

Burden and Distinctive Character of Allergic Bronchopulmonary Aspergillosis in India

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Abstract Allergic bronchopulmonary aspergillosis (ABPA) is an insidious pulmonary disorder caused by hypersensitivity reactions mounted against *Aspergillus fumigatus*. Usually, complicating the course of patients with asthma and cystic fibrosis, the affliction has recently been described in chronic obstructive pulmonary disease and pulmonary tuberculosis-related fibrocavitary disease. Patients commonly present with poorly controlled asthma, recurrent pulmonary infiltrates and bronchiectasis. More than six decades have elapsed since the first description of this entity; however, the condition remains poorly understood. The International Society for Human and Animal Mycology has formed a working group to address the deficiencies associated with understanding of this disorder. New criteria have been laid down for diagnosis and staging of the disorder, so as to simplify the identification and management of this condition. This review summarizes the recent advances that have taken place in this condition with special emphasis on the burden and distinct character of ABPA in the Indian subcontinent.

Keywords ABPM · Allergic bronchopulmonary mycosis · COPD · Tuberculosis · Fungal sensitization · SAFS

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder that occurs in response to *Aspergillus fumigatus* colonizing the bronchial mucus plugs of patients with asthma [and cystic fibrosis (CF)], with little or no tissue invasion by the organism [1]. *A. fumigatus* causes a myriad of pulmonary disorders depending on the interplay between the virulence of the organism and the immunological status of the host; ABPA is a hypersensitivity phenomenon in an apparently immunocompetent host [2]. The disorder was first described in 1952 by Hinson et al. from the United Kingdom [3], one-and-a-half decades later from the United States [4] and almost two decades later from the Indian subcontinent [5]. The interest in this entity is due to treatment-responsive nature of this condition. In fact, early diagnosis and treatment can prevent the onset and/or progression to end-stage lung disease (characterized by bronchiectasis and pulmonary fibrosis) [6]. India is the world's second largest populated country, and the prevalence of ABPA complicating asthma has been reported to be significantly higher in the Indian subcontinent [7, 8]. This review attempts to describe the burden and distinctive character of ABPA in India.

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Burden of ABPA

An increasing number of cases of ABPA have been diagnosed in the last two decades [9–19], possibly due to heightened physician awareness and the widespread availability of commercial immunological assays for the diagnosis of ABPA [20]. Initially, the disorder was thought to be rare in North America [21], but subsequent reports disproved this myth [22, 23]. ABPA is far more common than previously thought and truly has a global presence. The community prevalence of ABPA complicating bronchial asthma remains unknown because of the lack of population-based studies. The prevalence in sequentially referred patients to secondary care has been estimated between 0.7 and 3.5 % [9, 11, 18, 24, 25], with the average being about 2.5 % [26]. Most of the data on the prevalence of ABPA comes from tertiary care cohorts and is thus not representative of the general population. In a meta-analysis, we found the reported prevalence of ABPA in bronchial asthma ranging from 2 to 32 % from different centers with a pooled prevalence of about 12.9 % (95 % confidence intervals [CI] 7.9–18.9). The prevalence of ABPA in *Aspergillus*-sensitized bronchial asthma varied from 6 to 68 % with the pooled prevalence being 40 % (95 % CI 27–53) [8.] In a scoping review, Denning et al. [26] estimated the global burden of ABPA in asthma of about 4.8 million (worldwide asthma population of about 193 million), using the ABPA prevalence figure of 2.5 %.

The reported prevalence of ABPA involving asthma, from India, is generally higher than that reported from other centers. Of the ten studies published in this millennium on the prevalence of ABPA, seven are from India [9–18]. The prevalence of ABPA in asthma is significantly higher in the Indian studies compared to studies published from other countries (292/1855 [15.7 %] vs. 24/707 [3.3 %]; $p < 0.00001$) [9–18]. The prevalence of ABPA is even higher in severe acute asthma. In a study of 57 consecutive patients with severe acute asthma, the prevalence of ABPA was found to be 38.6 % compared to 20.5 % in the outpatient asthma group [27]. The best guesstimate for the population prevalence of ABPA complicating asthma in India is about 5 %. Using this figure, the burden of ABPA in India was estimated to be about 1.38 million in an adult asthmatic population of about 27.7 million (In peer review).

