ALLERGIC BRONCHOPUMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction that occurs in response to colonization of the airways with Aspergillus fumigatus and almost exclusively in patients with asthma or cystic fibrosis .

EPIDEMIOLOGY

asthma 1 to 2 percent, although rates up to 28 percent have been reported

In cystic fibrosis, reported prevalences range from 2 to 9 percent

Rarely, ABPA occurs in patients with bronchiectasis, chronic granulomatous disease, hyperimmunoglobulinemia E, and in lung transplant recipients [

**PATHOLOGY AND PATHOGENESIS**

Allergic bronchopulmonary aspergillosis (ABPA) is characterized pathologically by

mucoid impaction of the bronchi

, eosinophilic pneumonia,

bronchocentric granulomatosis

Septated hyphae with acute dichotomous branching may be seen in the mucus-filled bronchial lumen, but fungi do not invade the mucosa.

 Aspergillus is cultured from the sputum in up to two-thirds of patients with ABPA, but hyphae may not be seen by direct microscopy.

T cells also play an important role in ABPA. There are increases in Th2 CD4+ cell responses to Aspergillus antigens both in the bronchoalveolar lymphoid tissue and systemically

 Aspergillus-responsive T cells generate cytokines interleukin (IL)-4, IL-5, and IL-13, which in turn account for the increases in blood and airway eosinophils and IgE in ABPA.

**Signs and symptoms**

Asthma with recurrent exacerbations.

episodes of bronchial obstruction due to mucoid impaction

fever,

malaise,

expectoration of brownish mucus plugs

rarely hemoptysis.

asymptomatic pulmonary consolidation.

**investigations**

spirometry

Degree of airway obstruction with air trapping

Mixed pattern if bronchiectasis and fibrosis

Reversibility in only half of the patients

skin prick sensitivity to aspergillus(IgE)

Sputum

Aspergillus hyphae and eosinophils

Blood

Serum IgG precipitins

IgE RAST to aspergillus

Total serum IgE

Eosinophils count

CXR

Flitting infilterates

Bronchiectasis

A close-up of a fetus

Description automatically generated with low confidence

CT THORAX

CENTRAL BRONCHIECTASIS WITH UPPER LOBE PREDOMINANCE

A picture containing ceramic ware, fabric, porcelain

Description automatically generated

DIAGNOSTIC CRITERIA

**International Society for Human and Animal Mycology (ISHAM) working group diagnostic criteria for allergic bronchopulmonary aspergillosis**

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| --- |
| **Predisposing conditions (one must be present)\*:** |
| Asthma |
| Cystic fibrosis |
| **Obligatory criteria (both must be present):** |
| Serum IgE levels against *Aspergillus fumigatus* (>0.35 kU/L) or *Aspergillus*skin test positivity. |
| Elevated total IgE concentration (typically >1000 IU/mL, but if the patient meets all other criteria, an IgE value <1000 IU/mL may be acceptable, especially if *A. fumigatus*-specific IgG levels are >27 mg/L) |
| **Other criteria (at least two must be present):** |
| Precipitating serum antibodies to *A. fumigatus* or elevated serum *Aspergillus* IgG by immunoassay (>27 mg/L) |
| Radiographic pulmonary opacities consistent with ABPA |
| Total eosinophil count >500 cells/microL in glucocorticoid-naïve patients |

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TREATMENT

Acute ABPA —

For acute ABPA manifest by radiographic opacities (usually upper or middle lobes) and an elevated total serum IgE (generally >1000 international units/mL)

Systemic glucocorticoids —

PREDNISOLONE 0.5MG/KG DAILY FOR 14 DAYS FOLLOWED BY 0.5 MG/KG ALTERNATE DAYS AND FURTHER TAPERING AND DISCONTINUTION AT 3 MONTHS

Some patients may need a higher initial dose of prednisone (eg, 40 to 60 mg/day), if they are having an acute asthma flare. In an unblinded, randomized trial that included 92 patients, prednisolone 0.5 mg/kg per day for two weeks, then tapering to 0.5 mg/kg on alternate days, then further gradual tapering, was compared with prednisolone 0.75 mg/kg per day for six weeks followed by a more gradual taper [13]. No significant difference was noted in the number of patients with an exacerbation in the first year.

