delays in diagnosis of ABPA are known to have resulted in patients' presenting in stage V.<sup>39</sup>



**FIG 1.** A 42-year-old woman who had asthma for 4 years also reported a productive cough during that time. She was diagnosed with ABPA-central bronchiectasis. Her total serum IgE was 652 kU/L in the absence of prednisone. She had mild wheezing on examination. The high-resolution CT examination shows several areas of bronchiectasis and thickened bronchial walls. *Arrows* identify bronchiectasis.

## RADIOLOGY

CT with thin (1-2 mm) rather than conventional (10 mm) sections are extremely valuable in the diagnosis of ABPA. Proximal (central) bronchiectasis is defined as being present when there are bronchi that are dilated in comparison with the caliber of an adjacent bronchial artery in the inner two thirds of the lung CT field.<sup>40</sup> Bronchiectasis is described as *cylindrical* when the bronchus does not taper and is 1.5 to >3 times the caliber of diameter of an adjacent artery (Fig 1). Bronchiectasis can also be varicoid or cystic.<sup>40-43</sup> Ring shadows on chest roentgenograms are 1 to 2 cm in diameter; they represent dilated bronchi seen in an *en face* orientation. When the same dilated bronchus is visualized in a tangential (coronal) plane, it is called a *parallel-line shadow*. These findings are consistent with bronchiectasis. Some of the other findings include mucus plugs or mucoid impactions (Fig 2), bronchial wall thickening as occurs in asthma, atelectasis, lobar or whole lung collapse, pulmonary fibrosis, and cavities with or without air-fluid levels.

Patients with ABPA can have cylindrical, varicose, and cystic bronchiectasis that involves multiple bronchi.<sup>40-43</sup> When patients with asthma were examined, bronchial wall thickening was noted, and as many as 29% of patients had localized areas of cylindrical bronchiectasis.<sup>41</sup> Typically, just 1 or 2 lobes are affected in patients with asthma.<sup>40,41,43</sup> Thus, as seen on high-resolution CT, proximal bronchiectasis can be present in patients with asthma in the absence of ABPA; however, the CT results in patients with ABPA should have more areas of involvement.

## LABORATORY AND INVESTIGATIONAL FINDINGS IN ABPA

Antigens from *A fumigatus* range from 10 to 100 kD in weight, and there are approximately 40 components that bind with IgE antibodies.<sup>34,44,45</sup> There are 22 recombinant *Aspergillus* allergens that have been accepted by the Allergen Nomenclature Sub-Committee of the International Union of Immunological Societies.<sup>46</sup> Designated *Asp f 1* through *Asp f 22*, they have molecular weights ranging from 11 to 90 kD. The nomenclature designations include recombinant allergens from *Aspergillus niger* and *Aspergillus oryzae*, each having 2 identified recombinant allergens of its own that cross-react with *A fumigatus*. None of the 22 allergens is available commercially. A number of investigators have demonstrated that 10 to 20 amino acid peptides from the recombinant allergens are able to stimulate T and B cells.<sup>34,44-47</sup> Indeed, there are IgE-stimulating and IgE-suppressing polypeptides derived from *A fumigatus*.<sup>48</sup> T-cell clones generated from patients with ABPA produce IL-4 and are CD4<sup>+</sup> T<sub>H</sub>2 lymphocytes, which have been shown to be restricted to 6 MHC class II HL-DR subtypes.<sup>49,50</sup> In studies of peripheral blood, some patients with ABPA have at times of ABPA exacerbations (stage III) had high numbers of CD3<sup>+</sup> HLA DP, DQ, and DR<sup>+</sup> T cells or CD19CD23<sup>+</sup> B cells.<sup>51</sup> Lymphocyte activation has been reported indirectly by demonstration of peripheral blood concentrations of sIL-2R that are elevated in ABPA sera compared with sera from patients with asthma without ABPA and sera from nonatopic patients.<sup>52</sup> CD20<sup>+</sup> B cells from



**FIG 2.** Tissue from the patient shown in Fig 1. The high-resolution CT views on expiration demonstrate multiple areas of mucus plugging (arrows) and small areas of ground-glass appearance in the right lower lobe posteriorly. Air trapping is present as air spaces are seen in different areas.

