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OPINIONS IN ALLERGY

Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria

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Summary

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus*, manifesting with poorly controlled asthma, recurrent pulmonary infiltrates and bronchiectasis. There are estimated to be in excess of four million patients affected world-wide. The importance of recognizing ABPA relates to the improvement of patient symptoms, and delay in development or prevention of bronchiectasis, one manifestation of permanent lung damage in ABPA. Environmental factors may not be the only pathogenetic factors because not all asthmatics develop ABPA despite being exposed to the same environment. Allergic bronchopulmonary aspergillosis is probably a polygenic disorder, which does not remit completely once expressed, although long-term remissions do occur. In a genetically predisposed individual, inhaled conidia of *A. fumigatus* germinate into hyphae with release of antigens that activate the innate and adaptive immune responses (Th2 $CD4^+$ T cell responses) of the lung. The International Society for Human and Animal Mycology (ISHAM) has constituted a working group on ABPA complicating asthma (www.abpaworkinggroup.org), which convened an international conference to summarize the current state of knowledge, and formulate consensus-based guidelines for diagnosis and therapy. New diagnosis and staging criteria for ABPA are proposed. Although a small number of randomized controlled trials have been conducted, long-term management remains poorly studied. Primary therapy consists of oral corticosteroids to control exacerbations, itraconazole as a steroid-sparing agent and optimized asthma therapy. Uncertainties surround the prevention and management of bronchiectasis, chronic pulmonary aspergillosis and aspergilloma as complications, concurrent rhinosinusitis and environmental control. There is need for new oral antifungal agents and immunomodulatory therapy.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* (Fig. 1) that complicates the course of patients with asthma and cystic fibrosis (CF) [1, 2]. It presents with varied clinical and radiological manifestations usually with uncontrolled asthma, recurrent pulmonary infiltrates with or without bronchiectasis [3–11]. The disease remains under-diagnosed in many countries, and as many as one-third are misdiagnosed as pulmonary tuberculosis in developing countries [12]. Diagnostic delay of as long as 10 years

*Members of the ABPA working group are listed in the appendix.

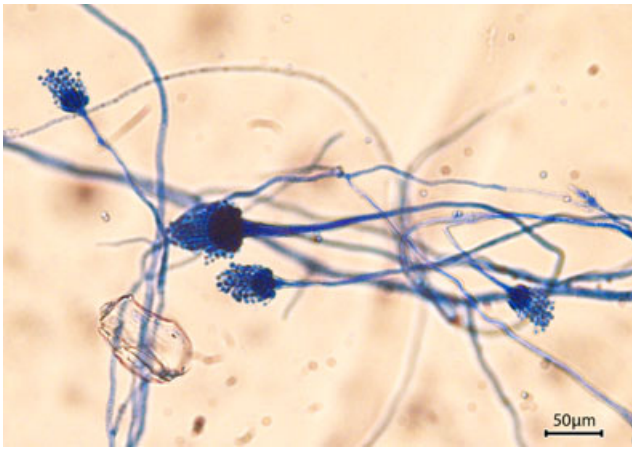

Fig. 1. Photomicrograph of *Aspergillus fumigatus* under lactophenol cotton blue mount (100×).

between the occurrence of first symptom and identification of ABPA is known [13]. Despite six decades of clinical experience, limited evidence exists on the epidemiology, pathogenesis, diagnosis, classification and optimal management of ABPA [2, 11]. A working group of 'ABPA in asthmatics' has recently been formed by the International Society of Human and Animal Mycology (ISHAM) to enable collaboration between clinicians and researchers world-wide with an aim to resolve problems in ABPA complicating asthmatics. An international consensus workshop was convened by the working group to summarize the advances made in the field of allergic aspergillosis and formulate consensus-based guidelines for diagnosis and therapy. The report provides a summary of the workshop proceedings.

Methodology

To support the workshop and review, a systematic search of the electronic databases (PubMed and EmBase) was performed to identify relevant studies published from 1952 to 2011 using the text terms: ('allergic bronchopulmonary aspergillosis' OR 'abpa' OR 'abpm' OR 'allergic bronchopulmonary mycosis').

