

Allergic bronchopulmonary aspergillosis in asthma: epidemiological, clinical and therapeutic issues

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Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder caused by immunologic reactions to antigens released by *Aspergillus fumigatus*, a ubiquitous fungi colonizing the tracheobronchial tree of asthmatic patients. The clinical presentation is usually poorly controlled asthma, recurrent pulmonary opacities and bronchiectasis. The prevalence of ABPA in asthma clinics may be as high as 13% with a global burden of almost 5 million patients. *A. fumigatus*-specific IgE level is the most sensitive test in diagnosis of ABPA, and all asthmatic patients should be routinely screened with *A. fumigatus*-specific IgE levels for early diagnosis. The goals of managing ABPA include control of asthma, prevention and treatment of acute exacerbations, and preventing the development or progression of bronchiectasis. Glucocorticoids are the treatment of choice with itraconazole reserved for those with recurrent exacerbations and glucocorticoid-dependent disease. There is a dire need for newer treatment approaches including oral antifungal agents and immunomodulatory therapy.

The disorders caused by *Aspergillus* spp. depend on the interaction between the virulence and load of the organism, and the host response to the fungi [1]. *Aspergillus* spp. can cause a variety of pulmonary diseases loosely classified as simple colonization (aspergilloma), allergic (allergic bronchopulmonary aspergillosis [ABPA] and allergic *Aspergillus* sinusitis) and invasive (chronic pulmonary aspergillosis [CPA] and invasive pulmonary aspergillosis) [2]. ABPA is a pulmonary disorder caused by an allergic response to the fungus *Aspergillus fumigatus* [3]. First described in 1952 by Hinson *et al.*, *A. fumigatus* can complicate the course of disease in patients with asthma and cystic fibrosis (CF) [4]. The disease can manifest in childhood [5] and may go unrecognized for years or even decades [6]. Patients usually present with poorly controlled asthma, recurrent pulmonary infiltrates and bronchiectasis [7]. In the last decade, the number of reported ABPA cases have been on the rise, which possibly reflects heightened physician awareness and the good availability of immunologic assays for the diagnosis of ABPA [8–11]. Recently, a working group on 'ABPA complicating asthmatics' has been formed under the auspices of the International Society for Human and Animal Mycology, which has laid down new criteria for diagnosis and staging [12]. Herein, we

summarize the advances in the epidemiology, diagnosis and treatment of ABPA complicating asthma.

Nomenclature

Aspergillus sensitization (AS), defined as demonstration of immediate cutaneous hypersensitivity to *A. fumigatus* antigens or presence of elevated IgE levels against *A. fumigatus*, is the first step in development of ABPA [13]. Fungal sensitization is common in asthma [14]; however, if the asthma is well controlled, the patients are classified as asthma associated with fungal sensitization [15]. Some patients with asthma and fungal sensitization manifest poor asthma control, and these patients are then termed as 'severe asthma with fungal sensitization' (SAFS) [14,16]. On exposure to *A. fumigatus*, patients of asthma associated with fungal sensitization/SAFS with genetic predisposition manifest, increasing Th₂ immune responses compared with those without, and eventually present with clinical and radiological manifestations of ABPA [17]. Other risk factors include exposure to a high concentration of *Aspergillus* spores [18], and the virulence of *A. fumigatus per se* [19]. Patients with ABPA who fulfill other diagnostic criteria but lack bronchiectasis on computed tomography (CT) of the chest, are labeled as serological ABPA

Keywords

■ ABPA ■ allergic bronchopulmonary aspergillosis ■ allergic bronchopulmonary mycosis ■ aspergillosis ■ *Aspergillus* ■ asthma ■ azoles

(ABPA-S) [20], while those with bronchiectasis on a CT scan of the chest are labeled as ABPA-B [12]. Allergic bronchopulmonary mycosis is an ABPA-like syndrome caused by fungi other than *A. fumigatus* [21].

