Allergic bronchopulmonary aspergillosis (ABPA) is a complex clinical entity that results from an allergic immune response to Aspergillus fumigatus, most often occurring in a patient with asthma or cystic fibrosis. Sensitization to aspergillus in the allergic host leads to activation of T helper 2 lymphocytes, which play a key role in recruiting eosinophils and other inflammatory mediators. ABPA is defined by a constellation of clinical, laboratory, and radiographic criteria that include active asthma, serum eosinophilia, an elevated total IgE level, fleeting pulmonary parenchymal opacities, bronchiectasis, and evidence for sensitization to Aspergillus fumigatus by skin testing. Specific diagnostic criteria exist and have evolved over the past several decades. Staging can be helpful to distinguish active disease from remission or end-stage bronchiectasis with progressive destruction of lung parenchyma and loss of lung function. Early recognition allows treatment with corticosteroids, which are effective but may be required indefinitely. There is some evidence to support the use of newer antifungal azoles as corticosteroid-sparing agents. Patients must be followed closely for recurrence. ABPA should be considered in all patients with asthma or cystic fibrosis, but especially in those with difficult-to-control disease.

**Keywords:** allergic bronchopulmonary aspergillosis; ABPA; asthma; cystic fibrosis; aspergillus

Allergic bronchopulmonary aspergillosis (ABPA) is an indolent and potentially progressive disease resulting from a hypersensitivity response to persistent Aspergillus fumigatus in the airways. Advances have been made in our understanding of the role of the allergic response in the pathophysiology of this disease (1, 2). ABPA occurs most commonly in patients with asthma or cystic fibrosis (CF), especially those with coexisting atopy (3, 4). Patients present with symptoms that may be attributed to their underlying disease; therefore, considering ABPA in these patient populations is important. Therapy is directed at mitigating the allergic inflammatory response (5). Early diagnosis and treatment has been thought to prevent disease progression, parenchymal damage, and loss of lung function. In this review we highlight salient clinical features and the current understanding of the pathophysiology of ABPA and review treatment options.

**BACKGROUND AND EPIDEMIOLOGY**

Aspergillus is a fungus that is found throughout the world. Its spores are hardy and ubiquitous, thriving in moist, organic materials. Aspergillus can be cultured from outdoor and indoor environments and grows optimally at core body temperature (1). Spores are tiny and easily aerosolized and deposit in distal and terminal airways, where they germinate if the airway environment is favorable. Aspergillus is variably pathogenic in humans. Host characteristics are a major determinant of the type of pulmonary disease that may develop in response to aspergillus exposure (6) (Table 1). ABPA, one of the many forms of aspergillus disease, results from a hyperreactive immune response to A. fumigatus without tissue invasion.

ABPA occurs almost exclusively in patients with asthma or CF who have concomitant atopy. The precise incidence of ABPA in patients with asthma and CF is not known but it is not high. Approximately 2% of patients with asthma and 1 to 15% of patients with CF develop ABPA (2, 4). Although the incidence of ABPA has been shown to increase in some areas of the world during months when total mold counts are high, ABPA occurs year round, and the incidence has not been definitively shown to correlate with total ambient aspergillus spore counts (1, 7). There is no gender predilection noted.

**PATHOPHYSIOLOGY**

The pathophysiology of ABPA is complex. In an allergic host, the persistence of A. fumigatus in the lung leads to T lymphocyte activation, cytokine, and immunoglobulin (Ig) release and inflammatory cell recruitment. Local inflammation results in mucus production, airway hyperreactivity, and ultimately bronchiectasis.

A viscous mucus layer in the airway, combined with dysfunctional clearance in the case of CF, may disrupt the natural process of effective spore removal (2, 8). Aspergillus proteolytic products may also interfere with airway clearance by damage to and disruption of the epithelial cell barrier (4, 9). Once resident, aspergillus germinates and proliferates, and antigen burdens can become high. Dendritic cells are local antigen-presenting cells that process spore and mycelia antigens. This processing leads to the release of specific cytokines by antigen-presenting cells and to antigen presentation to T lymphocytes (10). In the normal host, the response to antigen presentation is activation of nonallergic T helper (Th1) and allergic (Th2) lymphocytes (10, 11). The Th1 response is marked by macrophage and neutrophil cytotoxic action as well as IgG and IgA antibody production, which may protect against aspergillus infection (12). A frank defect in the Th1 cytotoxic pathway is not present in ABPA, although it is present in immunocompromised patients who are at risk for invasive disease. Activation of the Th2 pathway results in specific cytokine and immunoglobulin elaboration that mediate allergic inflammation. Th2 signaling predominates in the aspergillus allergic host; the imbalance of the Th2 over the Th1 response is thought to drive ABPA (1, 4).