Epidemiology of allergic bronchopulmonary aspergillosis

Aspergillus sensitization (AS) can be defined as the presence of immediate cutaneous hypersensitivity (or elevated IgE levels) against antigens of *A. fumigatus* [14]. Allergic bronchopulmonary aspergillosis is an advanced stage of AS, with AS being the first pathogenetic step in development of ABPA. On the other hand, allergic bronchopulmonary mycosis (ABPM) is ABPA-like syndrome caused by fungi other than *A. fumigatus* [15]. The identification of AS is also important as it is associated with higher rates of bronchiectasis and severe asthma [16–19]. Severe asthma with fungal sensitization (SAFS) is a recently described entity characterized by the presence of severe asthma and fungal sensitization akin to ABPA, but without bronchiectasis and mucus plugging, and total IgE values < 1000 IU/mL [20, 21]. The prevalence of ABPA in asthma is believed to be about 1–3.5% based on secondary care referral cohorts in South Africa, Ireland, Saudi Arabia, New Zealand and China [22–27]. The true prevalence of AS/ABPA in asthma remains speculative because of the absence of widespread community-based data for this purpose. The only population based data for AS available is from the National Health and Nutrition Examination Survey conducted in the United States where the prevalence of AS was found to be 6.4% using *A. fumigatus*-specific IgE levels [28]. However, the prevalence is likely to be higher in special clinics than in the community, and may vary by ethnicity and exposure risk. A recent systematic review demonstrated a high prevalence of AS and ABPA (28% [95% CI 24–34] and 12.9% [95% CI 7.9–18.9] respectively) in special (chest or asthma) clinics [29].

The prevalence of AS/ABPA reported over the last decade is shown in Table 1 [25–27, 30–36]. The prevalence of AS varies from 5.5% to 38.5% while the prevalence of ABPA ranges between 2.5 and 22.3% with a pooled prevalence of 8.4% (Table 1). Further, in a scoping review, Denning et al. estimated the global burden of 4.8 million (range 1.4–6.8) ABPA patients in a world-wide asthma population of 193 million [37].

Pathogenesis of allergic bronchopulmonary aspergillosis

The familial occurrence of ABPA may be as high as 5% [38]. Exposures to high concentrations of spores have been reported to cause ABPA [39–43]. As not all asthmatics develop ABPA despite being exposed to the same milieu, environmental factors may not be the only factors in the pathogenesis of ABPA. Fungal conidia are immunologically inert because of the presence of surface hydrophobin that prevents immune recognition of fungal spores [44]; however, defective clearance of conidia in asthma or CF allows them to germinate into hyphae. Normally, the hyphal forms are killed by neutrophils. Airway macrophages recognize fungi through pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and mannose-binding lectin (MBL), which trigger secretion of pro-inflammatory cytokines [45]. In ABPA, it is hypothesized that defects in innate and adaptive immunity (Table 2) cause persistence of *A. fumigatus* [46]. Many of these genetic defects have also been documented in ABPA complicating CF (Table 2). On a background of asthma in genetically susceptible individuals [47–64], (Table 2), inhaled

Table 1. Prevalence of *Aspergillus* sensitization (AS) and allergic bronchopulmonary aspergillosis (ABPA) complicating asthma in studies conducted in this millennium

Study	Country	Type of study	Skin test/antigen	Prevalence of AS, n/N (%; 95% CI)	Prevalence of ABPA, n/N (%; 95% CI)
Eaton et al. [25]	New Zealand	Prospective	SPT/commercial (Hollister-Stier, USA)	47/255 (18.4; 14.1–23.7)	12/243 (4.9; 2.8–8.5)
Kumar et al. [30]	India	Prospective	Intradermal/indigenous	47/200 (23.5; 18.1–29.9)	32/200 (16; 11.5–21.8)
Al-Mobeireek et al. [26]	Saudi Arabia	Prospective	SPT/commercial (SoluPrick, ALK labs)	12/53 (22.6; 13.3–35.8)	7/264 (2.7; 1.3–5.5)*
Maurya et al. [31]	India	Prospective	Intradermal/indigenous	30/105 (28.6; 20.8–37.9)	8/105 (7.6; 3.9–14.5)
Agarwal et al. [32]	India	Prospective	Intradermal/commercial (Hollister-Stier)	291/755 (38.5; 35.1–42.1)	155/755 (20.5; 17.8–23.6)
Prasad et al. [33]	India	Prospective	Intradermal/not available	74/244 (30.3; 24.9–36.4)	18/244 (7.4; 4.7–11.4)
Agarwal et al. [34]	India	Prospective	Intradermal/indigenous	87/242 (35.9; 30.2–42.2)	54/242 (22.3; 17.5–28)
Ghosh et al. [35]	India	Prospective	Intradermal/indigenous	54/215 (25.1; 19.8–31.3)	15/215 (6.9; 4.2–11.2)
Sarkar et al. [36]	India	Prospective	SPT/commercial (Creative Drug Industries, India)	40/126 (31.7; 24.2–40.4)	10/126 (7.9; 4.3–14.1)*
Ma et al. [27]	China	Prospective	–	11/200 (5.5; 3.1–9.7)	5/200 (2.5; 1.0–5.9)
Pooled prevalence				25.1 (19.6–31.6)	8.4 (5.3–13.1)