Distinct Character of ABPA in India

Occurrence of ABPA in Conditions Other than Asthma

Allergic bronchopulmonary aspergillosis most commonly complicates the course of patients with preexisting bronchial asthma (or CF). In fact, bronchial asthma is an essential diagnostic criterion for the diagnosis of ABPA [2, 28]. However, ABPA has been described *de novo* (i.e., in those without any predisposing condition) [29], and in several predisposing conditions other than bronchial asthma. We first documented a case of ABPA in a patient with chronic obstructive pulmonary disease (COPD) [30]. Subsequently, in a study of 200 consecutive COPD patients (and 100 healthy controls), *Aspergillus* sensitization was found in 17 (8.5 %) patients with COPD as compared to none in the control group while two (1.0 %) COPD patients fulfilled the serologic criteria for the diagnosis of ABPA [31]. These findings have also been confirmed from other centers [32–34].

The healed fibrocavitary lesions of pulmonary tuberculosis (PTB) favor the growth of *Aspergillus*, and we hypothesized that these patients may develop allergic *Aspergillus* sensitization and possibly ABPA. In a case–control study, 50 consecutive symptomatic new referrals with PTB-related fibrocavitary disease (and 50 controls) underwent spirometry, *Aspergillus* skin test, serum IgE levels (total and *A. fumigatus* specific), serum precipitins against *A. fumigatus*, eosinophil count and computed tomography of the chest. *Aspergillus* sensitization was defined as either a positive *Aspergillus* skin test or *A. fumigatus* IgE > 0.35 kUA/L. *Aspergillus* sensitization was present in 16 (32 %) cases and two (4 %) controls. Fourteen cases (one control) had IgE values $> 1,000$ IU/mL and two cases manifested eosinophilia [35].

Given the high prevalence of ABPA in India, we investigated the role of environmental factors in causation of ABPA. In a prospective case–control questionnaire-based study, 202 subjects of asthma (103 and 99 *Aspergillus* unsensitized and sensitized asthma, respectively) and 101 ABPA were investigated for living conditions (home environment, the presence of moisture in the walls, details of house type, the presence of separate kitchen), use of water coolers, type of fuel, and contact with farms, cattle and

pets. We found no significant differences in environmental factors in the ABPA population compared to asthmatic patients except for a higher rural residence in ABPA (47 vs. 66 %, $p = 0.007$) [36]. Thus, it is likely that environmental factors are probably of less significance than individual host genetic susceptibility. The reason for a higher prevalence of ABPA in rural areas of India remains unclear as McCarthy et al. [37] had reported that majority of their patients were urban dwellers. Familial occurrence of about 5 % has been documented in ABPA [38]. Several genetic polymorphisms have been described in patients with ABPA [2, 39]. Polymorphisms in the genes encoding mannose-binding lectin and surfactant protein A2 have been described in the Indian population [40, 41]; however, host susceptibility factors are yet to be systematically explored in the Indian patients.

Clinical Presentation

The most common presentation of ABPA is that with poorly controlled asthma [42]. Some patients may also manifest low-grade fever, hemoptysis, productive cough, weight loss and malaise. Interestingly, in our series of 155 cases, almost 19 % of our patients had well-controlled asthma although with the use of asthma medications [13]. In fact, several patients with extensive radiological involvement are relatively asymptomatic. Hence, ABPA should be actively sought for in all patients irrespective of disease severity or control. Despite the high burden of ABPA in India, almost one-third of the patients are still misdiagnosed as pulmonary tuberculosis [43] and underscores the need for better training of physicians and pulmonary physicians, in recognition of this malady [44].