Although the Th2 response predominates in patients with allergy to aspergillus and in patients with ABPA, the magnitude of the Th2 immune activation is greatest in ABPA (12). Activated Th2 cells release specific cytokines that orchestrate downstream cell signaling and the inflammatory response (11). IL-4 may be especially important. It is linked to B-cell isotype conversion to IgE production, the expression of vascular cell adhesion molecules on endothelial cells and vascular cell adhesion molecule ligands on eosinophils, and to IgE and IgA Fc receptor expression on eosinophils (7, 12). When bound to aspergillus antigen, locally produced IgE may activate mast cells. Mast cell chemokines, in concert with IL-5, recruit eosinophils. Eosinophils are the most conspicuous immune cells.
TABLE 1. PULMONARY MANIFESTATIONS OF ASPERGILLUS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergilloma</td>
<td>Cavity from sarcoid, previous TB, bullae, or bronchiectasis</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Asthma, cystic fibrosis</td>
</tr>
<tr>
<td>Chronic necrotizing aspergillosis</td>
<td>COPD, previous TB, corticosteroids, DM</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>Immunocompromised, especially neutropenia</td>
</tr>
<tr>
<td>Hypersensitivity pneumonia</td>
<td>Intense or repeated exposure to aspergillus</td>
</tr>
</tbody>
</table>

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; TB = tuberculosis.

in airway mucosa in patients with ABPA and are thought to be a major effector of inflammation (12, 13). Degranulation of activated mast cells and eosinophils results in the release of mediators of vasodilation and bronchoconstriction (12).

Activated T and B lymphocytes infiltrate lymphatics and release cytokines systemically. Circulating IL-4 is thought to drive total IgE production, and total serum IgE levels are increased out of proportion to aspergillus-specific IgE levels (7). IgE and IgG antibodies specific for aspergillus circulate systematically as well (14).

HOST CHARACTERISTICS

Susceptibility to ABPA is likely mediated by genetically determined inflammatory responses in atopic patients. Although atopy is an inheritable trait, familial occurrence of ABPA, though reported, is rare (15). ABPA occurs most commonly in patients with asthma and CF; two conditions strongly associated with atopy. Patients with ABPA also are noted to have higher rates of other atopic conditions, including allergic rhinitis and conjunctivitis, atopic dermatitis, and food hypersensitivity (16). Allergic fungal sinusitis results from an allergic response to aspergillus. Initially thought not to be related, allergic fungal sinusitis and ABPA share a history of atopy and asthma, and several reports document an association of these diseases (17, 18). The pathophysiology of allergic fungal sinusitis may involve abnormal sinus anatomy, which could explain why only a small fraction of patients with ABPA have concomitant allergic fungal sinusitis. In addition to atopic conditions, ABPA has been associated with chronic obstructive pulmonary disease, previous tuberculosis infection, and treatment of sarcoid with infliximab (19–21). ABPA has also been reported in hyper-IgE syndrome, bronchocentric granulomatosis, and chronic granulomatosis disease (6, 17).

ABPA in Asthma

The relationship between asthma and ABPA is incompletely understood. It is unclear whether having asthma directly increases the risk for ABPA or whether asthma and ABPA share a common predisposition. As many as 25% of subjects with asthma are sensitized to aspergillus, yet only a small fraction develop ABPA (22). In the aspergillus-specific IgE-mediated immune response, abnormalities of the airway and changes in mucus production and properties may contribute to the development of ABPA in patients with asthma. CFTR gene mutations are higher in patients with asthma and ABPA who do not have CF (23). The onset of ABPA typically occurs many years after the diagnosis of asthma is made but has been reported in new-onset asthma. Unlike other atopic conditions that are more common in childhood, the incidence of ABPA is highest in adults (5, 24).

ABPA in CF

Patients with CF are at risk for developing ABPA (4). The prevalence of ABPA is increased in patients with CF who are male, are adolescent, have lower lung function, have a history of wheezing or asthma, or have pseudomonas in the sputum. Atopy is present in up to 60% of patients with CF (4). The impaired airway clearance characteristic of CF may contribute directly to ABPA, although other factors likely play a role as well (25, 26).