*Allergic bronchopulmonary mycosis.

The prevalence with 95% confidence intervals (CI) for each study was calculated, and then the results were pooled using random-effects model to derive a pooled prevalence with 95% CI.

SPT, skin prick test.

conidia of *A. fumigatus* (and occasionally other fungi) are able to persist and germinate, leading to hyphal growth. *A. fumigatus* releases a variety of proteins, which promote release of pro-inflammatory cytokines by the airway epithelium [65–67]. In addition, certain *Aspergillus* proteases are directly toxic to pulmonary epithelium causing cell detachment and death [65, 67, 68]. All these events activate the innate immune system of the lung leading to production of several inflammatory cytokines [65, 69–71]. Exposure of *A. fumigatus* antigens to pulmonary dendritic cells prime naïve Th cells to *Aspergillus* specific T cells. The immune reaction of the human host to *Aspergillus* is a Th1 $CD4^+$ T cell response. However, the immune response in AS and ABPA (quantitatively greater in ABPA than AS [72–75]) is a Th2 $CD4^+$ T cell response with IL-4, IL-5 and IL-13 cytokine secretion [47, 72, 76–78]. The Th2 response causes profound inflammatory reaction with influx of various inflammatory cells (including neutrophils and eosinophils) [67, 79] and IgE (total and *A. fumigatus* specific) synthesis (Fig. 2) [80]. There is evidence for a regulatory T cell defect in some patients with CF and ABPA [81]; however, the role, if any, of Th17 and regulatory T cells in ABPA complicating asthma is yet to be fully explored [82].

Clinical features

Patients generally present with poorly controlled asthma, wheezing, hemoptysis and productive cough [83]. Other symptoms include low grade fever, weight loss, malaise and fatigue. Expectoration of brownish black mucus plugs is seen in only 31–69% of patients [12, 30, 32]. Patients can also be asymptomatic (albeit with asthma medications) and are diagnosed on routine investigations [25, 32, 84]. In a series of 155 cases of ABPA, 19% of ABPA patients had well-controlled asthma [32]. Clubbing is uncommon, and is seen in those with long-standing bronchiectasis [32]. Physical examination can also detect complications of ABPA such as pulmonary hypertension [85]. During ABPA exacerbations, patients are symptomatic with fever, wheezing, hemoptysis and productive cough. Examination may reveal localized findings of consolidation and atelectasis, which need to be differentiated from other pulmonary diseases.

Diagnostic test findings

Aspergillus *skin test*. An immediate cutaneous hypersensitivity to *A. fumigatus* antigens (either crude or recombinant) is hallmark of ABPA, and represents the presence of IgE antibodies specific to *A. fumigatus*. The test can be performed either using a skin prick test or an intradermal injection [86, 87]. When both are available, a skin prick test should be performed first, and if negative, some patients may only manifest hypersensitivity with an intradermal test. The sensitivity of a positive result in diagnosis of ABPA is about 90% [88], although up to 40% of asthmatics without ABPA can

Table 2. Genetic susceptibility in allergic bronchopulmonary aspergillosis (ABPA) complicating asthma and cystic fibrosis (CF)