Immunological Findings

Aspergillus sensitization is considered as the first step in the pathogenesis of ABPA [45, 46], which can be determined using either *A. fumigatus* specific IgE or *Aspergillus* skin test. The cutoff of *A. fumigatus* specific IgE for defining *Aspergillus* sensitization is a level >0.35 kUA/L [2]. At this value, the sensitivity and specificity of specific IgE was found to be 100 and 69 %, respectively, making *A. fumigatus* specific IgE the preferred test for screening asthmatic patients for ABPA [19]. *Aspergillus* skin test was previously

advocated as the screening test for *Aspergillus* sensitization. An immediate cutaneous hyperreactivity (type 1 hypersensitivity to *A. fumigatus* antigens) represents the presence of *A. fumigatus* specific IgE antibodies. Using latent class analysis, the sensitivity of skin test in diagnosis of ABPA was found to be 88–94 % [19] and is thus no longer the preferred test for ABPA screening.

Serum IgE values are useful investigation in the management of ABPA. Although not good as a screening test [19], a normal serum IgE (in a patient not on systemic glucocorticoids) excludes ABPA as the cause of patient's current symptoms. With treatment, serum IgE levels start declining, but in most patients do not reach normal values. Hence, serial estimations of IgE need to be performed to determine the 'new' baseline value. This new baseline value represents an important tool in follow-up of patients, and an increase in IgE levels may signify an impending exacerbation. IgE levels are significantly raised in the Indian asthmatic population even without ABPA possibly due to worm infestations and other allergies. In one study, almost 70 % of asthmatics in our chest clinic had IgE $> 1,000$ IU/mL [19]. Thus, increase in serum IgE has to be correlated with radiological and/or clinical manifestations.

Serum precipitins (or specific IgG) against *A. fumigatus* are not specific for ABPA and increased values can be encountered in other forms of aspergillosis especially chronic pulmonary aspergillosis (CPA) [47]. A peripheral blood eosinophil count $>1,000$ cells/ μ L has been considered as a major criterion for the diagnosis of ABPA. In a study involving 209 ABPA patients, we found the median eosinophil count at diagnosis of 850 cells/ μ L, and about 60 % of ABPA cases had an eosinophil count $<1,000$ cells/ μ L [48]. Thus eosinophil count is not a specific test in the diagnosis of ABPA. Unfortunately, in India, peripheral blood eosinophil count because of its low cost and easy availability, is used for screening asthmatic patients for ABPA and is one important cause for missed diagnosis [49].

Radiological Manifestations

Radiological investigations are helpful in establishing the initial diagnosis of ABPA and for assessment of the pathologic sequelae in different stages of the disease. High-resolution CT of the chest is more

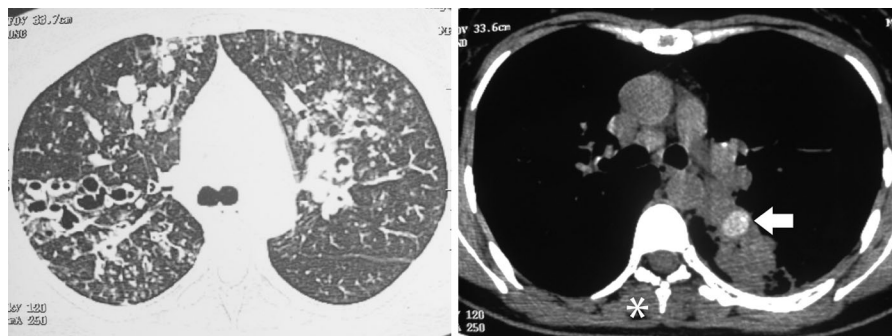


Fig. 1 High-resolution computed tomography images in two different patients with allergic bronchopulmonary aspergillosis. Lung windows (*right panel*) show extensive bronchiectasis, centrilobular nodules and tree-in-bud opacities. Bronchiectasis

can be seen extending to the periphery in the right lung. The soft tissue windows (*left panel*) show high-attenuation mucoid impaction (*arrow*). The mucoid impaction is visually denser than the paraspinal skeletal muscle (*asterisk*)

sensitive than chest radiograph in detecting radiological manifestations of ABPA [50]. The common radiological manifestations include fleeting pulmonary opacities, bronchiectasis, atelectasis, mucus plugging (both hypodense and hyperattenuating), centrilobular nodules and tree-in-bud opacities and mosaic attenuation due to air-trapping [51]. Central bronchiectasis with peripheral tapering of bronchi was believed to be *sine qua non* for the diagnosis of ABPA. Bronchiectasis is arbitrarily defined as central when confined to medial half or two-thirds of the lung field. In ABPA, bronchiectasis can extend to the periphery in 26–39 % of the lobes involved, depending on the definition used (Fig. 1) [51]. Hence, central bronchiectasis is no longer considered a specific criterion for ABPA [2]. It is important to diagnose ABPA before development of bronchiectasis, i.e., in the serological stage [52], as bronchiectasis indicates permanent lung damage. Unfortunately, in India, almost 75 % of the patients are diagnosed with bronchiectasis [53].