CLINICAL FEATURES

Symptoms

With the development of ABPA, asthma or CF typically worsens and may manifest with a new or worsening cough or an increase in sputum production or wheezing. Thick mucus production is common; mucus can be remarkably tenacious and resistant to suctioning (27). Patients may cough up well-formed, tan to brownish-black mucus plugs. Plugs are composed of degenerating eosinophils, desquamated epithelial cells, and mucin (28). Hemothysis may occur secondary to airway inflammation and bronchiectasis; however, massive hemothysis from ABPA alone is not well described in the literature (5, 29). Systemic symptoms of low-grade fever, malaise, and weight loss are variably part of the clinical spectrum of ABPA (16). These symptoms should trigger an evaluation for ABPA in a patient with asthma or CF.

Laboratory Evaluation

Total serum IgE levels of at least 1,000 IU/ml are a hallmark of ABPA (2). A. fumigatus–specific IgE levels are also elevated (30). Laboratory studies may show elevated serum levels of aspergillus-specific IgG antibodies, precipitins, and eosinophils (2, 14). Corticosteroids may blunt an allergic response; therefore, patients on systemic corticosteroids may not have eosinophilia or a significantly elevated total serum IgE level but may still have ABPA.

Radiographic Imaging

Chest radiographs that demonstrate fleeting parenchymal opacities or bronchiectasis should trigger a consideration of ABPA. Infiltrates are usually eosinophilic in nature and responsive to corticosteroids and may be misdiagnosed as infectious pneumonia (31). Opacities may also reflect bronchoceles, mucus plugging, atelectasis, or lobar collapse. The full extent of radiographic findings is best appreciated on chest CT imaging (Figures 1–3). Bronchiectasis, bronchial wall edema, mucus plugging, atelectasis, lobar collapse, nodules, and fibrosis also can be seen (32). Pleural changes may occur but are not common. The presence of central bronchiectasis in multiple lobes is highly suggestive of, and varicose or cystic changes are most specific to ABPA (33). Bronchiectasis is sometimes seen in the peripheral lung fields (34). Although central bronchiectasis may occur occasionally in patients with asthma who do not have ABPA, it is less severe and most often limited to one or two lobes (35). Mucus plugging can manifest a “finger in glove” appearance from impacted mucus opacifying an airway and its branches or as small nodules from impacted bronchioles cut on end (2, 31, 36). Airway mucus can have normal or high attenuation. In high-attenuation mucus, the concentration of ions such as calcium, iron, and manganese contributes to a Hounsfield density that can exceed that of surrounding skeletal muscle (33). Chemical deposition is a gradual process, and high-attenuation mucus suggests chronicity. In one report, this was found in 19%
of cases of ABPA (37). Although not as common as central bronchiectasis, high-attenuation mucus is characteristic of ABPA.

Fibrosis and cavitation of dilated airways are end-stage findings in ABPA. Peribronchiolar fibrosis is thought to be a result of persistent inflammation and progressive bronchocentric granulomas (29, 38). Fibrosis predisposes to cor pulmonale, and enlarged pulmonary arteries and right ventricular hypertrophy may be evident on chest CT scanning (39).

**Pulmonary Function Testing**

Airflow obstruction that is at least partially reversible is a common finding on pulmonary function tests, especially in mild or early ABPA. Fixed airflow obstruction and reduced lung volumes due to interstitial changes reflect progressive disease. The diffusing capacity may be decreased during an exacerbation and remains low in end-stage ABPA (2, 40). Pulmonary function test findings are not specific to ABPA because most patients typically have underlying lung disease. A more important role for pulmonary function tests is in tracking disease over time.

**Bronchoscopy and Histology**

Bronchoscopic evaluation, fungal culture, and histology are not required to make a diagnosis of ABPA. Bronchoscopy may be performed in patients with ABPA when the diagnosis is unclear. On bronchoalveolar lavage, eosinophil counts and levels of IgA, IgG, IgM, and IgE are elevated (41). Aspergillus is not reliably cultured, even in active disease, and the sensitivity of staining bronchoalveolar lavage washes or sputum samples for aspergillus is poor (17). Conversely, the recovery of aspergillus in culture may reflect colonization alone and is not specific for active disease. Given the lack of sensitivity or specificity of aspergillus culture, we agree with recent diagnostic algorithms that do not require culture for diagnosis. Finding aspergillus on lung pathology, however, is diagnostically helpful. Lung biopsy is not necessary for diagnosis but, when performed in ABPA, may also show infiltration of airways by eosinophils and lymphocytes, goblet cell hyperplasia, bronchocentric granulomas with distal exudative bronchiolitis, mucoid impaction, and fibrotic changes in end-stage disease (1, 42).