Mutations/ polymorphisms	Population	Number of patients	Control population	Significance OR (95% confidence intervals)	Author/reference
HLA (6p21.3)					
DR4	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Allergy: 0.9 (0.3–2.9), $P = 0.9$; Control: 22.8 (2.5–211.8), $P = 0.002$	Aron et al. [49]
DR5	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Control: 5.3 (1.4–20.7), $P = 0.02$	Aron et al. [49]
	Caucasian	35 ABPA (asthma and CF)	50 Af sensitized asthma/CF; 98 controls	Asthma: 1.8 (0.7–4.9), $P = 0.2$; Control: 2.8 (1.1-6.8), $P = 0.03$	Chauhan et al. [50]
DR7	Caucasian	16 ABPA (asthma)	56 allergy; 39 controls	Allergy: 1.7 (0.5–5.7), $P = 0.4$; Control: 35 (1.8-691.4), $P = 0.004$	Aron et al. [49]
DR2	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 4.9 (1.8–13.6), $P = 0.001$ Control: 3.7 (1.6–8.4), $P = 0.001$	Chauhan et al. [50]
DR2/DR5	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 5.1 (1.9–13.3), $P = 0.0005$; Control: 5.4 (2.3–12.9), $P < 0.0001$	Chauhan et al. [50]
DRB1*1501	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 3.1 (0.9–10.3), $P = 0.05$ Control: 4.5 (2.1–9.7), $P = 0.0001$	Chauhan et al. [50]
DRB1*1503	Caucasian	35 ABPA (both asthma and CF related)	50 Af sensitized asthma or CF; 98 controls	Asthma: 24.8 (1.4–452.7), $P = 0.008$ Control: 37.5 (4.4–316.8), $P < 0.0001$	Chauhan et al. [50]
DRB1*0701, DRB1*1501, DQB1*0602, DQB1*0201	Caucasian	38 ABPA (CF)	46 CF, 306 asthma, 176 controls	DRB1*0701, DRB1*1501, DQB1*0602 associated with ABPA susceptibility, while DQB1*0201 associated with possible protection	Muro et al. [64]
Mannose-binding lectin (10q11.2-q21)					
G1011A in intron 1	Indian	11 ABPA (asthma)	49 allergic individuals; 84 controls	Allergy: 1.2 (0.5–3.3), $P = 0.7$ Control: 8.2 (2.8–23.4), $P < 0.0001$	Kaur et al. [60]
Exon 1 (R52C, G54D, G57E), Promoter (H/L -550, Y/X -221, P/Q + 4)	Caucasian	38 allergic fungal disease (28 ABPA, 7 SAFS, 3 NOS)	Historical controls	No significant relationship, $P > 0.05$	Harrison et al. [61]
Surfactant Protein A2 (10q22.3)					
G1649C in exon 4	Indian	32 ABPA (asthma)	34 controls	2.6 (1.2–5.7), $P = 0.01$	Saxena (2003)[53]
	Caucasian	7 ABPA (asthma)	46 controls	2.7 (0.3-21.9), $P = 0.6$	Vaid (2007)[58]
T1492C in intron 3	Indian	32 ABPA (asthma)	34 controls	4.8 (1.1-21.6), $P = 0.03$	Saxena (2003)[53]
	Caucasian	7 ABPA (asthma)	46 controls	3.5 (0.7-16.7), $P = 0.2$	Vaid (2007)[58]
A1660G in exon 4	Indian	27 ABPA, 119 Af colonizers	–	5.3 (1.7-16.9), 0.002	Saxena et al. [53]
Toll-like receptor 9 (3p21.3)					
T1237C in 5′ promoter	Caucasian	22 ABPA (asthma)	14 SAFS, 80 controls	SAFS: 6.9 (0.8–58.2), $P = 0.09$; Control:2.5 (1.01–6.1), $P = 0.04$	Carvalho et al. [59]

(continued)

Table 2 (continued)

Mutations/ polymorphisms	Population	Number of patients	Control population	Significance OR (95% confidence intervals)	Author/reference
IL-4Rα (16p12.1-p11.2)					
−4G>A (ile75val) in promoter	Caucasian	40 ABPA (14 asthma, 26 CF)	56 non-ABPA (23 asthma, 33 CF)	3.3 (1.8–6.1), $P = 0.008$	Knutsen et al. [56]
IL-10 (13q13)					
−1082 G>A in promoter	Caucasian	27 ABPA (CF)	351 CF	GG genotype: 1.67 (0.64–4.36); AG genotype: 0.43 (0.15–1.18)	Brouard et al. [54]
	Caucasian	9 ABPA	24 CCPA	0.38 (0.21–0.67), $P = 0.0006$	Sambatakou (2006) [57]
TGF-β (19q13.1, 13.2)					
T869C in exon 1	Caucasian	9 ABPA	24 CCPA	0.42 (0.24–0.75), $P = 0.003$	Sambatakou et al. [57]
CFTR mutations (7q31.2)					
	Caucasian	79 ABPA in asthma	268 controls 94 asthmatics	Control: 10.4 (4.4–24.8) Asthma: 5.5 (1.6–18.8)	Miller et al., Aron et al., Marchand et al., Eaton et al., Agarwal et al. [48, 49, 51, 52, 62]
CHIT1 gene (1q31–32)					
24 bp duplication in exon 10	NA	6 ABPA	–	All six children had 24 bp duplication	Vicencio et al. [63]