Epidemiology

The incidence or prevalence of AS complicating asthma is unknown owing to the lack of community-based data for this purpose. The National Health and Nutrition Examination Survey found the prevalence of AS to be 6.4% using *A. fumigatus*-specific IgE levels [22], and these remain the only general population-based data for AS. In asthma and chest clinics, the prevalence of AS is very high. In a recent systematic review, the prevalence of AS in bronchial asthma was found to range between 15 and 48% with the pooled prevalence being 28% (95% CI: 24–34) [23]. The population prevalence of ABPA complicating asthma remains unclear; however, it is believed to be approximately 1–3.5% based on the prevalence reported from secondary care cohorts in various countries [8,24–28]. The prevalence of ABPA in chest or asthma clinics is very high, ranging from 2 to 32% with the pooled prevalence being 12.9% (95% CI: 7.9–18.9) [23]. The prevalence of AS and ABPA is even higher (51 and 39%, respectively) in patients with severe acute asthma admitted in the intensive care unit [29].

Using a mathematical model, Denning *et al.* estimated the worldwide asthma population to be 193 million with a global burden of 4.8 million (range: 1.4–6.8) ABPA patients, assuming a prevalence of ABPA in asthma of 2.5% [30]. The burden of ABPA in these calculations varies with the prevalence of ABPA in asthma. With the same estimates, the number of adult asthmatics and ABPA patients in India are estimated at 23.7 million and 592,719, respectively. However, if prevalence rates of ABPA in asthma of 5, 7 and 20% are applied, the gross numbers of ABPA patients are estimated to rise to 1.2, 1.7 and 4.7 million, respectively, in India alone [31].

Diagnostic tests

Clinical symptoms and signs have poor sensitivity and specificity in diagnosis of ABPA [7], and the diagnosis is always made on immunological investigations. Although the disorder can be suspected from clinical presentation and radiology, the aim should be to diagnose ABPA before bronchiectasis occurs. Thus, asthma clinics should routinely screen all asthmatic patients for ABPA using the strategy outlined below.

Serum IgE antibodies specific to *A. fumigatus*

An elevated level of *A. fumigatus*-specific IgE antibodies can be considered as the most sensitive test in the diagnosis of ABPA [32]. In a recent study using latent class analysis, we demonstrated that a *A. fumigatus*-specific IgE value >0.35 kUA/l has 100% sensitivity in the diagnosis of ABPA while the sensitivity of intradermal *Aspergillus* skin test was 88–94% [32]. However, this only applies to symptomatic patients and up to 30% of individuals sensitized to a given source may be asymptomatic [33]. Since AS is the first step in the development of ABPA, detection of *Aspergillus* hypersensitivity using specific IgE levels against *A. fumigatus* should be the first step in screening asthmatic patients for ABPA. One of the problems of *A. fumigatus*-specific IgE is the lack of standardized antigen preparations. Hence, it is recommended that the method and the antigen used for detection should be uniform to allow comparison. For example, we use the ImmunoCAP® fluorescent enzyme immunoassay system (Phadia, Stockholm, Sweden) for determining specific IgE levels in patients with ABPA.

Total serum IgE levels

The total serum IgE level is a quintessential tool both in the diagnosis and follow-up of ABPA. A normal serum IgE, in the absence of concomitant systemic corticosteroid therapy, virtually excludes active ABPA as the cause of a patient's current symptoms. There is no consensus on the cut-off value of total IgE level that should be used for the diagnosis of ABPA, owing to the wide variation of IgE concentrations in normal individuals, atopic asthmatics and ABPA patients [34,35]. Furthermore, the IgE values are reported in different units leading to erroneous interpretation (1 IU/ml = 2.4 ng/ml). The cut-offs may also be different in ABPA complicating asthma or CF [36]. The 'ABPA in asthmatics' working group has proposed a cut-off value of 1000 IU/ml rather than 500 IU/ml, as the latter is often encountered in AS and SAFS [12]. The diagnosis should be based on the earliest IgE report available, not on the value obtained after treatment as IgE levels fall rapidly after treatment. In a clinical context where pre-ABPA baseline IgE values are available (e.g., annual IgE screening in CF), a sharp (e.g., two- to four-fold) rise from the baseline indicates the diagnosis of ABPA despite the IgE value being <1000 IU/ml [37]. The serum IgE levels start declining after treatment, but in most patients

do not reach the normal value [38,39]. The serum IgE also represents an important tool in follow-up of patients, and a 50% increase in IgE levels may signify an impending exacerbation [39].