**DIAGNOSIS**

There is not a single test to diagnose ABPA; nor is there a universally recognized set of criteria. However, the diagnostic
When ABPA is suspected, a serum total IgE level and skin testing for hypersensitivity to *A. fumigatus* should be performed. A positive skin test in the form of an immediate IgE-mediated response is highly sensitive for aspergillus sensitization but not specific for ABPA (2). IgG-mediated late skin test responses are variably positive and not usually assessed (16). A wheal diameter of at least 3 mm is required; smaller wheal formation may occur in patients sensitized to aspergillus or in patients with non-ABPA aspergillus diseases (16). Intradermally placed skin tests are more sensitive than the epicutaneous prick test.

If skin testing is positive and total IgE is elevated, *A. fumigatus*–specific antibody levels help to distinguish ABPA from other conditions, such as asthma with aspergillus sensitivity (1, 2). Historically, precipitin antibodies were useful to make this distinction in cases of positive skin tests. Precipitins are not as commonly used for the initial diagnostic evaluation as the ability to detect aspergillus IgE, and IgG antibody levels are more easily obtained and are quantitative (27, 29). Although specific antibody levels are quantifiable, there is a lack of standardization of laboratory testing to permit precise laboratory to laboratory comparison of values (44).

Elevated eosinophil levels were a primary diagnostic feature, but recent criteria do not incorporate serum eosinophilia (Table 2). Serum eosinophilia is not sensitive or specific but if present supports a diagnosis of ABPA (45, 46).

Central bronchiectasis is a hallmark finding, although ABPA without bronchiectasis is also recognized (47). ABPA-S refers to ABPA diagnosed serologically, whereas ABPA-CB refers to patients with central bronchiectasis. This distinction does not correlate well with severity of asthma or degree of serologic abnormalities (34). Distinguishing between ABPA-S and ABPA-CB may have prognostic implications: The frequency of exacerbations and the likelihood of permanent lung damage are believed to be lower in patients with ABPA-S (48, 49). ABPA-S may be a more benign phenotype of ABPA, but most experts consider it a precursor of ABPA-CB.

The diagnosis of ABPA in patients with CF may be particularly challenging (4). Bronchiectasis, thick mucus, and mucus plugging are often present at baseline in CF. Development of ABPA is suggested by worsening baseline cough, dyspnea, or wheeze; increased or colored sputum; the onset of new fevers or weight loss; or a decline in pulmonary function tests. This should prompt skin testing and measurement of total serum IgE levels. Serial CT scanning may be helpful to distinguish infiltrates due to ABPA over an active infectious process (32) (Table 3). The diagnostic criteria in CF are reviewed extensively in the CF Foundation Consensus Conference statement (4). Annual screening with serum total IgE levels is advised. The degree to which development of ABPA results in accelerated decline in lung function in patients with CF requires further study (4, 50).

### Differential Diagnosis

The differential diagnosis for ABPA includes refractory asthma, newly diagnosed CF, tuberculosis, sarcoidosis, infectious pneumonia, eosinophilic pneumonia, aspergillus sensitive asthma, Churg-Strauss syndrome, and bronchocentric granulomatosis (2, 24). In addition, fungi other than aspergillus have caused allergic bronchopulmonary mycosis, a clinical condition identical to ABPA but with antibody and skin test reflecting allergy to the implicated mold (51).

### Natural History

The clinical course of ABPA is variable. There are five recognized stages of ABPA, and they are useful to appreciate the status and trajectory of a given patient (5, 48). Stage I defines new, active ABPA. Stage II is marked by clinical and serologic findings such as increased or colored sputum, a decline in pulmonary function tests, and a decline in weight (4). Bronchiectasis, thick mucus, and mucus plugging are often present at baseline in CF. Development of ABPA results in accelerated decline in lung function in patients with CF requires further study (4, 50).

