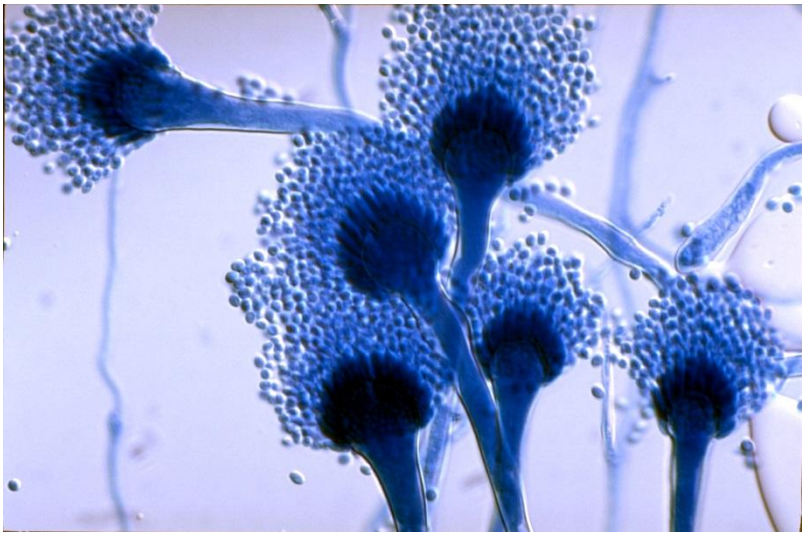
Allergic Bronchopulmonary Aspergillosis: The Fungus Amongst Us



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Purpose and Overview:

The purpose of the presentation is to educate the clinician regarding how to recognize, evaluate and manage patients with allergic bronchopulmonary aspergillosis (ABPA). Specifically, the immunopathology of ABPA, the genetics underlying its development, and characteristic clinical features all will be discussed in the first part of the presentation. The second part will focus upon diagnostic strategies and management approaches.

Educational Objectives:

1. To understand the pathology and genetics of allergic bronchopulmonary aspergillosis
2. To recognize the key clinical features of the disease and to understand the various stages that may be seen
3. To determine a step-wise approach to evaluating patients presenting with clinical features suggestive of ABPA
4. To devise management strategies for patients fitting the clinical criteria for ABPA.

Introduction

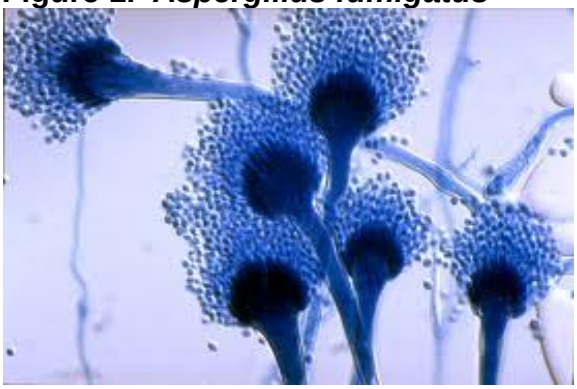
Aspergillus fumigatus is a ubiquitous thermophilic fungus that colonizes the bronchial mucosa and it is thought that allergic bronchopulmonary aspergillosis (ABPA) results from an activation of the immune system by *Aspergillus* spores. This activation leads to tissue damage including proximal bronchiectasis and distal bronchiolitis obliterans [6]. ABPA occurs predominately in patients who are atopic and who have asthma or in those who have cystic fibrosis (CF). However, while colonization is common in both these patient groups, ABPA is not, occurring in only 1-2% of patients with persistent asthma and in only 2-15% of patients with CF [7].

ABPA was originally described by Hinson and colleagues in 1952 [8]. While eight cases were described in this original report, three of these were unique in that they appeared to result from allergic sensitization to the *Aspergillus* fungus. Thus, the term "allergic" bronchopulmonary aspergillosis was coined. These patients demonstrated consolidation in different parts of the lungs, exudative sputum that contained characteristic "plugs" and *A. fumigatus* fungus and a blood eosinophil count above 1,000 cells/mm^3.

Aspergillus fumigatus biology

Aspergillus fumigatus is a ubiquitous, saprophytic mold that is found in both outdoor and indoor air, in potting soil, crawl spaces, compost piles, mulches, freshly cut grass, decaying vegetation and sewage treatment facilities [9]. It is found throughout the world including the U.S. where it is predominantly found on the East coast and in the Midwest. *Aspergillus* species are thermotolerant and they grow especially well at 37^o to 40^o C. which favors growth in human bronchi. Septated hyphae are 7 to 10 µm in diameter and hyphae can be found in sputum, mucus plugs or sinus secretions (Figure 1).

Figure 1. *Aspergillus fumigatus*



Aspergillus-Associated Lung Diseases

In addition to ABPA, *Aspergillus fumigatus* has been associated with a variety of other pulmonary disorders including:

- IgE-mediated asthma - Asthma patients may develop IgE antibodies to *Aspergillus fumigatus* and other molds. However, only a minority of these patients develop ABPA.

- Invasive aspergillosis - Invasive aspergillus disease occurs in individuals who become neutropenic secondary to chemotherapy and in patients with certain congenital immunodeficiencies including those with chronic granulomatous disease (CGD) and leukocyte adhesion defects (LAD). In invasive aspergillosis, *Aspergillus fumigatus* invades the bronchial epithelia resulting in pneumonia, tracheobronchitis, abscesses, central nervous system infections and septicemia.

- Aspergilloma (mycetoma) – An aspergilloma forms in individuals who have pre-existing pulmonary diseases such as bronchogenic carcinoma, cavitary tuberculosis, pulmonary histoplasmosis, cystic fibrosis, sarcoidosis and bronchiecstasis. In these pulmonary disorders, *Aspergillus* spores germinate forming a tangled mass of hyphae. Hemoptysis is a common presenting finding. While *Aspergillus*-specific IgG antibodies usually are present, *Aspergillus*-specific IgE antibodies are not. Treatment consists of antifungal agents and, in some instances, surgery [10].