Serum IgG (precipitins) against

A. fumigatus

Serum precipitins (IgG) against *A. fumigatus* can be demonstrated in 69–90% of patients with ABPA [11,40–43], but also in 10% of asthmatics without ABPA [3]. Two commercial assays (ImmunoCAP and *Aspergillus* IgG, Plate-lia™ [Bio-Rad, CA, USA]) are more sensitive measures of *Aspergillus* IgG antibodies compared with the traditional counterimmuno-electrophoresis, as the former are isotype-specific while the latter is not [44]. The sensitivity and specificity of *Aspergillus* IgG in ABPA remains unknown, and high levels can be encountered in other forms of aspergillosis, especially CPA.

Peripheral eosinophilia

A peripheral blood eosinophil count of over 1000 cells/ μ l has been conventionally considered a major criterion for the diagnosis of ABPA. We have also observed asthmatic patients being screened for ABPA with eosinophil counts; however, the sensitivity of total eosinophil count >1000 cells/ μ l is only 30%. In a large study it was demonstrated that only 40% of patients with ABPA manifested an eosinophil count >1000 cells/ μ l at diagnosis [45]. Hence, the 'ABPA in asthmatics' working group has proposed that the cut-off value of eosinophil count be reduced to 500 cells/ μ l [12]. The earliest eosinophil count should be employed for diagnosis, as the counts decline with steroid therapy.

Aspergillus skin test

An immediate cutaneous hypersensitivity to *A. fumigatus* antigens represents the presence of IgE antibodies specific to *A. fumigatus*. The test can be performed using either a skin prick test or an intradermal injection [13,15]. The sensitivity of a positive result in the diagnosis of ABPA is approximately 90% [32], and approximately 40% of asthmatics without ABPA can also demonstrate a type 1 response to *Aspergillus* antigen [46]. The sensitivity of the skin test may vary on the quality of the antigen (commercial vs indigenous) used for performing the test [23], and also depends of the quality of the extract used. None of the extracts commercially available are able to detect all patients allergic to *A. fumigatus* independently of the ABPA status.

Sputum cultures for *A. fumigatus*

A. fumigatus is an ubiquitous fungi and its growth in sputum is not diagnostic of ABPA; moreover, the growth of this fungus can also be seen in other pulmonary diseases [40]. In ABPA, the rates of culture positivity vary depending on the number of specimens examined and the method employed for sputum processing [9,47]. It is of interest to note that the vast majority of culture-negative ABPA patients have detectable *A. fumigatus* DNA in their sputum [48].

Pulmonary function tests

Routine pulmonary function tests are helpful for categorizing the severity of asthma and the underlying lung disease. However, lung function tests can be normal in ABPA and a normal spirometry should not exclude the diagnosis of ABPA [10]. Spirometry is extremely helpful during follow-up of the patient and can serve as an objective criteria for improvement.

Role of recombinant *Aspergillus* antigens

The recombinant allergens Asp f1, f2, f3, f4 and f6 have been assessed for their analytical performance in differentiating AS from ABPA [49–53]. Antibodies against recombinant (r)Asp f1 and rAsp f3 are elevated in both AS and ABPA while antibodies against rAsp f4 and rAsp f6 are elevated only in ABPA [50,53]. The quality of a recombinant protein depends not only on the expression system used but also on the purification and refolding protocols used for their production. This may be a factor for inconsistency in results obtained from different centers [49]. There is need for a large multicentric study on the diagnostic value of these allergens.

Radiological investigations

High-resolution CT scan of the chest is the preferred radiological investigation in ABPA as it discerns findings not visualized on the chest radiograph and allows better evaluation of small airway abnormalities [54]. The findings from CT scans of the chest include bronchiectasis, mucoid impaction, centrilobular nodules, tree-in-bud opacities, mosaic attenuation and pleuropulmonary fibrosis [55,56]. Bronchiectasis has been arbitrarily classified as central if confined to the medial two-thirds (or medial half) of the lung [57]. Central bronchiectasis (CB) with peripheral tapering of bronchi considered the most characteristic finding of ABPA (FIGURE 1). However, bronchiectasis in ABPA can extend to the periphery, and peripheral bronchiectasis can be observed in