### Table 2. Evolution of Diagnostic Approach

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Clinical features described</td>
<td>Asthma</td>
<td>ABPA-CB</td>
<td>ABPA-CB</td>
</tr>
<tr>
<td></td>
<td>Total IgE elevated</td>
<td>ABPA with central bronchiectasis</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Immediate skin test positive</td>
<td>ABPA-S</td>
<td>Immediate skin test positive</td>
</tr>
<tr>
<td></td>
<td>Serum eosinophilia</td>
<td>Clinical and serologic features without</td>
<td>Total IgE elevated</td>
</tr>
<tr>
<td></td>
<td>Precipitins</td>
<td>central bronchiectasis</td>
<td>Specific IgG &amp; IgE elevated</td>
</tr>
<tr>
<td></td>
<td>Parenchymal infiltrates</td>
<td></td>
<td>Central bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>Central bronchiectasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: ABPA-CB = allergic bronchopulmonary aspergillosis–central bronchiectasis; ABPA-S = Allergic bronchopulmonary aspergillosis–serological.
serological remission. Stage III is recurrent active ABPA. Patients with chronic, steroid-dependent asthma secondary to ABPA are stage IV. Fibro-cavitary disease secondary to progressive inflammation and airway dilation defines stage V, which may lead to progressive respiratory failure and death. ABPA does not necessarily evolve through these stages in a sequential manner. At presentation, it is not always clear who will enter remission, who will have recurrent disease, or who will progress. Early diagnosis and treatment is thought to be associated with a lower risk of advanced disease in the future (5, 7, 27, 47).

Changes in serum total IgE level or pulmonary function tests are useful for objectively assessing remission or recurrence of ABPA (5, 52). Establishing a patient’s total IgE level during remission is important to be able to interpret serial values because levels even in remission are typically above normal (1). A common approach is to use a sustained decrease of 25 to 35% to identify remission and an increase of 100% to identify recurrent disease (2, 27, 52, 53). Changes in total IgE levels may precede the onset of symptoms or new radiographic infiltrates, and regular monitoring in high-risk patients can be useful to screen for the recurrence or development of ABPA.

**TREATMENT**

The goal of therapy is to induce remission by suppressing the inflammatory pathway so that further lung destruction does not occur while minimizing side effects. Remission is defined by improvement in clinical symptoms, decrease in total serum IgE level, resolution of radiographic opacities, and improvement in lung function. A number of medications have been tried in the treatment of ABPA. These include systemic and inhaled corticosteroids, antifungal agents, and omalizumab, a monoclonal antibody directed against IgE (2, 27). None of these medications have been shown to be of benefit in large, randomized, double-blind, placebo-controlled trials, but there is considerable support based on case series and expert opinion for the benefit of oral corticosteroids to induce remission and prevent progression of disease (Table 4). Corticosteroids decrease the inflammatory response to aspergillus in the lung but at considerable cost in terms of side effects if used chronically. Corticosteroids do not inhibit the growth of aspergillus. Antifungal agents decrease the antigen burden and subsequent immune response but cannot be recommended as monotherapy. The benefit of environmental evaluation and remediation of ongoing exposure to aspergillus has been debated. Failure to respond to therapy should prompt consideration of comorbidities such as allergic rhinitis or sinusitis or alternate diagnoses. Treatment of ABPA in patients with CF is similar, although higher doses of prednisone are recommended initially (4).

**Corticosteroids**

Systemic corticosteroids are the mainstay of therapy for ABPA. They are associated with decreased wheezing, serum total IgE levels, and eosinophilia, and with resolution of parenchymal opacities (54, 55). A number of dosing regimens have been recommended. Some experts think a more aggressive regimen with higher doses of systemic corticosteroids at disease onset results in the best long-term outcomes, but the evidence for this is limited (Table 4). This aggressive regimen involves prednisolone 0.75 mg/kg daily for 6 weeks, then 0.5 mg/kg daily for 6 weeks, then tapered by 5 mg daily every 6 weeks, for a total of 6 to 12 months (5, 34). A more conservative approach is to treat with prednisone 0.5 mg/kg daily for 1 to 2 weeks, then on alternate days for 6 to 8 weeks, then tapered by 5 to 10 mg daily over 3 to 4 weeks. These regimens may be modified based on individual patient response and tolerance.