- Hypersensitivity pneumonitis – This disorder occurs when there is a Th1 immunologic reaction in the airways and lung parenchyma to a variety of inhaled antigens including: micro-organisms (actinomycetes, bacteria, fungi, amoebae), animal proteins (avian, cat, rodent), plant products, low molecular weight chemicals and various drugs. There are acute, subacute and chronic forms of the disease. While the acute form is characterized by cough, dyspnea, fever, chills and myalgias, the subacute and chronic forms are characterized by anorexia and weight loss, in addition to progressive dyspnea. Precipitating antibodies to the offending antigen often are present and a lymphocytosis in bronchial lavages fluids can be found (increased CD8+ cells; decreased CD4/CD8 ratio).

Genetics and Immunopathogenesis

The fact that *Aspergillus fumigatus* spores 3 to 5 µm in size are inhaled and that they germinate into hyphae deep within the bronchi imply that it is likely that high concentrations of *Aspergillus fumigatus* allergens are exposed to the respiratory epithelium and the immune system. In these individuals, inhaled conidia of *Aspergillus fumigatus* mycelia germinate into hyphae and release antigens that decrease mucociliary clearance, that stimulate and impair the airway epithelial barrier and that activate pulmonary innate immune responses [5]. *Aspergillus fumigatus* is known to

release various proteins including superoxide dismutases, catalases, proteases, ribotoxin, phospholipases and numerous other toxins [10] and it has been suggested that these proteins have a direct and detrimental effect on the pulmonary epithelia and macrophage inflammation [11]. Not only do the fungal proteases induce epithelial cell detachment, but also they appear to induce the production of proinflammatory chemokines and cytokines, such as IL-8, IL-6, and MCP-1.

In addition to innate immune responses, fungal antigens, presented by antigen-presenting cells (APC) bearing HLA-DR2 or HLA-DR5 markers, activate Th2 CD4+ T-cell responses. In a normal host, APC presentation of fungal allergens results in a Th1 response and organism eradication. While a Th1 response is elicited in susceptible hosts too, these individuals also display exaggerated Th2 responses. The resulting IL-4, IL-5 and IL-13 production that occurs leads to increased production of total IgE, increased production of *Aspergillus fumigatus*-specific IgE, IgG and IgA, mast cell degranulation and eosinophilia. A central question is how ABPA patients differ from *Aspergillus*-sensitive atopic patients and patients with CF. Knutson and Slavin [10] propose that ABPA occurs in genetically susceptible individuals with asthma and CF because of an increased frequency and/or activity of *Aspergillus fumigatus*-specific Th2 CD4+ cells. In addition, they further propose that polymorphisms of the IL-4 receptor alpha chain subunit and HLA-DR2/DR5 are the genetic susceptibility risk factors responsible ABPA development.

In addition to the HLA-DR genetic associations and *IL-4RA* polymorphisms, several other host factors that have been identified to possibly explain the selective development of ABPA in those who are *Aspergillus*-sensitive and these are presented in Table 1.

Table 1. Genetic Factors in the development of allergic bronchopulmonary aspergillosis [10]

Increased Susceptibility
• HLA-DR2 and HLA-DR5
• *IL-4RA* polymorphisms
• IL-10 promoter polymorphisms
• Surfactant protein polymorphism
• Cystic fibrosis transmembrane conductance regulator (*CFTR*) mutations
• Toll-like receptor polymorphisms
Protective
• HLA-DQ

Pathology

The pathology of ABPA varies greatly, not only from patient to patient but also within the same patient at the same time since different areas of the lung can demonstrate different pathologies. Typically, upon histologic examination, there is mucus, fibrin, Curschmann spirals, Charcot-Leyden crystals and inflammatory cells present in the airway. In addition, mucoid impaction, eosinophilic pneumonia and bronchocentric

granulomatosis also are found and bronchiectasis may develop in areas of pulmonary infiltrates. Septated hyphae with dichotomous branching may be seen in the mucus-filled bronchial lumens but mucosal invasion is not seen.

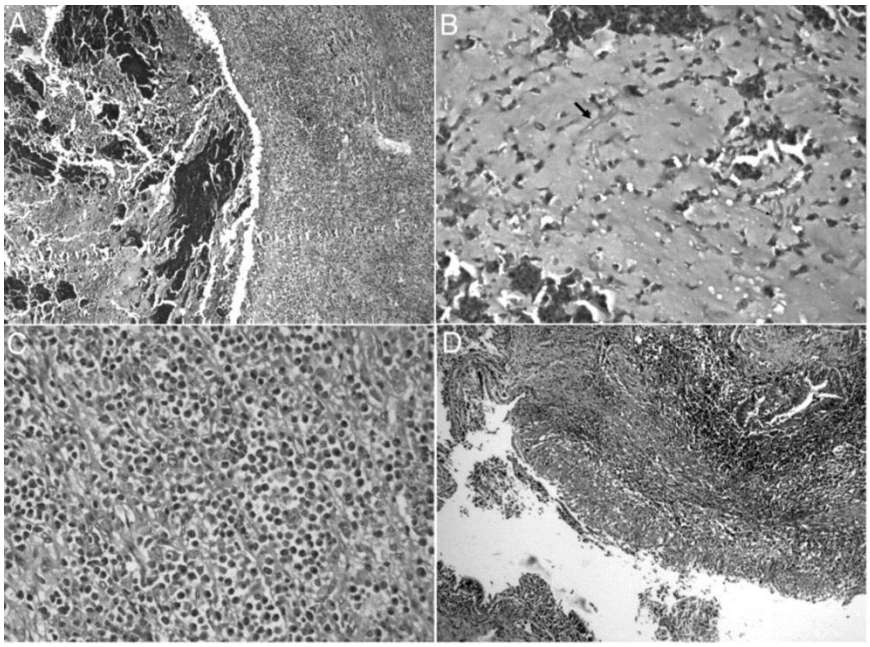


Figure 1. Histopathologic findings in a patient with ABPA. A: Photomicrograph showing bronchial lumen containing allergic mucin. B: High-magnification photomicrograph of allergic mucin having variegated appearance, necrotic eosinophils, Charcot-Leyden crystals, and an occasional septate fungal hyphae. C: Photomicrograph showing eosinophilic pneumonia. D: Photomicrograph showing bronchocentric granulomatosis. [5]