patients with ABPA have been found to have greater numbers of CD23 molecules (signifying activation).<sup>52</sup> Subsequent incubation with IL-4 led to greater numbers of CD23 and CD86 molecules on these B cells, which is consistent with “hypersensitivity” in this *in vitro* system.<sup>53</sup> In addition to participating in IgE synthesis by B cells and inducing the expression of CD23 (FcεRII), IL-4 has many other actions, such as increasing the expression of CCR-3 and VLA-4 on T cells and eosinophils and VCAM molecules on endothelial cells, all of which could contribute to allergic inflammation in ABPA.<sup>53</sup>

Serum isotypic antibodies to *A fumigatus* are increased greatly in sera from patients ABPA compared with sera from patients with asthma without ABPA who also have 3 or 4+ immediate skin reactivity to *Aspergillus*.<sup>54,55</sup> Surprisingly, nearly all of the total serum IgE, which is so useful in diagnosis and in follow-up of patients with ABPA, is not directed at *A fumigatus*.<sup>56</sup> This has led to the notion of nonspecific total IgE production.<sup>56</sup> When bronchoalveolar lavage (BAL) fluid was analyzed, the BAL IgE-*A fumigatus* antibodies corrected for albumin were 48 times the peripheral blood amount.<sup>57</sup> The BAL IgA-*A fumigatus* antibodies were 96 times peripheral blood IgA-*A fumigatus*, which is also consistent with local bronchoalveolar compartment synthesis of these antibodies. BAL IgG-*A fumigatus* antibodies were not increased in comparison with sera. Unexpectedly, the ratio of BAL total IgE to serum total IgE was 0.9, which suggests that the bronchoalveolar compartment and perhaps the interstitium are not the sources of total IgE in peripheral blood.

These studies are consistent with divergent controls on production of total and allergen-specific IgE antibodies.

Laboratory assays depend on a number of factors, one of the most important being the source material used for sensitization of the solid phases. Antibody assays (and skin test results) will be falsely negative when poorly reactive extracts are used. Furthermore, some laboratories do not use a specific positive control serum for each assay when panels are performed. In this scenario, it is possible that the positive control serum in an assay for IgE-*A fumigatus* is a ragweed-positive serum. This positive serum might or might not have detectable IgE-*A fumigatus* antibodies. Thus, interpretation of a negative result in such an assay could be misleading, inasmuch as the assay could be insensitive and the technician unaware of this fact. Advances in the characterization and molecular detection of *A fumigatus* allergens has led to the hope that certain reactive recombinant allergens might serve as superior source material. In one study, the serodiagnosis of ABPA was improved through use of a battery of Asp f 2, Asp f 4, and Asp f 6, whereas Asp f 1 and Asp 3 were not discriminatory.<sup>58</sup> At the Northwestern University Allergy-Immunology Laboratory, we use a reactive mix of 3 strains of *A fumigatus*. Depending on the conditions under which these fungi are grown, the reactivity might or might not be acceptable for precise use in laboratory assays. It is hoped that in the near future a sensitive and specific test will be developed that will involve the use of selected recombinant allergens and that will be available for widespread application.

**TABLE IV.** Suggestions for initial treatment of ABPA

1. For new ABPA infiltrates, administer prednisone 0.5 mg/kg/day for 1-2 weeks, then on alternate days for 6-8 weeks. Then attempt to discontinue prednisone by tapering by 5-10 mg every 2 weeks.
2. Repeat the total serum IgE concentration in 6-8 weeks, then every 8 weeks for 1 year to determine the range of IgE concentrations. Increases of  $\geq 100\%$  over baseline can signify a silent ABPA exacerbation.
3. Repeat the chest roentgenogram or CT of the lung after 4-8 weeks to demonstrate that infiltrates have cleared.
4. Consider environmental sources of fungi (eg, moldy basements, leaking roofs, water damage in walls) and recommend remediation.
5. Monitor pulmonary function tests.
6. If the patient cannot be tapered off prednisone despite optimal anti-asthma treatment and avoidance measures, then he or she has evolved into stage IV (corticosteroid-dependent asthma). Try to manage with alternate-day prednisone as opposed to daily prednisone.
7. New ABPA infiltrates may be identified by:
  - a. Cough, wheeze, or dyspnea with sputum production
  - b. Unexplained declines in expiratory flow rates
  - c. Sharp ( $>100\%$ ) increases in total serum IgE concentration
  - d. Absent symptoms but new infiltrates on chest roentgenograms or chest CT examinations.
8. Diagnose and manage concomitant conditions such as allergic rhinitis, sinusitis, and gastroesophageal reflux disease.