The pathognomonic radiological finding of ABPA is high-attenuation mucus (Fig. 1) [54]. Mucus impaction in ABPA is usually hypodense but in several patients the mucus is denser than the paraspinal skeletal muscle, which is then termed as high-attenuation mucus [55]. The presence of high-attenuation mucus is conclusive evidence that the etiology of bronchiectasis is ABPA. Uncommonly described from other centers, high-attenuation mucus is seen in almost 20 % of our patients. This could reflect recognition bias or could really represent a different spectrum of ABPA. We have also found that patients with HAM have severer immunological findings compared to other patients and are also prone for

recurrent relapses [13, 15, 53]. Several other radiological findings also have prognostic implications in ABPA. We have shown that the severity of bronchiectasis and the presence of aspergilloma are also markers of recurrent relapses [13, 15, 56].

Diagnostic Criteria and Staging

The Rosenberg–Patterson criteria (8 major, 3 minor) are the most commonly used benchmark for the diagnosis of ABPA [28]. However, this criterion has several limitations. There is no agreement on the number of major criteria that should be present to make the diagnosis. All the components offer equal weightage, while obviously some are more important than others. Finally, there is no consensus on the cutoff values for IgE levels and eosinophil counts. ABPA was also classified into five stages by Patterson et al. [57], although a patient need not pass through all the stages sequentially. The major drawback of this staging system was the lack of precise definitions at each stage. To overcome these shortcomings, the International Society for Human and Animal Mycology has formed a working group, which convened an International workshop to discuss these issues. The working group has laid down new criteria for diagnosis and staging (Table 1). The criteria are objective and precise; however, they are still consensus-based and require more evidence for cutoffs of IgE and eosinophil count. It is likely that there would be different cutoffs for different ethnic populations. For example, the cutoff of IgE > 180 IU/mL was 91 %

Table 1 Newly proposed criteria for diagnosis and staging of allergic bronchopulmonary aspergillosis

Diagnostic criteria for ABPA	
<i>Predisposing conditions</i>	
Bronchial asthma, cystic fibrosis	
<i>Obligatory criteria (both should be present)</i>	
<i>Aspergillus</i> skin test (type I) positivity or increased <i>A. fumigatus</i> specific IgE levels (>0.35 kU/L)	
Increased total IgE levels ($>1,000$ IU/mL) ^a	
<i>Other criteria (at least two of three)</i>	
The presence of serum precipitating or IgG antibodies against <i>A. fumigatus</i>	
Chest radiographic pulmonary opacities consistent with ABPA	
Total eosinophil count >500 cells/ μ L in steroid naive patients	
Stages of ABPA	
0	Asymptomatic
1	Acute
1a	With mucoid impaction
1b	Without mucoid impaction
2	Response
3	Exacerbation
4	Remission
5a	Treatment-dependent ABPA
5b	Glucocorticoid-dependent asthma
6	Advanced ABPA

^a An occasional may meet all the criteria with IgE level $<1,000$ IU/mL

sensitive and 90 % specific in a United Kingdom CF cohort for the diagnosis of ABPA [58]. Recently, we have compared the immunological findings in patients with ABPA and asthma using receiver operating characteristic curve analysis [59]. ABPA (76 patients; 64 bronchiectasis, 12 without bronchiectasis) was separated from asthma using the best cutoff values of total IgE, *A. fumigatus* IgE and total eosinophil count of 2,347 IU/mL, 1.91 kUA/L and 507 cells/ μ L, respectively. The sensitivity and specificity of these parameters were 87 and 81 %; 99 and 87 %; and, 79 and 76 %, respectively. The combination of these three tests at the aforementioned cutoffs provided 100 % specificity [59].