Total serum IgE levels decrease by approximately 25 percent after one month of treatment and 60 percent after two months . A decrease of 35 percent is considered a good therapeutic response, such that tapering of prednisone is appropriate.

Antifungal therapy —

Two randomized trials, a retrospective cohort study, and a small prospective study have demonstrated the utility of itraconazole in addition to glucocorticoids for the therapy of ABPA [. The larger of the randomized trials compared itraconazole with placebo in 55 patients already receiving glucocorticoids . The addition of itraconazole for 16 weeks was associated with a significant increase in the likelihood of a clinical response (46 versus 19 percent).

A response was defined as a reduction of at least 50 percent in the glucocorticoid dose,

a decrease of at least 25 percent in the serum IgE concentration, and one of the following:

an improvement of at least 25 percent in exercise tolerance or pulmonary function tests

Reosolution of pulmonary infilterates

●Itraconazole

loading dose of 200 mg three times a day for three days

followed by200 mg twice daily for 16 weeks.

Liver function tests should be monitored closely for evidence of hepatotoxicity. It is recommended that itraconazole serum concentrations be obtained to ensure appropriate absorption of the drug

●Voriconazole —

loading dose of 400 mg every 12 hours for two doses, followed by

a maintenance dose of 200 mg twice daily for 16 weeks.

Liver function tests should be monitored closely for any evidence of hepatotoxicity.

Voriconazole levels should be measured after about five days of therapy to ensure adequate absorption and avoid toxicit

Monitoring —

The clinical response to glucocorticoids should be monitored with serial measurement of the serum total IgE concentration every one to two months .

Resolution of radiographic opacities and clinical improvement are generally accompanied by at least a 35 percent reduction in serum total IgE

ABPA in remission —

Remission of ABPA is characterized by a normal or mildly elevated serum total IgE

absence of radiographic opacities in a patient who has been off systemic glucocorticoids for longer than six months.

Inhaled glucocorticoids are continued to maintain asthma control as per current guidelines.

ABPA is monitored by serum total IgE levels every three to six months.

Spirometry is performed annually and in response to changes in symptoms

Use of biologic agents in ABPA

Biologics in patients with ABPA and recurrent exacerbations or inability to taper off oral glucocorticoids despite a course of antifungal therapy and optimal inhaled therapy for asthma, particularly those with asthma as a predisposing condition.

1ST LINE

anti-interleukin (IL)-5 agents (eg, mepolizumab, benralizumab) due to their favorable safety profile and less frequent dosing intervals.

Other options include

omalizumab (anti-immunoglobulin [Ig]E) and dupilumab (anti-IL-4 subunit antibody). Like mepolizumab and benralizumab, these agents target one of the allergic mechanisms that are upregulated in ABPA. Each has been shown to improve outcomes in case series of patients with ABPA and are approved for the treatment of severe asthma.

While awaiting long-term studies of efficacy and safety in ABPA, we suggest addition of a biologic agent based upon on the eligibility criteria for asthma (table 1), which include age, weight, total serum IgE, and blood eosinophil counts. It should be noted that because all patients with ABPA will have an elevated IgE level and most will have an elevated eosinophil count, they will have biomarkers that support the use of one or more of the approved biologic agents.

Anti-IgE therapy — Omalizumab, a humanized monoclonal antibody against IgE, may be beneficial in the treatment of ABPA in the setting of poorly-controlled asthma.

A benefit to omalizumab is suggested by systematic reviews of omalizumab [39,40] and by the studies outlined below. For asthma, the dosing of omalizumab follows a nomogram based on weight and total serum IgE level. However, the nomogram is more difficult to apply in ABPA due to high serum levels of IgE (ie, above the upper limit of nomogram-based dosing). Based on clinical experience and limited published data, we typically administer omalizumab 375 mg, subcutaneously, every 14 days in patients with ABPA [39,41-43]. Proof of efficacy in ABPA for patients with and without cystic fibrosis (CF) awaits more definitive clinical trials. (See "Anti-IgE therapy", section on 'Administration'.)

●The effect of omalizumab was examined in 13 patients with ABPA and poorly-controlled asthma (mean total IgE 2314 ± 2125 international units/mL) who were randomly assigned to omalizumab 750 mg subcutaneously or placebo once a month for four months, followed by a three month washout phase, and then cross-over to the opposite treatment group [41]. Other asthma treatments remained constant through the trial. During the active treatment phases, exacerbations were significantly less frequent with omalizumab (2 versus 12 events).