Rarely, patients present with ABPA and are found to have concomitant cystic fibrosis. Conversely, varying percentages of patients with cystic fibrosis will be diagnosed with ABPA.<sup>6-21</sup> In studies in which patients with ABPA with sweat chloride concentrations of less than 60 meq/L were tested for transmembrane conductance regulator mutations, they were found to have an increased number of abnormalities in comparison with controls.<sup>59,60</sup> Some of the mutations included being heterozygous for F508 and being heterozygous for R117H. Perhaps future investigations will reveal similarities in some genotypes between cystic fibrosis, ABPA, Kartagener's syndrome, and chronic sinusitis. As of now, there are definite different genotypes, so this notion might be too simplistic.

Sputum cultures might reveal *A fumigatus* when plugs are expectorated. Often, the patient will stop producing plugs after the initial 2-month course of prednisone administration. CT examinations of the lung will show clearing of mucus plugs as well. Other patients expectorate plugs despite continued prednisone administration, and it is not always apparent that itraconazole has helped eliminate the plugs. Conversely, while demonstration of *A fumigatus* is not required for the diagnosis of ABPA, some microbiology technicians do not report out *A fumigatus* because they do not think that the ordering physician is interested in a fungus that is so frequently recovered in the microbiology laboratory.

### PATHOGENESIS OF ABPA

Discussions on pathogenesis are available in greater detail in several additional references.<sup>34,36,44-50,53,61-63</sup>

After inhalation of spores of *A fumigatus*, there is saprophytic growth in the hyphal form. It remains unclear what survival factors there might be in *A fumigatus*, or what abnormalities there might be in bronchial mucus, that permit its growth in contrast to the clearing seen in all other patients with asthma who do not develop ABPA.

Many of the recombinant allergens have enzymatic activity, such as (1) a ribonuclease (Asp f 1) that has been found to be cytotoxic by inhibiting protein synthesis, (2) a fibrinogen-binding protein (Asp f 2) favoring epithelial cell injury and inflammation, (3) a metalloprotease (Asp f 5), (4) a manganese superoxide dismutase (Asp f 6), (5) a ribosomal protein (Asp f 8), and (6) serine proteases (Asp f 13 and Asp f 18).<sup>44,46</sup> Many of these allergens bind to IgE or IgG antibodies and stimulate T and B cells. The mechanistic roles in damaging bronchial walls, causing bronchiectasis, causing bronchiolitis obliterans (which occurs distally in ABPA), and supporting growth of *A fumigatus* are not understood sufficiently. It is known that when patients have had negative CT examinations of the lung but have sufficient criteria for the diagnosis of ABPA-seropositive,<sup>64</sup> future infiltrates that have not been treated can cause bronchiectasis. The growth of *A fumigatus* in bronchial mucus permits antigenic glycoproteins and enzymes (perhaps collagenase<sup>65</sup>) to interact with bronchial lumen and tissue mast cells, epithelial cells, lymphocytes, macrophages, and eosinophils. For unknown reasons, the mucus becomes extremely viscid, in that even 30 minutes of attempted removal by experienced pulmonologists will be unsuccessful. In contrast, in cystic fibrosis without ABPA, the mucus is not as tenacious.