**TABLE 4. SELECTED STUDIES OF THE TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reference</th>
<th>Study Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone 0.5 mg/kg QD × 1 wk then QOD</td>
<td>Rosenberg 1977 (43)</td>
<td>Case series of 20 patients</td>
<td>“Complete remission” in all cases</td>
</tr>
<tr>
<td>Prednisone 0.5 mg/kg QD × 2 wk then QOD × 3 mo</td>
<td>Patterson 1986 (47)</td>
<td>Case series of 84 patients</td>
<td>38 (45%) corticosteroid dependent</td>
</tr>
<tr>
<td>Prednisolone 0.75 mg/kg QD × 6 wk, 0.5 mg/kg QD × 6 wk then taper by 5 mg Q 6 wk</td>
<td>Agarwal 2006 (34)</td>
<td>Case series of 126 patients</td>
<td>126 “remission” at 6 wk, 25 (20%) “relapse,” 17 (13.5%) corticosteroid dependent</td>
</tr>
<tr>
<td>Prednisone 2 mg/kg QD × 1 wk then 1 mg/kg QD × 1 wk then QOD and intraconazole</td>
<td>Nepomuceno 1999 (68)</td>
<td>Case series of 16 patients with CF; 12 on dual therapy, 2 on prednisone alone</td>
<td>1: Decreased wheezing, serum eos, radiographic infiltrates, and IgE 2: Fewer acute episodes with intraconazole</td>
</tr>
<tr>
<td>Methylprednisolone IV 15–20 mg/kg QD × 3 d Q 4 wk</td>
<td>Thompson 2006 (56)</td>
<td>Case series of 4 patients with CF</td>
<td>Disease “control” 3 (75%)</td>
</tr>
<tr>
<td>Budesonide inhaled 400 μg daily vs. placebo</td>
<td>Chest 1977 (59)</td>
<td>Double-blind trial in 32 patients</td>
<td>No benefit asthma score or FEV1</td>
</tr>
<tr>
<td>Nebulized amphotericin B and budesonide</td>
<td>Laudi 2008 (58)</td>
<td>Case series of 3 patients with CF</td>
<td>Decreased serum eos, and total and specific IgE and improved FEV1</td>
</tr>
<tr>
<td>Itraconazole 200 mg BID vs. placebo × 16 wk; prednisone &gt; 10 mg daily</td>
<td>Stevens 2000 (66)</td>
<td>Randomized double-blind trial in 55 patients</td>
<td>Decreased prednisone dose and total IgE 13/28 (46%), Itraconazole vs. 5/27 (19%) placebo</td>
</tr>
<tr>
<td>Itraconazole 400 mg QD vs. placebo × 16 wk</td>
<td>Wark 2003 (67)</td>
<td>Randomized double-blind trial in 29 patients</td>
<td>Decreased IgE and fewer exacerbations requiring prednisone with Itraconazole</td>
</tr>
<tr>
<td>Itraconazole/prednisone vs. intracranial 200–600 mg QD</td>
<td>Skov 2002 (69)</td>
<td>Retrospective in patients with CF (9 both, 12 intraconazole alone)</td>
<td>Decreased precipitins, increased FEV1 in all; IgE decreased in 56% on both vs. in 42% on Itraconazole</td>
</tr>
<tr>
<td>Voriconazole × 1 yr</td>
<td>Erwin 2007 (71)</td>
<td>Case report, 1 patient</td>
<td>Improved symptoms, tapered prednisone off</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Kanu 2008 (75)</td>
<td>Case report, 1 patient</td>
<td>Improved symptoms and FEV1</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CF = cystic fibrosis; Eos = eosinophils; Q = every; QD = daily; QOD = every other day.*
every 2 weeks (27, 54). With either regimen, serum total IgE concentration is followed closely until clinical and radiographic remission is achieved. Serum total IgE is repeated every 8 to 12 weeks for 1 year, then annually (5). An increase of greater than 100% over baseline suggests recurrent disease and may precede the development of active clinical disease. The chest roentgenogram or CT scan should be repeated in 4 to 8 weeks to look for resolution of pulmonary opacities. Pulmonary function tests are monitored and should improve on therapy. Patients who cannot be tapered off systemic corticosteroids have evolved to Stage IV disease and should be managed with alternate-day corticosteroid therapy if possible and are candidates for antifungal therapy. In a small series, intravenous pulse methylprednisolone was given to children with CF and severe ABPA because of relapse or intolerance to high-dose oral corticosteroids, with disease control achieved in three of the four patients (56) (Table 4). Patients with CF may have incomplete absorption of enteric-coated prednisolone (4).