Af, *Aspergillus fumigatus*; CCPA, chronic cavitary pulmonary aspergillosis; CFTR, CF transmembrane conductance regulator; HLA, human leucocyte antigen; IL, interleukin; MBL, mannose-binding lectin; NOS, not otherwise specified; OR, odds ratio; SAFS, severe asthma with fungal sensitization; SNP, single nucleotide polymorphism; SP, surfactant protein; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumour necrosis factor.

also demonstrate a type 1 response to *Aspergillus* antigen [29].

Total serum IgE levels. The serum total IgE level is a useful test in both diagnosis and follow-up of ABPA. A normal serum IgE (in the absence of systemic glucocorticoid therapy) generally excludes active ABPA as the cause of patient's current symptoms. There is no consensus on the cut-off value of IgE level that should be used for diagnosis of ABPA, and the cut-off value remains speculative. Further, the IgE values are reported in different units that leads to erroneous interpretation (1 IU/mL equals 2.4 ng/mL; 1000 ng/mL equals 417 IU/mL). The first paper documenting raised IgE values in patients with allergic aspergillosis was published in 1970; however, this study reported IgE values only in a semi-quantitative fashion (> 0.8 μg/mL) [89]. Thereafter in several studies, the Patterson group suggested a cut-off value of > 2500 ng/mL (> 1042 IU/mL) [5, 90]. Subsequently, they proposed cut-offs of < 1000 ng/mL for 'ABPA probably excluded' and > 2000 ng/mL (833 IU/mL) for 'Further serological studies required' [6]. However, over the years, the IgE cut-off has been cited as > 1000 ng/mL without any clear explanation [91–94]. Thus some groups use the cut-off value of 417 IU/mL, while others employ a value of 1000 IU/mL [95].

Unfortunately, there is a wide variation in IgE concentrations in normal persons, atopic asthmatics and ABPA patients [90, 96]. Moreover, there has been no receiver operating characteristic curve (ROC) analysis on the IgE values between ABPA, SAFS and *Aspergillus*-sensitized asthma; the cut-offs may be different in ABPA complicating asthma or CF. In a series of 146 CF patients, ABPA-S and *Aspergillus*-sensitized CF patients were separated from each other using total IgE [area under the curve (AUC), 0.91] and *A. fumigatus*-specific IgE levels (AUC, 0.90). The sensitivity and specificity of total IgE > 400 IU/mL and *A. fumigatus*-specific IgE > 8.5 kUA/L was 78% and 95%, and 78% and 79% respectively. Applying the CF consensus criteria, the IgE value of > 500 IU/mL (minimum diagnostic criteria for ABPA) separated ABPA from all other patient groups including sensitization with a sensitivity of 70% and specificity of 99%, whereas a level of > 1000 IU/mL (classic ABPA) gave a sensitivity of 39% and specificity of 100%. ROC curve analysis showed the optimum total IgE level of > 180 IU/mL to be 91% sensitive and 90%