●In an open-label study that included 16 adult ABPA patients without CF, use of omalizumab for one year was associated with a marked decrease in the number of asthma exacerbations and in oral glucocorticoid dose compared with the year prior to starting omalizumab [44].

●In eight case reports, 13 children with CF and ABPA received omalizumab at doses ranging from 300 to 450 mg every two to four weeks, resulting in improved forced expiratory volume in one second (FEV1), fewer respiratory symptoms, and decreased glucocorticoid use in most, but not all, patients [45].

A systematic review that included one study of omalizumab in 14 patients with cystic fibrosis and ABPA concluded that the evidence was insufficient to determine benefit in this setting [46].

Anti-interleukin-5 agents —

Two anti-interleukin (IL)-5 agents have been assessed in observational studies of patients with ABPA: mepolizumab (anti-IL-5) and benralizumab (anti-IL-5 receptor alpha [IL-5R]) [47-52].

one of these agents in patients with ABPA who meet criteria for severe asthma and have a blood eosinophil count ≥300/microL.

●In a series of 20 patients with ABPA and severe asthma, addition of mepolizumab 100 mg every four weeks for six months was associated with a decrease in the annualized number of exacerbations (3 to 0),

reduction in the dose of systemic glucocorticoids needed for asthma control

improvement in asthma symptom scores compared with the year prior to mepolizumab .

Further study is needed to determine the appropriate role of anti-IL-5/5R agents in the treatment of ABPA and whether these agents interrupt progression of bronchiectasis.

Anti-IL-4 receptor alpha subunit antibody — Dupilumab is a monoclonal antibody that binds to the alpha subunit of the IL-4 receptor and is approved for the treatment of moderate-to-severe, eosinophilic asthma (eg, peripheral blood eosinophils ≥150/microL) in patients age 12 years and older. In case reports of patients with ABPA, addition of dupilumab was associated with successful tapering of oral glucocorticoid . A multi-center randomized clinical trial testing the efficacy of dupilumab in ABPA (with asthma as the predisposing condition) is currently underway.

The dosing and administration of dupilumab in severe asthma are described separately. (See "Treatment of severe asthma in adolescents and adults", section on 'Anti-lL-4 receptor alpha subunit antibody (dupilumab)'.)

Fibrotic lung disease — Fibrotic lung disease due to ABPA is characterized by impaired respiratory function and chronic scarring on imaging studies. Laboratory studies in one case series revealed serum Aspergillus specific IgE and IgG levels that were elevated compared with a control pool of serum samples from patients with asthma but not ABPA [56]. Patients with fibrotic lung disease may require long-term prednisone for control of asthma. Patients with a FEV1 of 0.8 L or less (after initial glucocorticoid treatment) tend to have a poor prognosis.

Patients with cystic fibrosis — Treatment of acute ABPA in CF mirrors that described above for patients without cystic fibrosis, although this has not been studied in prospective trials [5,57]. Systemic glucocorticoids are used as in ABPA with asthma, and therapy should result in a reduction in IgE level. Clinical trial data for the use of antifungal therapy to treat ABPA in patients with CF are lacking, but observational data are supportive [58].

●Prednisone (tapering dosing for 18 days) and itraconazole (guided by serum trough levels for at least 12 months) were administered to 65 patients with CF and ABPA in an observational study [20]. Serial lung function measurements demonstrated near return in FEV1 to pre-ABPA levels by three months. Additionally, FEV1 values over a median of 4.8 years after the ABPA diagnosis were comparable to those of 127 patients with CF without ABPA. In previous studies, ABPA was associated with accelerated loss of lung function [59,60].

●In one retrospective series of 16 patients with CF and ABPA, the use of itraconazole was associated with a 47 percent reduction in average daily glucocorticoid dose and a 55 percent reduction in the number of acute ABPA episodes [59].

Case reports and small case series have also described benefit from omalizumab in the long-term management of patients with CF and ABPA [45,61,62]. (See 'Anti-IgE therapy' above.)

Other interventions — The role of reducing exposure to environmental sources of Aspergillus has not been formally studied, but it seems prudent for patients to avoid high levels of Aspergillus exposure at home and at work [1,63-66].