Inhaled corticosteroids have been studied in the treatment of ABPA (57, 58). A case series of three children with CF and ABPA showed improvement with nebulized budesonide and amphotericin B. However, a double-blind, placebo-controlled study in patients with non-CF ABPA failed to demonstrate the benefit of beclomethasone 400 μg daily (59).

The side-effects of systemic corticosteroids are numerous and include weight gain, psychosis, hypertension, hypokalemia, gastric ulcers, thinning and bruising of skin, osteoporosis, development or worsening of diabetes, aseptic joint necrosis, cataracts, glaucoma, and immune, adrenal, and growth suppression and in most cases preclude long-term use. Patients treated with corticosteroids should receive vaccination for pneumococcus and influenza as well as calcium plus vitamin D with monitoring for osteoporosis. Cases of invasive pulmonary aspergillosis and central nervous system disease have been reported in patients receiving systemic corticosteroids for the treatment of ABPA (60–62).

**ANTIFUNGAL AGENTS**

To decrease the burden of fungal organisms and prevent continued antigenic stimulation and subsequent inflammation, antifungal therapies such as nystatin, amphotericin B, natamycin, and ketoconazole have been tried (2, 27). Ketoconazole showed some benefit but was associated with significant side effects. Itraconazole has been used with greater success and tolerability (5, 63–69). A number of case reports and a few randomized studies attest to its beneficial effects (Table 4). Current recommendations are to consider it as a corticosteroid-sparing agent if or corticosteroids alone are ineffective (2, 62). Itraconazole is administered at a dose of 200 mg twice daily for 4 to 6 months, then tapered over 4 to 6 months. Serum levels drawn 4 hours after a dose after 1 to 2 weeks of therapy should be checked in patients with severe disease or not responding to therapy or in those on medications that might interact with itraconazole.

Voriconazole, a newer antifungal azole with greater bioavailability, has the potential to be more effective, with case reports attesting to its benefit (70–73). It is given at a dose of 200 mg twice daily. The authors have personal experience with its use in a patient with long-standing asthma who was treated with voriconazole for presumed invasive aspergillosis. By the time the patient was correctly diagnosed with ABPA, he had resolution of ABPA-related clinical and radiographic abnormalities, with serum total IgE falling from 7,822 IU/ml to 2,243 IU/ml on voriconazole treatment alone. Antifungal therapy should be considered as a corticosteroid-sparing agent or for patients who have not responded to corticosteroids alone.

Adverse effects of azole therapy include nausea, vomiting, diarrhea, fever, rash, headaches, fatigue, and decreased libido. Elevations in transaminase levels occur and are usually transient, but liver failure has been reported, and monitoring liver enzymes is advised. Drug interactions have been reported with numerous agents including midozolam, cyclosporine, tacrolimus, oral hypoglycemic agents, and methylprednisolone but not prednisone (4, 74). Agents that lower gastric acid may decrease the effectiveness of these agents. Response to therapy is assessed by the criteria outlined above.

**MONOCLONAL ANTIBODY AGAINST IgE**

Case reports of improvement with omalizumab suggest that anti-IgE therapy may be of benefit (75, 76). In addition to the risk of anaphylaxis, a recent FDA advisory suggests that cardiac and thromboembolic events may occur with increased frequency in patients using omalizumab (77). We do not recommend this therapy based on the limited evidence for benefit and potential toxicity.

**ALLERGEN AVOIDANCE**

Although aspergillus is ubiquitous, identification of environmental sources that are particularly high in or support the active growth of aspergillus is advised but may not be possible. Remediation should be considered, although definite evidence of benefit is lacking. Theoretically, this may reduce the ongoing antigen exposure. Marijuana use may be an unidentified risk factor, with case reports attesting to an association of marijuana smoking and aspergillus exposure (78).

**CONCLUSIONS**

ABPA is a complex hypersensitivity response to *A. fumigatus* in atopic patients with CF or asthma. It is characterized by worsening symptoms, serum eosinophilia, and fleeting pulmonary opacities on radiographs. An elevated serum total IgE, central bronchiectasis, and hypertrenuating mucus on chest CT scan heightens the suspicion for ABPA. The pathophysiology of ABPA is allergic in nature, characterized by activation of eosinophils and elaboration of IgE. Immune suppression therefore is the mainstay of treatment. Early identification allows treatment with corticosteroids with a potential role for newer antifungal azole medications as corticosteroid-sparing agents, which may improve the long-term outcome in this potentially relapsing condition.

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