Clinical Features and Diagnostic Criteria

There are several classic diagnostic features of ABPA and these are shown in Table 1 and include: asthma, pulmonary infiltrates, immediate cutaneous reactivity to *Aspergillus*, elevated total IgE level, precipitating antibodies to *Aspergillus fumigatus,* peripheral blood eosinophilia (usually 1000-3000 eosinophils/mm^3), elevated serum IgE and IgG antibodies to *Aspergillus fumigatus* (IgE-*Af* and IgG-*Af*) and proximal bronchiectasis.

Table 1. Diagnostic criteria for ABPA [7]

	Clinical or Laboratory Features	*Essential for Diagnosis*	*Comment*
1.	Asthma	Yes	Severity variable
2.	Chest roentgenographic infiltrate	No	Often in upper lobes simulating tuberculosis; may be present historically; may be absent at time of evaluation, possibly due to prednisone therapy
3.	Immediate cutaneous reactivity	Yes	Prick or intracutaneous test
4.	Elevated total serum IgE	Yes, > 1000 ng/ml (>416 IU/mL)	Total IgE may be suppressed by steroids used for asthma therapy
5.	Precipitating antibodies to *Aspergillus fumigatus (Af)*	Yes	Unless suppressed by steroid therapy, sera may require fivefold concentration
6.	Peripheral blood eosinophilia	No	May be absent in patients receiving steroids
7.	Elevated serum IgE-*Af* and IgG-*Af*	Yes	IgE-Af should be at least twice the pool of sera from Af prick-positive asthmatic patients with no ABPA; IgG-Af may not be twice control
8.	Central bronchiectasis		In absence of CF, a sine qua non of "classic" ABPA

*Criteria 1 through 7, ABPA-S (seropositive); shaded items are the minimal diagnostic criteria for ABPA-S; criteria 1 through 8, ABPA-CB (central bronchiectasis)

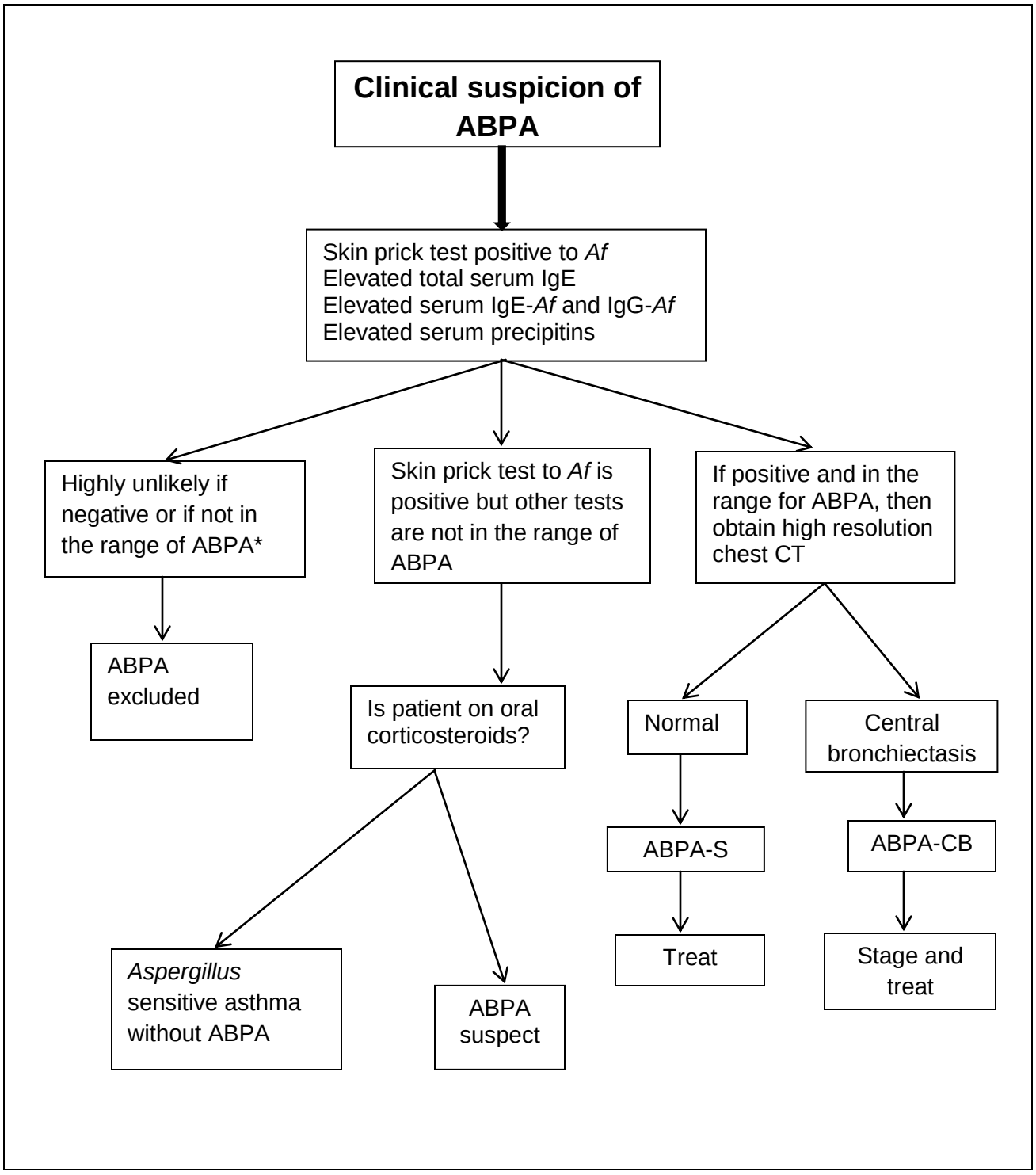
When all of the 8 outlined criteria are present, the diagnosis of ABPA is readily made and the notation ABPA-CB is used. If central bronchiectasis is absent but all other criteria are present, then the notation, ABPA-S (seropositive) is used.