Figure 1. High-resolution computed tomography of the chest (lung windows) showing evidence of bronchiectasis. Please note that the bronchiectasis is not strictly central.

up to 61% of the lobes involved in bronchiectasis [58]. The significance of CB as a specific finding for ABPA is thus questionable. In fact, in one study, the sensitivity of CB in the diagnosis of ABPA was only 37% [59]. Muroid impaction of airways is a common finding. Mucus plugs in ABPA are generally hypodense but can have high CT attenuation values in up to 20% of patients [10,60]. High-attenuation mucus (HAM), defined as mucus visually denser than paraspinal skeletal muscle is a pathognomonic finding of ABPA (FIGURE 2) [11,61–63], and has the highest specificity in diagnosis of ABPA [32]. HAM remains an important radiological sign in distinguishing ABPA from other causes of bronchiectasis as its presence confirms ABPA as the cause of the underlying bronchiectasis. Upper lobe pleural thickening, fibrocavitary disease and aspergilloma probably represent another complication, namely CPA [64].

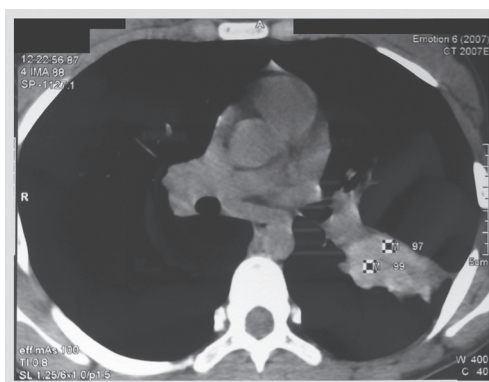


Figure 2. High-resolution computed tomography of the chest (mediastinal windows) showing presence of mucoid impaction. The mucoid impaction is high-attenuation; that is, the mucus is denser than the paraspinal skeletal muscle with computed tomography Hounsfield values exceeding 90.

Diagnostic criteria

There is no single test that can confirm the diagnosis of ABPA, and in a recent study no test was found to demonstrate both good sensitivity and specificity [32]. The Patterson criteria (eight major, three minor) are the most widely used yardstick for diagnosing of ABPA [65,66]. However, there is no agreement on the number of major or minor criteria required to make a diagnosis, and the criteria offers similar score for all parameters [67]. Moreover, the cut-off values for IgE levels and eosinophil count have not been defined [68]. The 'ABPA in asthmatics' working group have proposed revisions to the criteria (Box 1). Bronchiectasis has been removed from the diagnostic criteria as ABPA may present without bronchiectasis. The minor criteria recommended by Patterson *et al.* have also been removed as they are not essential for diagnosis [65].

Diagnostic algorithm

The first test in the workup of an asthmatic being evaluated for ABPA should be *A. fumigatus*-specific IgE levels, with a value <0.35 kUA/l practically excluding ABPA. In the past, skin prick or intradermal reactivity to *Aspergillus* antigen was the preferred method for screening asthmatic patients for ABPA. However, we have recently shown that up to 12% of patients can be potentially missed if skin test is used for screening [32]. If *A. fumigatus*-specific IgE levels are raised, total serum IgE and precipitins to *Aspergillus* should be assayed. ABPA is excluded if the serum total IgE concentration is <1000 IU/ml and serum precipitins to *Aspergillus* are negative. If either of the tests are positive, then other investigations like chest radiograph, eosinophil count and high-resolution CT of the chest should be performed. Many patients may not meet all diagnostic criteria for ABPA. These patients should be labeled as 'ABPA-at risk' and require close follow-up.

Stages of ABPA

Once a diagnosis of ABPA is made, the disease should be staged on clinical and radiological criteria. This is an important step in management as it allows accurate definition of response to therapy and helps identify exacerbations at the earliest stage. Although ABPA has been classified into five stages [69] there is lack of precise definitions and, hence, considerable ambiguity in description of these stages [10]. The 'ABPA in asthmatics' working group have provided a new staging with precise definitions (TABLE 1) that would be helpful in managing patients in daily practice as well as in clinical trials. The new staging includes seven

Box 1. Diagnostic criteria for allergic bronchopulmonary aspergillosis.**Predisposing condition**

- Bronchial asthma

Obligatory criteria (both should be present)

- *Aspergillus fumigatus*-specific IgE level >0.35 kUA/l or type 1 skin reaction to *Aspergillus* antigen
- Total IgE value >1000 IU/ml[†]

Other criteria (at least two of three)

- Presence of serum IgG antibodies (precipitins) against *A. fumigatus*
- Radiographic pulmonary opacities consistent with ABPA[‡]
- Total eosinophil count >500 cells/μl in steroid-naïve patients

[†]If the patient meets all other criteria, an IgE value <1000 IU/ml may be acceptable.

