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THE TREATMENT OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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1. ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is a disease characterized by asthma, peripheral eosinophilia, pulmonary infiltrates, hypersensitivity to *Aspergillus fumigatus* and bronchiectasis. The treatment of ABPA depends on the stage of the disease, and includes following clinical symptoms, serum IgE levels, pulmonary function tests, and chest radiographs. This review covers the current treatment options for ABPA.

2. INTRODUCTION

The treatment of allergic bronchopulmonary aspergillosis (ABPA) depends on the extent and stage of the disease. Subjective symptoms, including asthma and constitutional symptoms, and objective measurements including serologic evaluation of total IgE levels and eosinophilia, pulmonary function tests, and radiographic studies of the chest, are all important in both staging and monitoring the disease. Monthly measurement of IgE levels, at least for the first few months, may certainly be reasonable, since acute increases in IgE are frequently associated with new radiographic findings. Control of ABPA also includes treatment of other associated conditions such as rhinitis and sinusitis. Corticosteroids have been the mainstay of treatment for ABPA, but there have also been more recent studies to suggest that the use of the newer imidazole antifungal antibiotic, itraconazole, may also be effective in the treatment of ABPA patients.

Therapy of the underlying asthma should include the use of anti-inflammatory treatment, especially inhaled corticosteroids, and bronchodilator agents, as rescue, and environmental controls to reduce any focus of mold exposure, especially if it is identified as aspergillus species. Immunotherapy for aeroallergens such as pollen or dust may be useful to control the asthmatic response, and aggressive management of allergic rhinitis and sinusitis with anti-inflammatory treatment will help control the upper airway component of the respiratory disease. Immunotherapy with aspergillus has not been studied, but is not recommended at this time because of the uncertainty regarding the formation of circulating immune complexes.

3. PHARMACOTHERAPY

The recommended treatment for different stages of ABPA is listed in Table 1. Oral corticosteroid therapy is still considered the mainstay of ABPA pharmacotherapy. Oral corticosteroids were first reported to be effective in the treatment of ABPA in 1973 by Safirstein *et al*,[1] but no controlled clinical trials using oral corticosteroids have been done. The action of the corticosteroids is not directly on the aspergillus, but is likely anti-inflammatory—decreasing the conditions that favor aspergillus growth. For stages I(acute) and III(exacerbation), the dose of prednisone is usually 0.5 mg/kg/day for 2 weeks, and then tapered to alternate day steroids for up to 3 months (1,2). Repeat chest x-ray should indicate clearing of the infiltrates, and IgE levels should decrease by 1 month. If the infiltrates do not clear, or the symptoms do not improve, the dose of prednisone can be increased again for an additional 2 weeks, and then attempts to decrease to an alternate day regimen can be attempted at that time. If prednisone can be discontinued, the patient should be evaluated monthly or at least every 6-8 weeks to see if the patient is in stage II (remission), or whether stages III, IV, or V occur. IgE levels should also be followed at regular intervals, noting that the IgE levels do not decrease to normal, but stabilizes, even with high dose prednisone therapy. Acute increases in IgE levels (100% over baseline) can be a harbinger of new radiographic infiltrates, and of more active disease (3). Aggressive treatment with prednisone at the time of elevation in IgE levels can prevent or terminate the active stage. Stage IV patients need careful monitoring since despite chronic steroid therapy, these patients may develop acute exacerbations. Some do not have acute exacerbations, but will require chronic oral steroid therapy and inhaled steroid therapy as

Table 1. ABPA Stage with Treatment Recommendations

ABPA Stage	Treatment
Stage I (acute)	• Control of asthma, rhinitis, and sinusitis.* • Treat with prednisone 0.5 mg/kg/d for 2 weeks. • Consider itraconazole 200-400 mg/day with food as additive therapy, maintaining itraconazole levels above 5 microgram/ml. • Taper prednisone levels according to clinical symptoms, total serum IgE levels, spirometry, and chest radiographs.
Stage II (remission)	• Control of asthma, rhinitis, and sinusitis.* • Measure total serum IgE levels and spirometry at intervals (1-4 months), and chest radiographs on yearly basis.
Stage III (exacerbation)	• Follow recommendations for stage I. • Total serum IgE levels every 2 weeks until remission, then at intervals (1-4 months). • Chest radiograph, and repeat CT of chest at remission. • Spirometry, lung volumes and diffusion capacity.
Stage IV (steroid-dependent)	• Control of asthma, rhinitis, and sinusitis.* • Treat with lowest possible dose of prednisone. • Consider itraconzaole therapy. • Total serum IgE levels at intervals (1-4 months). • Chest radiograph, and CT of chest every 1-2 years. • Spirometry, lung volumes, diffusion capacity, and arterial blood gases with and without exercise.
Stage V (end-stage disease)	• Control of asthma, rhinitis, and sinusitis.* • Treat with lowest possible dose of prednisone, antibiotics if necessary, sputum thinners, and chest physical therapy. • Total serum IgE levels at intervals (4-6 months). • Chest radiographs at intervals (6-12 months), and CT of chest every 2 years. • Spirometry, lung volumes, diffusion capacity, and arterial blood gases with and without exercise.