In the absence of the classic findings, ABPA should be suspected in patients with asthma who also have bronchiectasis, a prior history of prior pneumonias or lung collapse, sputum plugs, anti-*Aspergillus fumigatus*-specific IgE antibodies, unexplained eosinophilia of 8 to 40%, worsening asthma severity or evidence of mucoid impaction of the bronchi and/or bronchocentric granulomatosis.

As stated recently by Greenberger [12], it is most concerning when a health care professional excludes ABPA inappropriately based upon a single negative test result. Examples of this type situation include the following: excluding ABPA if serum precipitins to *Aspergillus fumigatus* are absent; basing a skin test response to *Aspergillus fumigatus* on a prick test alone (without intradermal testing); excluding ABPA when the total IgE level is less than 417 IU/mL during the remission phase or in the prednisone-dependent asthma phase or dismissing the presence of ABPA when bronchiectasis is not present (thus overlooking the diagnosis of seropositive ABPA).

Figure 2 provides the sequence of events that can lead to the diagnosis of ABPA depending upon the initial clinical or laboratory findings.

Figure 2. Algorithm for ABPA in patients with asthma [13]



*****Serologic parameters may not be abnormal in certain stages of ABPA, including remission, corticosteroid-dependent ABPA, and end-stage ABPA.

In addition to the various criteria that are necessary to make the diagnosis, there are different stages of ABPA that exist and these are outlined in Table 2.

Table 2. Features of the five stages of Allergic Bronchopulmonary Aspergillosis[7]

Stage	*Total serum IgE*	*Precipitins*	*Peripheral blood eosinophilia*	*Chest roentgenographic abnormalities*	*Serum IgE-Af*	*Serum IgG-Af*
I. Acute	+++	+	+	+	+	+
II. Remission	+	±	-	-	±	±
III. Exacerbation	+++	+	+	+	+	+
IV. Corticosteroid-dependent asthma	++	±	±	±	±	±
V. Fibrotic	+	±	-	+	±	±

It is important to note that the stages in ABPA are not phases, since some patients actually present with end-stage pulmonary fibrosis (stage V) at the time of disease recognition [14]. Stage I, or acute disease is present when many of the classic disease findings are present. Treatment of this stage involves oral prednisone 0.5 mg/kg for two weeks given as a single dose and then alternate day therapy for 2 months. Treatment leads to resolution of pulmonary infiltrates, reduction of eosinophilia, a decrease in sputum plugs, improvement in asthma symptoms and a decrease in total serum IgE by at least 35% in 6 weeks [15]. Stage II or remission then occurs when there are no further radiographic infiltrates for at least 6 months after initial therapy. While remissions can be permanent, exacerbations may occur after many years. Stage III disease occurs when there are new infiltrates on CXR that cannot be explained by any other cause and that are associated with a markedly elevated total IgE serum concentration, at least a 100% increase. There may or may not be associated constitutional symptoms, wheezing, shortness of breath and sputum production. Prednisone again is used for treatment of this stage as in stage I. Stage IV ABPA occurs when attempts to decrease prednisone therapy in stage I or stage III leads to uncontrolled asthma, an increase in serum IgE or development of new pulmonary infiltrates. This diagnosis also should be considered in patients presenting with steroid-dependent asthma. Finally, repeated episodes of ABPA can lead to end-stage lung disease or stage V disease. Patients with this stage of disease have both irreversible obstructive and restrictive findings on pulmonary function testing and fibrosis on chest radiographs. These patients also have diffuse bronchiectasis, “honeycomb” fibrosis, cyanosis, arterial hypoxemia and respiratory failure.

Differential Diagnosis

The differential diagnosis of ABPA includes diseases that have one of the two following clinical findings: asthma, eosinophilia and radiographic infiltrates. These diseases are listed in Table 3.

Table 3. Differential diagnosis of ABPA

Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Churg-Strauss syndrome
Asthma with middle lobe syndrome or lobar collapse
Parasitic infestations (*Ascaris, Strongyloides*, etc.)
Allergic bronchopulmonary mycosis
Asthma and atopic dermatitis

Patients with both allergic and nonallergic asthma can have peripheral blood eosinophilia but the majority of these individuals do not have ABPA. Peripheral blood eosinophilia also is characteristic of chronic eosinophilic pneumonia, but it is not seen in acute eosinophilic pneumonia. Pulmonary infiltrates are common in both eosinophilic pneumonia and ABPA but the infiltrates differ between the two disorders and sputum plugs and bronchiecstasis are not present in eosinophilic pneumonia. Elevated IgE levels may be seen in patients with eosinophilic pneumonia.

Churg-Strauss vasculitis is another disorder that is associated with asthma, pulmonary infiltrates and elevated IgE levels but unlike ABPA there often is associated sensory or motor neuropathy and cutaneous purpuric lesions.

There are fungi other than *Aspergillus fumigatus* that cause an allergic bronchopulmonary mycosis (ABPM) that is clinically identical to ABPA. However, the implicated molds are not *Aspergillus fumigatus*. Causative agents of ABPM include: *Curvularia*, *Fusarium*, *Drechslera*, *Stemphylium*, *Pseudallescheria*, *Helminthosporium*, *Torulopsis* and other *Aspergillus* species.