[‡]Chest radiographic features may be either transient (i.e., consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities and fleeting opacities) or permanent (i.e., parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

ABPA: Allergic bronchopulmonary aspergillosis.

Reproduced with permission from [12].

stages (stage 0–6); however, a patient need not progress from one stage to the other sequentially.

Patients in stage 0 have fully controlled asthma and ABPA is diagnosed on routine screening of asthmatic patients. Symptomatic patients who meet all the criteria for diagnosis of ABPA (Box 1) are classified as stage 1. Patients in stage 1 are further classified as 1a or 1b on the presence or absence of mucoid impaction on the chest radiograph. With treatment, there is improvement in symptoms and lung function, clearing of radiographic opacities and at least a 25% decline in IgE levels by 8 weeks; this is stage 2. Repeated measurements of IgE levels need to be performed to determine the 'new' baseline value for every individual patient, and an increase in IgE levels by 50% over the new baseline associated with clinoradiological worsening is defined as an exacerbation of the disease (stage 3). The radiological finding of aspergilloma and/or HAM predicts a patient who is likely to experience recurrent exacerbations [70,71]. If there are no ABPA exacerbations over the next 6 months after stopping therapy, the patient is said to be in remission (stage 4). Patients in remission should be followed up every 3–6 months for the first year and then annually, depending on the clinical status of the patient. Although some patients in stage 4 may enter into prolonged remission, it does not mean cure as exacerbations of the disease have been documented several years after remission [72]. Patients in stage 5 are of two types: the 'treatment-dependent ABPA', wherein the patients requiring repeated courses of steroids or azoles for prevention of ABPA exacerbations; while the 'glucocorticoid-dependent asthma' group requires continuous use of steroids for asthma control. Patients in stage 6 are those with widespread bronchiectasis and/or fibrosis

with poor lung function and eventual development of type II respiratory failure and cor pulmonale. It is important to note that the disease can be clinically, as well as immunologically active even in advanced stages, and may require treatment [73,74].

ABPA is classified radiologically as ABPA with CB (ABPA-CB) or ABPA-S, respectively, depending on the presence or absence of bronchiectasis [20,66]. ABPA-S is probably the earliest stage of ABPA with less severe immunologic findings compared with ABPA-CB [75]. ABPA has also been divided into three groups namely ABPA-S, ABPA-CB and ABPA-CB with other radiological findings [76]. In a study involving 234 patients with ABPA, we have categorized ABPA into ABPA-S, ABPA-CB and ABPA-CB with HAM [70]. The HAM-based classification scheme is most consistently associated with immunological severity from ABPA-S (mild), ABPA-CB

Table 1. Clinical staging of allergic bronchopulmonary aspergillosis in asthma.

Stage	Definition
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

ABPA: Allergic bronchopulmonary aspergillosis.

Reproduced with permission from [12].

Box 2. Radiological classification of allergic bronchopulmonary aspergillosis based on findings from computed tomography of the chest.

- Serological ABPA
- ABPA with bronchiectasis
- ABPA with high-attenuation mucus
- ABPA with chronic pleuropulmonary fibrosis

ABPA: Allergic bronchopulmonary aspergillosis.
Reproduced with permission from [12].

(moderate) to ABPA-CB with HAM (severe) [70]. The 'ABPA in asthmatics' working group has laid down a new radiological classification that incorporates all the current evidence on the radiological findings in ABPA. ABPA is now classified into four major categories (Box 2), namely ABPA-S, ABPA-B, ABPA-HAM and ABPA with chronic pleuropulmonary fibrosis. The radiological staging is helpful in predicting severity of the disease and has prognostic implications.