A new radiological staging for ABPA has also been proposed [2]. This summarizes all the previous radiological classifications into one composite staging system. ABPA is now classified based on CT chest into four stages namely: (a) Serological ABPA (ABPA-S): these are patients who meet the diagnostic criteria for ABPA but do not manifest any abnormality resulting from ABPA on CT chest; (b) ABPA with bronchiectasis (ABPA-B): patients meeting all criteria for ABPA along with bronchiectasis on CT chest; (c) ABPA with high-attenuation mucus (ABPA-HAM): all the diagnostic features of ABPA including the presence of high-attenuation mucus; and, (d) ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF): patients with ABPA with at least two to three radiological features such as pulmonary fibrosis, parenchymal scarring, fibrocavitary lesions, aspergilloma and pleural thickening without the presence of mucoid impaction or high-attenuation mucus.

Diagnostic Algorithm

In our chest clinic, we now screen all asthmatic patients with *A. fumigatus* specific IgE [60]. If the value is less than 0.35 kUA/L, then the patient has no ABPA and investigations for sensitization to other fungi is required only if the asthma is uncontrolled or there are unexplained pulmonary opacities. If the value is greater than 0.35 kUA/L, the next step is to order a total IgE. If the value of total IgE is less than 500 IU/mL, then ABPA is excluded. However, if the value is greater than 500 IU/mL, then other tests including serum precipitins, *Aspergillus* skin test, eosinophil count and CT of the thorax need to be

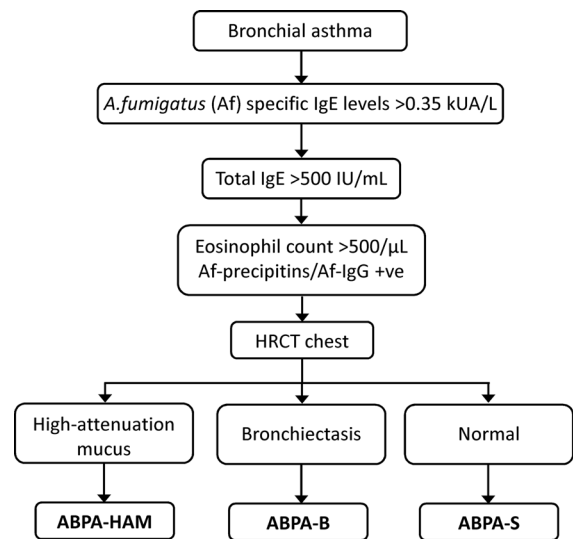


Fig. 2 Algorithm for diagnosis of ABPA followed in our Institute

performed to confirm the diagnosis and determine the stage of the disease (Fig. 2) [7].

Treatment Considerations

The principles of managing ABPA include institution of anti-inflammatory therapy (systemic glucocorticoids) to control the immune hyperactivity, and the use of antifungal agents (azoles, nebulized amphotericin B) to diminish the fungal load in the tracheo-bronchial tree. The goals of therapy include control of asthma, prevention/treatment of acute exacerbations of ABPA and preventing the development/progression of bronchiectasis.

Oral Glucocorticoids

Oral corticosteroids are considered the treatment of choice although there are no randomized trials on its efficacy, dose and duration. Two regimes are commonly used namely the low-dose regimen (prednisolone 0.5 mg/kg/day for 1–2 weeks, then on alternate days for 6–8 weeks, subsequently taper by 5–10 mg every 2 weeks and discontinue) [61], and the high-dose regimen (prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks, taper by 5 mg every 6 weeks; treatment duration for at least 6 months) [43]. Currently, the choice between the two regimens is based on the

institutional preference. However, patients treated with high-dose steroids had a lower propensity to develop glucocorticoid-dependent ABPA compared to low-dose steroids (17/126 [14 %] vs. 38/84 [45 %]) [62]. A randomized trial on the efficacy and safety of these two regimens in ABPA has been completed (clinical trials.gov; NCT00974766).