Clinical features

The clinical picture of ABPA is dominated by asthma and the symptoms vary across a wide spectrum. Those with unilateral or bilateral pulmonary infiltrates often present with cough and golden-brown sputum plugs containing *Aspergillus* hyphae. There also is associated wheezing, fever, malaise, and sometimes hemoptysis. Those with more advanced disease (i.e., Stage V), have cyanosis, respiratory failure or both. In patients

with prednisone-dependent asthma, ABPA should be considered, especially if there is associated pulmonary consolidation noted on chest x-ray.

The physical exam findings range from a normal exam to mild wheezing to end-stage fibrotic lung disease with tachypnea, clubbing, cyanosis and cor pulmonale.

Pulmonary function studies are not all that helpful in ABPA since a spectrum of abnormalities can be found. These abnormalities range from normal lung function to obstruction during an ABPA exacerbation to both severe obstruction and restriction in end-stage disease.

Laboratory findings

Studies that support the diagnosis of ABPA include elevated *Aspergillus*-specific IgE antibodies and positive *Aspergillus* precipitins. While aspergillus presence in sputum is not required for diagnosis, the presence of hyphae in the sputum along with eosinophilia is suggestive of the diagnosis. Moreover, if eosinophilia is present it is usually greater than 1000 eosinophils/mm^3 with values greater than 3000 eosinophils/mm^3 being common [10].

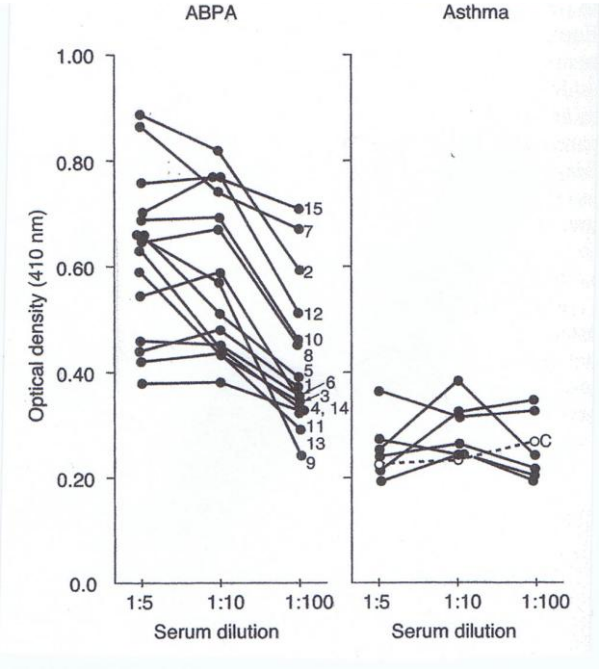


Figure 3. *Aspergillus fumigatus*-specific IgE determined by ELISA in 15 patients with ABPA and patients with asthma and skin test reactivity to *Aspergillus fumigatus* [3]

Serologic tests are the most useful in confirming or excluding ABPA. These include total serum IgE, *Aspergillus fumigatus*-specific IgE and IgG and *Aspergillus fumigatus* precipitins. Serum IgE levels typically are markedly elevated in patients with ABPA and values may be as high as 30,000 IU/mL. In one study by Ricketti et al. [15], levels ranged from 58,000 ng/mL to 697 ng/mL in 40 patients who had known ABPA. Moreover, all 40 patients had >35% reduction in total serum IgE levels after 2 months of corticosteroid treatment. Importantly, IgE levels may not be elevated in patients in remission (stage II disease), in those receiving prednisone and in those with end-stage lung disease.

Preciptating antibodies can be demonstrated by double gel immunodiffusion in greater than 90% of ABPA patients who have stage I or stage III ABPA but they are not as frequently found in patients in other disease stages. In addition, *Aspergillus fumigatus*-specific IgE and IgG antibodies are demonstrated by ELISA, especially those with Stage 1 and Stage 3 disease. In order to differentiate ABPA patients from those with asthma and *Aspergillus* skin test reactivity, ABPA sera must have antibody concentrations at least twice as high as those found in patients with asthma and aspergillus sensitivity.

Radiographic findings

There are numerous radiographic findings in ABPA. These include: parenchymal infiltrates that usually involve the upper lobes, atelectasis due to mucoid impaction and central bronchiectasis. Mucoid impactions and infiltrates are transient findings and they reflect disease activity. Pulmonary fibrosis, blebs and bullae and spontaneous pneumothorax, while not diagnostic of ABPA, can be found in stage V disease and should entertain this diagnosis if present in a patient with asthma.

In addition to infiltrates, there are two other reversible radiographic findings that are found in patients with ABPA:

- “Tram line” shadows – parallel lines that extend distally from the hilum; they represent thickened walls of non-dilated bronchi (can also be seen in patients with asthma, CF and left ventricular failure with elevated pulmonary venous pressure)

- “Toothpaste” shadows – mucoid impactions of dilated bronchi

Central bronchiectasis, which is a diagnostic of ABPA, is associated with a number of radiographic findings. These include:

- Ring shadows – 1-2 cm dilated bronchi seen “en face”

- Parallel line shadows – when a dilated bronchus is seen in a tangential, coronal perspective

- “Gloved finger” shadows – due to intra bronchial exudates within dilated bronchi (as is seen in bronchiectasis); they appear as tubular or branching opacities