Treatment

The goals in management of ABPA include asthma control, prevention and treatment of acute exacerbations, and inhibiting the development or progression of bronchiectasis [12]. Not all ABPA patients require treatment. Patients with ABPA-S and well-controlled asthma may be safely followed up with treatment given only for asthma control. However, those with ABPA-B generally require an initial course of steroids, and the IgE levels and spirometry following treatment serving as the new 'baseline' against which further treatment is decided. Patients need close monitoring and treatment should be started once there is clinical and/or radiological worsening

with 50% increase in IgE levels above baseline. The treatment strategy of ABPA includes the use of anti-inflammatory therapy (systemic glucocorticoids) to control the immunologic activity, and the use of antifungal agents to diminish the fungal burden in the airways [2,3,77]. It is not clear whether treatment with steroids or itraconazole will prevent bronchiectasis and CPA.

Systemic glucocorticoids

Oral corticosteroids are widely accepted as the treatment of choice for ABPA although there are no randomized trials of steroids in ABPA. There is no agreement on the dose and duration of steroids, and broadly two different regimens (low dose vs high dose) have been used (Box 3). The use of low doses of glucocorticoids without antifungal therapy is associated with higher occurrence of recurrent relapses or glucocorticoid dependence (45%) [66]. A higher dosage of glucocorticoids has been shown to be associated with higher remission rates and a lower prevalence of glucocorticoid-dependent ABPA (13.5%) [10]. It is unclear whether a high dose or longer duration of corticosteroids is associated with better outcomes. A randomized controlled trial on the efficacy and safety of two different glucocorticoid dose regimens in ABPA has been completed [201]. Hopefully, the results of this trial will help to answer the question regarding dose of glucocorticoids in ABPA.

Itraconazole

Although systemic steroids are highly efficacious in the management of ABPA, up to 50% of patients can experience an exacerbation once they are tapered and almost 20–45% can become

Box 3. Drugs used in the management of allergic bronchopulmonary aspergillosis.**Oral glucocorticoids**

- Low-dose glucocorticoids [118]: Prednisolone 0.5 mg/kg/day for 1–2 weeks, then on alternate days for 6–8 weeks. Then taper by 5–10 mg every 2 weeks and discontinue
- High-dose glucocorticoids [10,119]: Prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks, then tapered by 5 mg every 6 weeks to continue for a total duration of at least 6–12 months
- Initial treatment of stages I and III should be started with steroids

Oral itraconazole

- Dose: 200 mg twice a day, for at least 16 weeks
- First relapse of ABPA (treatment should be started concomitantly with steroids) or glucocorticoid-dependent ABPA (to prevent exacerbations after controlling the exacerbation with glucocorticoids)

Monitoring

- History and physical examination, chest radiograph, total IgE levels and spirometry every 8 weeks
- Clinoradiological improvement along with $\geq 25\%$ decline in IgE level signifies satisfactory response to therapy
- Observe for adverse effects of treatment

ABPA: Allergic bronchopulmonary aspergillosis.
Data taken from [2,3,12].

glucocorticoid-dependent [10,66]. The risk of chronic steroid therapy also increases the propensity of adverse effects [78,79]. Azoles decrease the antigenic stimulus consequent to a reduction in fungal load, and thus attenuate the immune response [80]. Two randomized controlled studies (84 patients) have evaluated the role of itraconazole in ABPA [81,82]. Stevens *et al.* randomized 55 patients with 'glucocorticoid-dependent' ABPA to receive either itraconazole 200 mg twice daily or placebo, and itraconazole was demonstrated to have marginal benefits compared with placebo [81]. Wark *et al.* randomized 29 'clinically stable' ABPA patients to receive itraconazole or placebo. There was decline in sputum inflammatory markers, serum IgE levels and the number of exacerbations in the itraconazole arm [82]. Apart from the limitation of small sample size, neither study reported outcomes longer than 8 months in terms of relapses of ABPA. Itraconazole has also been used as a sole therapy in acute exacerbations of ABPA [82,83]. However, more data are needed to confirm the use of itraconazole as a monotherapy in acute stages of ABPA. A head-to-head comparison of itraconazole monotherapy with prednisolone in ABPA is underway (MIPA study) [202] and hopefully the results of this trial will clear this issue.