Whether nebulized amphotericin is effective at reducing exacerbations is unclear. In a trial of 174 patients with ABPA, six months of nebulized liposomal amphotericin (25 mg once weekly) versus placebo resulted in a similar proportion of patients experiencing a severe exacerbation within 24 months (50.7 versus 51.3 percent) [67]. However, the extended median time-to-first event (337 versus 177 days) and fall in aspergillus markers during amphotericin treatment suggest the potential for benefit while on active therapy. In contrast, a previous observational study in 21 patients with ABPA suggested that nebulized amphotericin B (10 mg twice daily three times a week) may reduce ABPA symptoms and exacerbations [68]. Further study is needed to determine the clinical role for nebulized amphotericin therapy.

Immunotherapy with fungal allergens has not been evaluated in high-quality studies. Evidence to support the initiation of fungal immunotherapy for the treatment of ABPA is lacking, although patients already receiving immunotherapy for the treatment of other allergic disorders may safely continue it [19].

PROGNOSIS

. Patients without central bronchiectasis at the time of diagnosis tend to maintain their lung function despite occasional exacerbations.

In an observational study, 55 patients with a diagnosis of ABPA, but normal high resolution computed tomography, were followed for 2 to 6.5 years ,

Sixteen experienced exacerbations and six remained glucocorticoid dependent.

The mean forced expiratory volume in one second improved, and none developed central bronchiectasis

Rare patients have presented with pulmonary fibrosis despite few preceding episodes or symptoms .

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Aspergillosis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topics (see "Patient education: Allergic bronchopulmonary aspergillosis (The Basics)")

SUMMARY AND RECOMMENDATIONS

●Treatment goals – Treatment of allergic bronchopulmonary aspergillosis (ABPA) aims to control episodes of acute inflammation and to limit progressive lung injury. The general teaching is that early treatment is important to try to prevent the development of bronchiectasis or pulmonary fibrosis. (See 'Treatment' above and 'Prognosis' above.)

●Systemic glucocorticoids – For patients with an acute flare or recurrent exacerbation of ABPA, we recommend systemic glucocorticoid therapy (Grade 1B). The usual initial dose is prednisone 0.5 mg/kg (or equivalent) daily for 14 days followed by conversion to an every other day regimen and a slow taper over three to six months. An exception to this initial dose is the patient with a concomitant asthma exacerbation that requires a higher initial dose. (See 'Systemic glucocorticoids' above and 'ABPA exacerbation' above.)

●Antifungal therapy – We suggest antifungal therapy with itraconazole or voriconazole for patients who are unable to taper oral glucocorticoids or have an exacerbation of ABPA (Grade 2B). Alternatively, antifungal therapy can be given to all patients with acute ABPA with the goal of enabling a reduction in the long-term glucocorticoid dose. Antifungal therapy is typically continued for 16 weeks. (See 'Acute ABPA' above and 'ABPA exacerbation' above and "Acute exacerbations of asthma in adults: Emergency department and inpatient management", section on 'Systemic glucocorticoids' and "Acute exacerbations of asthma in adults: Home and office management".)

●Biologic agents for severe asthma – For patients with ABPA with recurrent exacerbations or inability to taper off oral glucocorticoids despite a course of antifungal therapy and optimal inhaled therapy for asthma, we suggest addition of a biologic agent (Grade 2C). The biologic agents omalizumab, mepolizumab, benralizumab, and dupilumab have improved outcomes in case series, but data are limited. Eligibility criteria for the individual biologic agents in severe asthma include age, weight, total serum IgE, and blood eosinophil count and are listed in the table (table 1). (See 'Use of biologic agents in ABPA' above.)

●Inhaled glucocorticoids – Patients with ABPA in remission may need inhaled glucocorticoids to maintain asthma control, possibly with long-acting beta-agonists, to control the underlying asthma. However, inhaled glucocorticoids do not have documented efficacy in preventing acute episodes of ABPA. (See 'Treatment' above.)

●ABPA in cystic fibrosis – Treatment of acute ABPA in cystic fibrosis mirrors that described above for patients without cystic fibrosis, although this has not been studied in prospective trials. (See 'Patients with cystic fibrosis' above.)

●Aspergillus exposure – The role of reducing exposure to environmental sources of Aspergillus has not been formally studied, but it seems prudent for patients to avoid high levels of Aspergillus ex

posure at home and at work. (See 'Other interventions' above.)