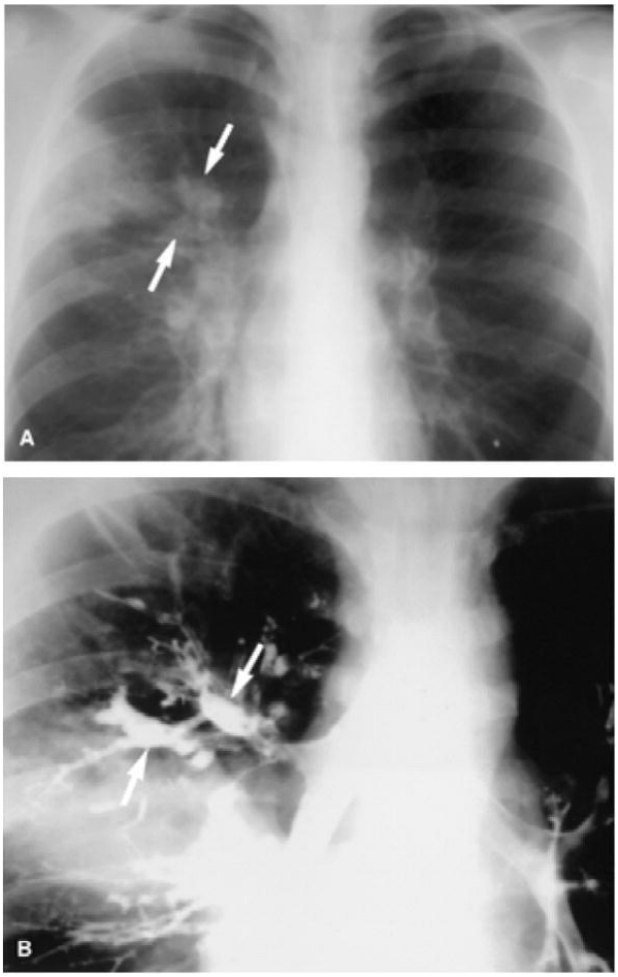


Figure 4. Allergic bronchopulmonary aspergillosis. A. Frontal chest radiograph reveals tubular opacities consistent with impacted bronchi (arrows) as well as right upper lobe consolidation. B. Bronchography in same patient reveals dilated bronchi (arrows) in the same distribution as seen on the chest radiograph [4].

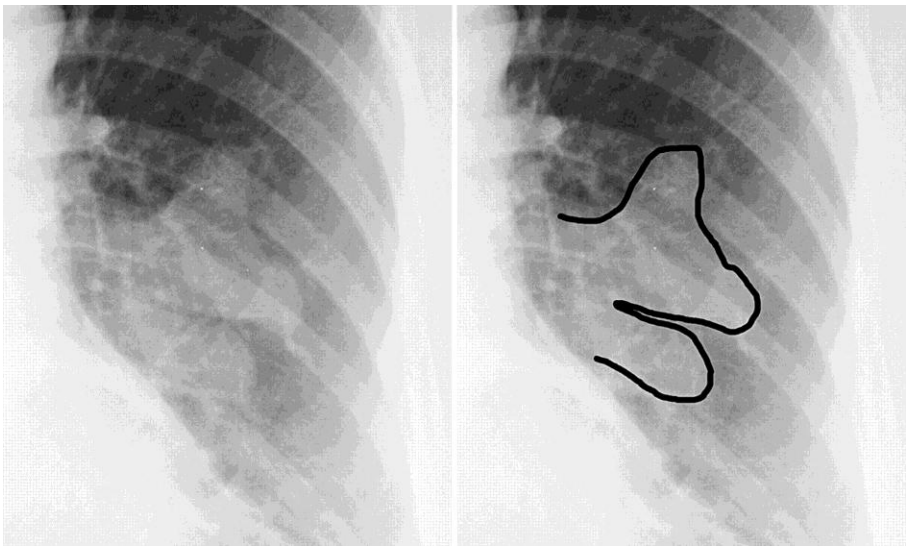


Figure 5. Finger-in-glove sign in a case of allergic bronchopulmonary aspergillosis. Posterioranterior radiograph (left) depicts a homogeneous branching opacity that radiates from the left hilum, a feature perhaps more easily discerned with the aid of a superimposed contour line (right) [2].

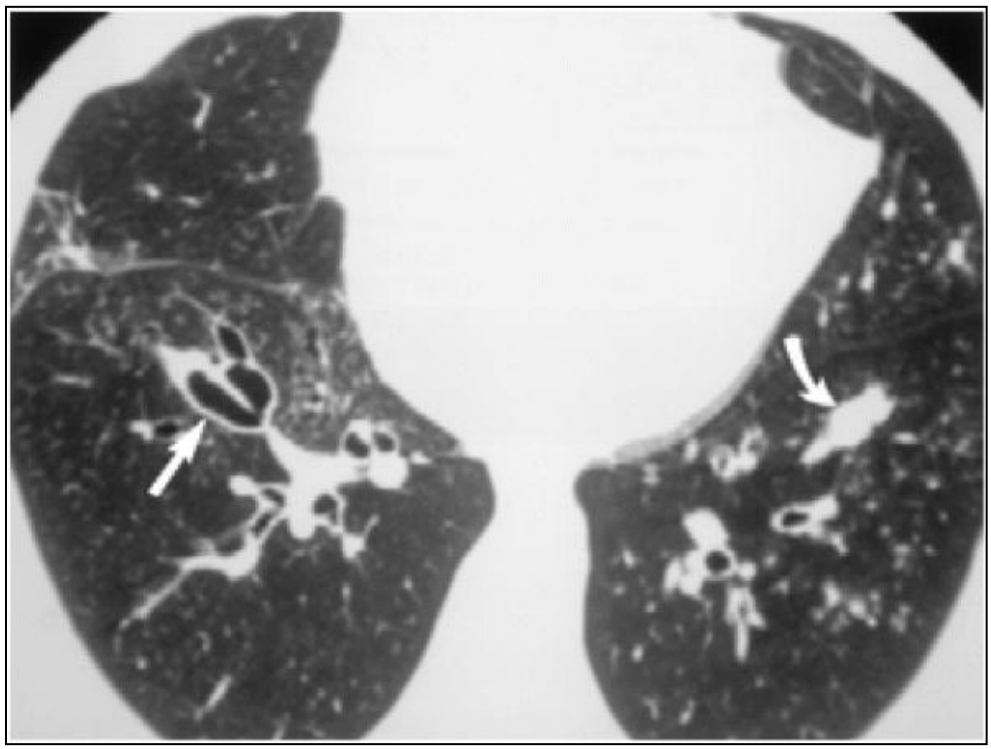


Figure 4. Allergic bronchopulmonary aspergillosis. Axial high resolution CT image reveals central bronchiectasis (straight arrow) and mucoid impaction (curved arrow), characteristic of allergic bronchopulmonary aspergillosis [4].