*Recommended guidelines of National Heart, Lung, and Blood Institute for asthma therapy, and other therapy could include antihistamines, nasal steroids, decongestants, antibiotics or immunotherapy.

well. Stage V patients may require daily prednisone, and when considerable lung destruction occurs, may develop cor pulmonale, arterial hypoxemia, or chronic bronchiectasis with *Pseudomonas aeruginosa* pneumonia until death.

Prednisone therapy should also be administered to ABPA patients with recurrent exacerbation or for those already on prednisone for control of their persistent asthma. Inhaled corticosteroids as maintenance therapy, long acting bronchodilators, and/or leukotriene modifiers for control should all be utilized as well. Monitoring of pulmonary lung function is important in ABPA patients as well. The characteristic inflammatory infiltrates cause reductions in gas transfer, vital capacity, FEV1, and total lung capacity, and are normalized by prednisone therapy. An FEV1 of less than 800 ml is not a good prognostic sign (4). With recurrent infiltrative disease, fibrosis and bronchiectasis can occur, so it may be helpful to repeat tomographic evaluation of the respiratory tract every few years. There is evidence to suggest that if ABPA is stabilized, progression of the disease to the fibrotic stage can be prevented (1,5). In patients that have the fibrotic stage of ABPA, there may be increased sputum production, and organisms like *Pseudomonas*, atypical mycobacteria and *Staphylococcus* may be found, similar to patients with cystic fibrosis. In those patients, treatment with antibiotics and postural drainage may be helpful. With further decline, exercise tolerance is diminished, and oxygen therapy may be necessary. DNAse preparations may be useful to liquefy the sputum, and offer relief of symptoms. Lung transplantation may be necessary for end-stage ABPA, but successes have yet to be reported.

Because of the potential long-term side effects of corticosteroids, other treatments have been tried, including antifungals. It has been hypothesized that decreasing the fungal burden in the respiratory tract would decrease chronic antigenic stimulation, reduce the inflammatory response, diminish symptoms, and possibly slow the progression of the disease. The administration of aerosolized nystatin, natamycin, and amphotericin B have been reported with limited success (6,7,8). Shale *et al* (9) treated 7 ABPA patients with oral ketoconazole or placebo for 1 year. The results showed that the ketoconzole treatment group (n=4) had a 40% decrease in specific IgG antibody to *Asp fumigatus* after three months, and a specific reduction of total and specific IgE levels. There was also a decrease in the daily asthma symptom scores, and chest radiographs did not show any new infiltrates. Spirometric indices did not change however. A larger study was attempted, but had to be discontinued due to toxicity from the ketoconazole. That same year however, Fournier *et al* (10) did not show benefit from one year of ketoconazole treatment in an open label study in nine cases of ABPA. Other oral antifungals that have been tried included hamycin, miconazole, and clotrimazole—again with limited success (11,12,13).

Itraconazole has been tried as a steroid sparing agent as early as 1991. In studies or case reports by Denning *et al* (14), Germaud *et al* (15), and Pacheco (16), overall itraconazole had significant steroid sparing effects. Itraconazole has also been used in a few patients with ABPA and cystic fibrosis, with symptomatic improvement and decreases in corticosteroid use (17,18). Itraconazole levels should exceed 5 microgram/ml for adequate concentrations into the pulmonary fluids and tissues (14,19). Most recently, in 2000, Stevens *et al* (20) conducted a large, randomized, double-blind trial of itraconazole 200 mg administered orally twice daily for 16 weeks compared to placebo. Response was defined as a reduction of at least 50 % in the corticosteroid dose, a decrease of at least 25% in the serum IgE concentration, and at least one of the following: at least 25% improvement of exercise tolerance or pulmonary function tests, or resolution or absence of pulmonary infiltrates. There was also a second, open label part of the trial, where all patients received itraconazole 200 mg once daily for 16 weeks. The results showed that there were responses in 46% of the itraconazole group compared to 19% with placebo, with similar rates of adverse events in both groups. In the subsequent open label phase, 36% of the non-responders in the double-blind phase had responses, and none of the prior responders relapsed. Although the authors' results show significant clinical improvement, as well as reduction in corticosteroid dosage, and corroborate with the previous uncontrolled trials, the duration of treatment with itraconazole is still not well defined, nor is it clear whether it would be beneficial in all stages of the disease.

4. CONCLUSION

The management of ABPA depends on the stage of the disease. Underlying asthma and allergic rhinitis should be treated with environmental changes, pharmacotherapy, and immunotherapy as appropriate. Serial IgE levels, pulmonary function tests, and chest radiography should be followed at intervals to assess the patients' response to treatment. Aggressive therapy with oral corticosteroids should be instituted promptly, depending on the stage and extent of disease. Antifungal treatment with itraconazole should also be considered, especially in light of its steroid sparing effect. Clinical data suggests that early and aggressive institution of treatment may halt the progression of disease to end stage fibrosis.

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