Other therapies

The delivery of corticosteroid aerosol achieves a high concentration in the airways with minimal systemic absorption. Although several small case series have reported the use of inhaled steroids in ABPA [84–90], the benefit is negligible. Not only are the studies heterogeneous in their inclusion of patients, but also, in many studies, the patients continued to receive oral steroids. A combination of nebulized amphotericin B and inhaled steroids has also been used for treatment of ABPA complicating CF [91–94]. The use of omalizumab (anti-IgE) in ABPA has been associated with marginal improvement in symptoms, reduction in exacerbations, improvement in lung function and decline in requirement of oral steroids [95–102]. However, the dose required is very high and thus expensive, and the data are mainly from case reports and case series. Monthly pulse doses of intravenous methylprednisolone have also been used for treatment of severe exacerbations and as a steroid-lowering strategy [103–105]. Newer antifungal agents including voriconazole [106–109] and posaconazole [110] are also possibly efficacious in ABPA, if tolerated. Currently, all these therapies may be tried in individuals with steroid-dependent

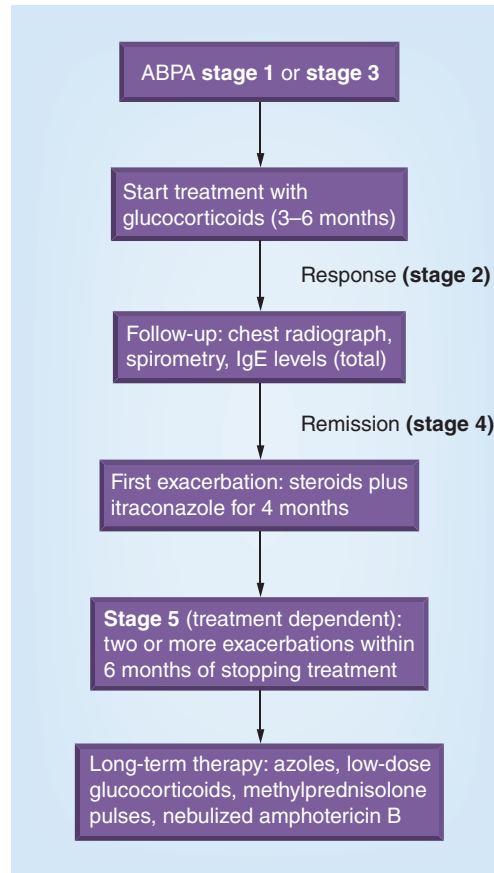


Figure 3. Treatment protocol followed in the chest clinic at the Postgraduate Institute of Medical Education and Research (Chandigarh, India).

ABPA: Allergic bronchopulmonary aspergillosis.

ABPA or in patients who develop treatment-related adverse reactions to glucocorticoids or itraconazole [77]. All patients with ABPA should be encouraged to participate in clinical trials to validate and refine the indications, risks and benefits of these new therapies.

Approach to treatment

The treatment protocol followed in our chest clinic (Postgraduate Institute of Medical Education and Research, Chandigarh, India) for the management of ABPA is shown in Figure 3. Patients in stage 0 may be followed up without any specific therapy in the absence of bronchiectasis. However, those with bronchiectasis or fleeting pulmonary opacities generally require treatment. Patients in stage 1 or 3 should receive treatment with steroids. The aim of therapy in ABPA is not normalization of IgE levels but a 25–50% decline in IgE associated with clinical, spirometric and radiological improvement [38,39]. Patients with lobar collapse should be reassessed at 3 weeks, and if the atelectasis persists

despite adequate therapy, therapeutic bronchoscopy should be performed. The initial treatment with steroids should be continued for at least 3–6 months. Serial measurements of IgE levels need to be performed during therapy to determine the 'new' baseline value for every individual patient during treatment. For the first exacerbation, a combination of steroids and itraconazole is recommended. Some patients after treatment may enter into remission. In those with recurrent exacerbations, one should consider prolonged therapy with any of the following, namely itraconazole, low-dose glucocorticoids, monthly pulses of methylprednisolone or nebulized amphotericin B. As many patients with ABPA require long-term therapy, patients should be advised about any side effects of therapy especially those of glucocorticoids. High doses of inhaled steroids should not be used as a single agent in the management of ABPA. The combination of inhaled steroids, especially budesonide (and also fluticasone) and itraconazole, in some patients can lead to cushingoid effects and long-term adrenal failure, if the dose of inhaled steroids is not significantly reduced [111–115].