Treatment

In the 1960's attempts were made to treat ABPA with antifungal agents and cromolyn. However, when oral prednisone was compared to cromolyn, it was noted that better results were obtained with steroids [16]. While there have been no randomized controlled trials to assess the efficacy of systemic corticosteroids in treating ABPA, several case series and expert opinion support their use. Currently there are two regimens that have been suggested, one by Greenberger and colleagues [17] and the other by Agarwal and colleagues [18] and these are outlined in Table 4. While it appears that the higher-dose, longer-duration regimen leads to higher remission rates and lower prevalence of glucocorticoid-dependent ABPA [18], there have been no direct comparisons between these two regimens. With respect to inhaled corticosteroids, they have not been shown to be effective in the treatment of ABPA but are used for treatment of the associated asthma.

Table 4. Prednisone regimens for treatment of ABPA

1. Greenberger regimen [17]: 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 as tolerated until discontinued.

2. Agarwal regimen [18]: Prednisone equivalent of 0.75 mg/kg/day for 6 weeks, then 0.5 mg/kg/day for 6 weeks, then a taper by 5 mg every 6 weeks to continue for a total duration of 6 to 12 months.

The response to prednisone should be monitored with monthly or bimonthly total serum IgE concentrations. Resolution of infiltrates and clinical improvement (remission or stage II disease) are typically accompanied by at least a 35% decrease in total IgE [15]. Following resolution of the exacerbation, a stable serum level of total IgE should be established to serve as a guide for detection of future relapse. Flares are typically accompanied by a 100% increase in total IgE.

While there are few studies that have evaluated the use of antifungal agents in ABPA, there are two randomized, controlled trials that have suggested efficacy of itraconazole in this disease. In the larger study by Stevens et al. [19], patients who had corticosteroid-dependent ABPA were treated with either 200 mg of itraconazole twice daily or placebo for 16 weeks. After the treatment period, 13 of 28 or 46% of those in the itraconazole group compared to 5 of 27 or 19% in the placebo group had a clinical response as defined by a reduction of at least 25% in total serum IgE and one of the following: an improvement of at least 25% in exercise tolerance or pulmonary-function tests or resolution or absence of pulmonary infiltrates. Wark et al. [20] too also demonstrated fewer exacerbations requiring oral corticosteroids in those treated with itraconazole compared to those treated with placebo in a subsequent smaller randomized, double-blind, placebo-controlled trial. It is important to note that itraconazole not only has numerous adverse side effects, but also that it can cause

adrenal suppression when used with inhaled corticosteroids. In light of this adverse effect profile, the newer antifungal, voriconazole, an agent that has improved tolerance and bioavailability, has been shown in case studies to be an effective possible alternative [21, 22].

More recently, there has been a small study evaluating the use of omalizumab, a humanized monoclonal antibody against IgE. In a recent open-label study that included 16 adult patients with ABPA, use of omalizumab for one year was associated with a marked decrease in both asthma exacerbations and in oral glucocorticoid use compared with the year prior to treatment [1].

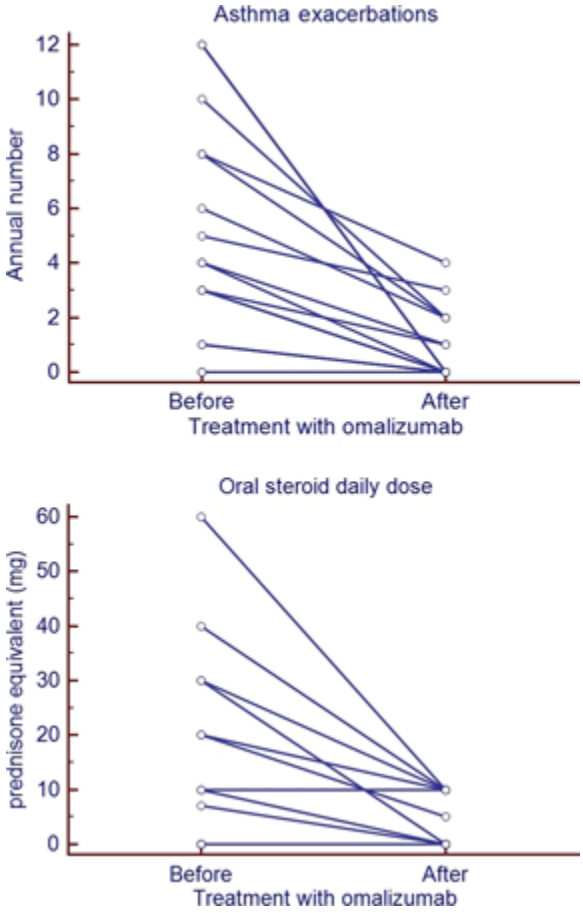


Figure 5. Effect of omalizumab on exacerbations and prednisone use in 16 patients with ABPA [1].

ABPA in Cystic Fibrosis

Since ABPA is known to occur in up to 15% of patients with CF, it is important that a high level of suspicion for this disease is maintained in these patients. A Consensus

Conference held in 2003 outlined diagnostic and screening criteria for these patients and these are outlined in Table 5.

Table 5. Consensus Conference Proposed Diagnostic and Screening Criteria for ABPA in CF [23].