The array of antibody production, cytokine generation, cellular proliferation (*A fumigatus* can function as a growth factor for eosinophils in vitro), and effector molecules creates an intense immunologically mediated set of reactions. To date, primarily CD4<sup>+</sup> T<sub>H</sub>2 clones have been identified.<sup>49,50</sup> These cells could secrete IL-4, IL-5, IL-9, IL-10, and IL-13 and favor IgE and IgG<sub>1</sub> synthesis, eosinophil growth and survival, and mast cell proliferation.<sup>66</sup>

Many issues remain unclear, including how on histologic examination of patients with ABPA there can be, either individually or in combination, eosinophilic pneumonia, bronchocentric granulomatosis, granulomatous bronchiolitis, exudative bronchiolitis, *A fumigatus* hyphae in microabscesses, lipid pneumonia, lymphocytic or desquamative interstitial pneumonia, pulmonary vasculitis, and bronchiolitis obliterans.<sup>67</sup>

### TREATMENT

In the 1960s, attempts were made to treat ABPA with antifungal agents, often by inhalation, and cromolyn.<sup>68</sup> When prednisone was compared with cromolyn, it became apparent that the oral corticosteroid provided much better results.<sup>68</sup> This was at a time when serial monitoring with total serum IgE concentrations was not done (IgE was not isolated and characterized until 1968). The current recommended approach is presented in Table IV.

Prednisone is not indicated for indefinite use, and some outcome markers include overall respiratory status, pulmonary function results, level of wheezing or cough on examination, total serum IgE concentration (it might not reach normal concentrations), and chest roentgenogram and/or chest CT findings. After 2 months of prednisone administration and whatever is required for allergic rhinitis, sinusitis, and gastroesophageal reflux disease (if these are present), the prednisone can be tapered and discontinued. If the patient does not have any additional ABPA exacerbations (new pulmonary infiltrates and 100% rise in total serum IgE concentration) over the next 6 months, the patient has entered stage II (remission). However, if it becomes clear that the patient must receive prednisone for persistent asthma, then the patient is in stage IV (corticosteroid-dependent asthma). When the dose of prednisone is <30 mg on alternate days, ABPA exacerbations can occur in some patients. Thus, if a patient has been diagnosed with ABPA and has had several previous "pneumonias," it is likely that he or she is currently in stage III and will enter remission, will have additional exacerbations in 6 months (stage III), or will enter stage IV. Patients in stage V might require higher doses of alternate-day prednisone or lower daily doses, but they do not have a good prognosis.<sup>39</sup>

The antifungal agent itraconazole is considered adjunctive but not primary therapy.<sup>69</sup> It might have an indication as a steroid-sparing agent.<sup>70-72</sup> In a randomized, double-blind study of twice-daily itraconazole 200 mg or placebo for 16 weeks, there was improvement in responses.<sup>73</sup> However, a response consisted of a decline of at least 50% in the corticosteroid dose, a decrease of at least 25% in the total serum IgE concentration, and at least one of the following: (1) a 25% improvement in exercise tolerance; (2) a 25% improvement in pulmonary function test results; (3) resolution of chest roentgenographic infiltrates.<sup>73</sup> Thirteen (46.4%) of the 28 itraconazole-treated patients responded; this compared with 5/27 (18.5%) of those in the placebo group. There was an additional treatment period with itraconazole for those patients who had not responded to itraconazole. The dose was 200 mg daily for another 16 weeks; the authors reported that 12 of 33 patients then responded.<sup>73</sup> The issue of whether itraconazole would be beneficial in patients with new ABPA infiltrates was not answered. As regards patients who had either resolution or continued absence of ABPA infiltrates, there were 18 of 22 in the itraconazole group and 18 of 23 in the placebo group.<sup>73</sup> Furthermore, the overall response rate was 43% in patients without bronchiectasis and 20% in patients with bronchiectasis, regardless of whether itraconazole was administered. Itraconazole might play a role in helping to clear *A fumigatus* plugs or provide adjunctive benefit. Because of its cost and drug interactions or toxicities, however, its use should be considered only after prednisone has not been sufficient. Resistance to itraconazole is not uncommon,<sup>73</sup> and it might become even more widespread with use of various antifungals for ABPA or AAS (in which it is not even adjunctive).

With early diagnosis and treatment, ABPA can enter a remission stage, a recurrent exacerbation stage, or perhaps a corticosteroid-dependent asthma stage. Patients who have end-stage fibrocavitary lung disease often present in that stage without having been identified and treated previously. The other modalities for management of asthma should be instituted, and patients should be encouraged not to be overly pessimistic. The goal is to avoid progressive loss of lung function and maintain good respiratory status, which is achievable for many patients.

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