Monitoring of patients

Patients should be closely monitored, initially every 6–8 weeks with serum IgE levels, chest

radiograph and lung function test (Box 3). The clinical response is reflected by symptomatic and radiologic improvements along with decline in the total serum IgE values. Repeated measurements of IgE levels need to be performed to establish a stable serum total IgE level, which then serves as a new baseline for future detection of exacerbations, and helps in management of the patient.

Conclusion

In conclusion, ABPA should be suspected in all asthmatics regardless of the severity or the level of control. All asthmatic patients should be routinely investigated for ABPA using *A. fumigatus*-specific IgE levels. The new staging and diagnostic criteria laid down by the International Society for Human and Animal Mycology ABPA working group with precise definitions should go a long way in proper classification and follow-up of patients with ABPA. Glucocorticoids should be used as the first-line of therapy in ABPA, and itraconazole reserved in those with exacerbations and glucocorticoid-dependent disease. Newer therapies may be tried in those with steroid-dependent ABPA or in patients who develop treatment-related adverse reactions to glucocorticoids or itraconazole.

Executive summary

Background

- Allergic bronchopulmonary aspergillosis (ABPA) is an allergic disorder caused by *Aspergillus fumigatus*. The prevalence of ABPA complicating asthma is very high in the asthma clinics and the global burden of 5 million patients has been estimated.

Diagnosis

- A. fumigatus*-specific IgE is the most sensitive test in the diagnosis of ABPA, and is the preferred test for screening asthmatic patients for ABPA. All asthmatic patients (irrespective of severity or control) should be routinely investigated for ABPA using *A. fumigatus*-specific IgE levels.
- A working group on 'ABPA complicating asthmatics', formed under theegis of the International Society for Human and Animal Mycology, has laid down new criteria for diagnosis and staging.

Staging

- ABPA is now divided into seven stages (stage 0–6) namely asymptomatic, acute, response, exacerbation, remission, treatment-dependent ABPA and advanced ABPA.
- ABPA is radiologically classified as serological ABPA, ABPA with bronchiectasis, ABPA with high-attenuation mucus and ABPA with chronic pleuropulmonary fibrosis.

Treatment

- The treatment strategy in ABPA includes the use of systemic glucocorticoids to control the immunologic activity, and the use of itraconazole to diminish the fungal burden in the airways.
- Patients should be closely monitored, initially every 6–8 weeks with serum IgE levels, chest radiograph and lung function test.
- The aim of therapy in ABPA is not the normalization of IgE levels, but a 25–50% decline in IgE that is associated with clinical, spirometric and radiological improvement.
- Inhaled corticosteroids should not be used alone in the management of ABPA.
- In those with recurrent exacerbations, one should consider prolonged therapy with any of the following, namely itraconazole, low-dose glucocorticoids, monthly pulses of methyl prednisolone or nebulized amphotericin B.
- There is a need for newer treatment modalities in the management of this debilitating disorder.

Future perspective

Despite six decades of research, there is considerable lacuna in the understanding of the disease. The susceptibility of only a proportion of asthmatics to ABPA remains an enigma, and there is an urgent need for whole-genome sequencing studies from different centers to determine host susceptibility factors. Although global burden and prevalence of ABPA has been estimated, it is based on data from secondary and tertiary care cohorts. There is a need for larger multicenter community-based studies to ascertain the true prevalence of AS and ABPA in the population. There is no 'gold standard' investigation for ABPA and there is a dire need for better antigens including recombinant proteins for diagnosis. Finally, the treatment of ABPA is far from perfect.

Newer treatment modalities need to be tested by way of randomized trials, preferably multi-institutional. New 'anti-Th2' molecules, such as mepolizumab (anti-IL-5) and lebrikizumab (anti-IL-13), have been shown to be efficacious in asthma [116,117], and this approach may also be investigated in ABPA.

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