Classic diagnostic criteria
1. Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) not explained by another etiology 2. Serum total IgE levels > 1,000 IU/mL 3. Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *Aspergillus fumigatus* 4. Precipitating antibodies to *Aspergillus fumigatus* or serum IgG antibody to *Aspergillus fumigatus* 5. New or recent abnormalities or chest radiograph or chest CT scan that have not cleared with antibiotics and standard physiotherapy
Minimal diagnostic criteria
1. Acute or subacute clinical deterioration (cough, wheeze, and other pulmonary symptoms) note explained by another etiology 2. Total serum IgE levels >500 IU/mL. If total IgE level is 200-500 IU/mL, repeat testing in 1-3 months is recommended 3. Immediate cutaneous reactivity to Aspergillus or presence of serum IgE antibody to *A. fumigatus* 4. One of the following: 1) precipitins to *A. fumigatus* or demonstration of IgE antibody to *A. fumigatus*; or 2) new or recent abnormalities on chest radiography (on chest radiography or chest CT scan that have not cleared with antibiotics and standard physiotherapy)
Screening for ABPA in CF
1. Maintain a high level of suspicion for ABPA in patients with CF 2. Determine the total serum IgE levels annually. If the total serum IgE levels is >500 IU/mL, perform *A. fumigatus* skin test or use an IgE antibody to *A. fumigatus*. If results are positive, consider diagnosis on the basis of minimal criteria 3. If the total serum IgE levels is 200-500 IU/mL, repeat the measurement if there is increased suspicion for ABPA and perform further diagnostic tests (immediate skin test reactivity to *A. fumigatus*, IgE antibody to *A. fumigatus*, *A. fumigatus* precipitins, or serum IgG antibody to *A. fumigatus* and chest radiography

Conclusions

In conclusion, ABPA is a very complex hypersensitivity disease. While the immunopathogenesis of ABPA is still not clearly known, it appears to primarily involve an exaggerated Th2 responses to Aspergillus antigens. Unfortunately, since the clinical, laboratory and radiologic findings often are so varied and not specific, a delay in diagnosis may occur. Since permanent lung damage often results from a delayed

diagnosis, the clinician should always have a high index of suspicion for this disorder in both patients with asthma and CF.

References

1. Tillie-Leblond, I., et al., *Allergic bronchopulmonary aspergillosis and omalizumab.* Allergy, 2011. 66(9): p. 1254-6.
2. Martinez, S., et al., *Mucoid impactions: finger-in-glove sign and other CT and radiographic features.* Radiographics, 2008. 28(5): p. 1369-82.
3. Greenberger, P.A. and R. Patterson, *Application of enzyme-linked immunosorbent assay (ELISA) in diagnosis of allergic bronchopulmonary aspergillosis.* J Lab Clin Med, 1982. 99(2): p. 288-93.
4. Gotway, M.B., et al., *The radiologic spectrum of pulmonary Aspergillus infections.* J Comput Assist Tomogr, 2002. 26(2): p. 159-73.
5. Agarwal, R., *Allergic bronchopulmonary aspergillosis.* Chest, 2009. 135(3): p. 805-26.
6. Greenberger, P.A., *Chapter 18: Allergic bronchopulmonary aspergillosis.* Allergy Asthma Proc, 2012. 33 Suppl 1: p. S61-3.
7. Greenberger, P.A., *Allergic bronchopulmonary aspergillosis*, in *Middleton's Allergy Principles and Practice*. 2003, Mosby: Philadelphia. p. 1353-1371.
8. Hinson, K.F., A.J. Moon, and N.S. Plummer, *Broncho-pulmonary aspergillosis; a review and a report of eight new cases.* Thorax, 1952. 7(4): p. 317-33.
9. Slavin, R.G., et al., *A pathologic study of allergic bronchopulmonary aspergillosis.* J Allergy Clin Immunol, 1988. 81(4): p. 718-25.
10. Knutsen, A.P. and R.G. Slavin, *Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis.* Clin Dev Immunol, 2011. 2011: p. 843763.
11. Kauffman, H.F., et al., *Protease-dependent activation of epithelial cells by fungal allergens leads to morphologic changes and cytokine production.* J Allergy Clin Immunol, 2000. 105(6 Pt 1): p. 1185-93.
12. Greenberger, P.A., *When to suspect and work up allergic bronchopulmonary aspergillosis.* Ann Allergy Asthma Immunol, 2013. 111(1): p. 1-4.
13. Bains, S.N. and M.A. Judson, *Allergic bronchopulmonary aspergillosis.* Clin Chest Med, 2012. 33(2): p. 265-81.
14. Lee, T.M., et al., *Stage V (fibrotic) allergic bronchopulmonary aspergillosis. A review of 17 cases followed from diagnosis.* Arch Intern Med, 1987. 147(2): p. 319-23.
15. Ricketti, A.J., P.A. Greenberger, and R. Patterson, *Serum IgE as an important aid in management of allergic bronchopulmonary aspergillosis.* J Allergy Clin Immunol, 1984. 74(1): p. 68-71.
16. Safirstein, B.H., et al., *Five-year follow-up of allergic bronchopulmonary aspergillosis.* Am Rev Respir Dis, 1973. 108(3): p. 450-9.
17. Greenberger, P.A., *Allergic bronchopulmonary aspergillosis.* J Allergy Clin Immunol, 2002. 110(5): p. 685-92.
18. Agarwal, R., et al., *Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India.* Chest, 2006. 130(2): p. 442-8.
19. Stevens, D.A., et al., *A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis.* N Engl J Med, 2000. 342(11): p. 756-62.
20. Wark, P.A., et al., *Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial.* J Allergy Clin Immunol, 2003. 111(5): p. 952-7.

21. Erwin, G.E. and J.E. Fitzgerald, *Case report: allergic bronchopulmonary aspergillosis and allergic fungal sinusitis successfully treated with voriconazole.* J Asthma, 2007. 44(10): p. 891-5.
22. Glackin, L., et al., *Voriconazole in the treatment of allergic bronchopulmonary aspergillosis in cystic fibrosis.* Ir Med J, 2009. 102(1): p. 29.
23. Stevens, D.A., et al., *Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference.* Clin Infect Dis, 2003. 37 Suppl 3: p. S225-64.