Anti-Fungal Agents

Two randomized trials have demonstrated the efficacy of azoles in ABPA; however, both the trials have limitations of a small sample size and limited duration of follow-up [63, 64]. Currently, itraconazole is used at a dose of 200 mg twice daily for at least 16–20 weeks. The indications include first relapse of ABPA (to induce remission) or glucocorticoid-dependent ABPA (to maintain remission without steroids). Therapeutic drug monitoring has recently been recommended for azoles as it increases the likelihood of a successful outcome, potentially prevents drug-related toxicity and can decrease the chances of emergence of drug resistance [65]. In India, azoles are either not used because of cost considerations or are used at lower doses or shorter duration with predominance of generic preparations [66]. Further, therapeutic drug monitoring is not widely available, even at tertiary care centers. All these factors may contribute to the risk of drug resistance [67]. Azoles are generally used in combination with steroids; however, monotherapy with azoles is an attractive proposition. A monotherapy of itraconazole (and voriconazole) versus oral glucocorticoids has completed recruitment of patients and the results of this trial will possibly help in elucidating the role of azole monotherapy in ABPA (clinicaltrials.gov; NCT01321827, NCT01621321). Two clinically important drug interactions that should not be forgotten while using azoles is the profound increase in drug levels of methylprednisolone and certain inhaled steroids (especially budesonide) due to inhibition of cytochrome p450, which can cause cushingoid effects and long-term adrenal failure [68, 69].

Novel Therapies

Newer azoles (voriconazole, posaconazole) should be reserved in patients who experience no/poor response (or encounter adverse reactions) with itraconazole [70, 71]. Aerosolized amphotericin B can be used along

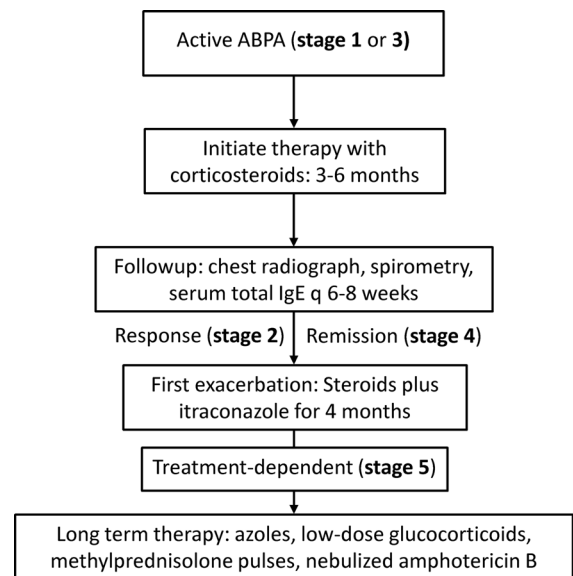


Fig. 3 Algorithm for treatment of ABPA followed in our Institute

with oral steroids or azoles and its primary role is likely to be in the maintenance of remission in ABPA [72]. Pulse doses of methylprednisolone can be used in patients refractory to conventional therapies, in refractory ABPA exacerbations or to decrease the adverse effects associated with daily oral prednisolone [73]. Omalizumab (anti-IgE) has also been evaluated in ABPA in cases not responding (or in those experiencing adverse reactions) with standard treatment [74].

Treatment Protocol

In our chest clinic, we initiate therapy with oral steroids in treatment-naïve patients. The patients are followed up at 6–8 weeks interval with inquiry into clinical symptoms along with chest radiograph, spirometry and IgE measurements. On first exacerbation, the patient is started on itraconazole and steroids. In treatment-dependent patients, long-term therapy with one or more of the following is initiated: low-dose steroids, azoles, pulse methylprednisolone or nebulized amphotericin B (Fig. 3) [7, 60].

Future Directions

Further research is required to determine the cause for higher prevalence of ABPA in Indian asthmatic

patients. Similarly, the higher prevalence of certain radiological findings such as high-attenuation mucus in the Indian population requires investigation. It is likely that environmental factors are of less significance than individual host genetic susceptibility in the pathogenesis of ABPA. Future research should focus on host susceptibility factors in causation of ABPA.

Conflicts of interest None.

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