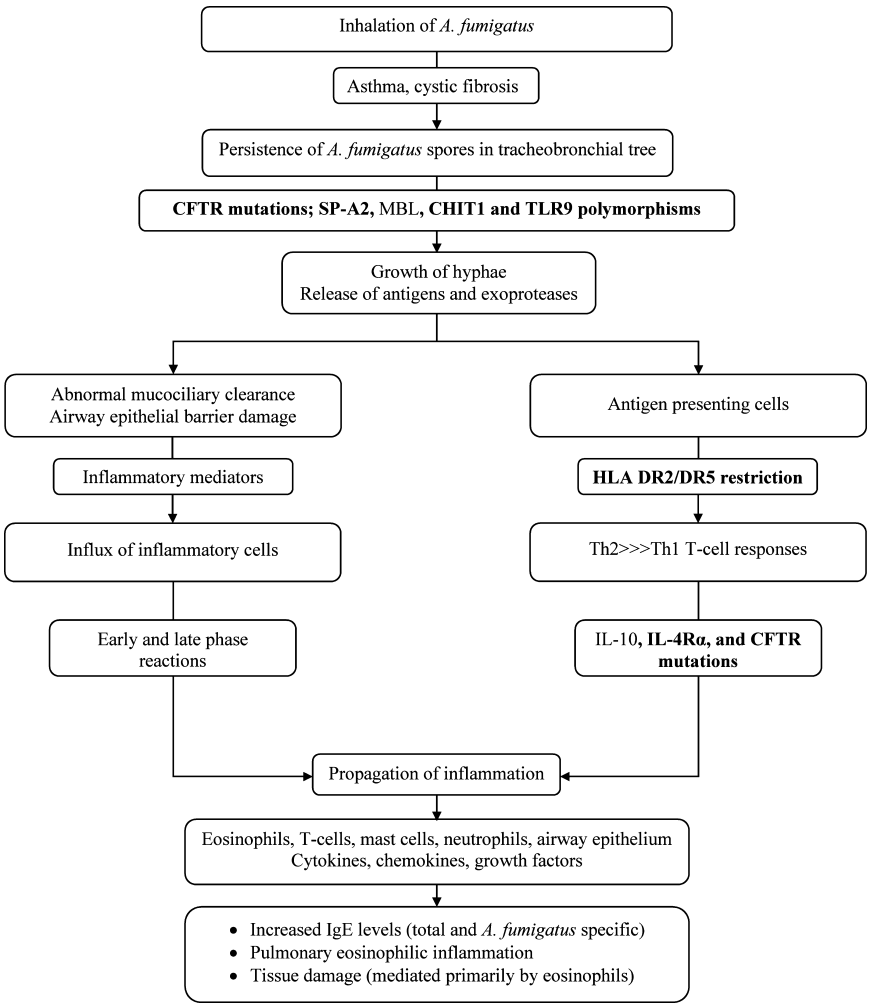

Fig. 2. Current concepts in the pathogenesis of allergic bronchopulmonary aspergillosis (statistically significant genetic associations have been indicated in bold font). CFTR, CF transmembrane conductance regulator; HLA, human leucocyte antigen; IL, interleukin; SP, surfactant protein; TLR, toll-like receptor.

specific (AUC 0.97) [97]. On the other hand, in a series of 372 asthmatic patients (R. Agarwal, personal communication), ABPA (56 patients) was separated from asthma using the best cut-off values of total IgE of 2346.5 IU/mL (sensitivity 87.5%, specificity 66.9%) and *A. fumigatus* IgE of 5.23 kUA/L (sensitivity 96.4%, specificity 88%). These gave ROC values of AUC 87.7 (95% confidence interval [CI] 82.9–92.4) and AUC 93.5 (95% CI 91.0–96.1) respectively. Clearly, an occasional patient with ABPA would meet all criteria, but IgE would be < 1000 IU/mL.

The expert group felt that a cut-off of 500 IU/mL may lead to over-diagnosis of ABPA as these levels are often encountered in AS and SAFS, and hence a cut-off value of 1000 IU/mL should be employed. Additional validation cohorts examining the prevalence of IgE values are required to arrive at a better consensus value. Diagnosis should be based on the earliest IgE test available, not on that obtained in a referral clinic after months, or years of therapy, recognizing that levels may fall spontaneously and with therapy. After treatment, serum IgE levels start declining [34, 98], but in most patients do not reach normal value. Repeated measurements of IgE levels are required to determine the 'new' baseline value for an individual patient during remission. The serum IgE also represents an important tool in follow-up of patients, and an increase in IgE levels may signify an impending exacerbation.

Serum IgE antibodies specific to A. fumigatus. An elevated level of IgE antibodies specific to *A. fumigatus* is considered a characteristic finding of ABPA [84]. The cut-off value of specific IgE against *A. fumigatus* in diagnosis of ABPA is not clear but a value more than twice the pooled serum samples from patients with

Aspergillus-sensitized asthma is proposed [90]. As this is not always feasible, the expert group felt that a value > 0.35 kUA/L should be used as cut-off.

Radiological investigations. Although consolidation is described as the most common chest radiographic finding in ABPA, most studies describing this finding are from the pre-computed tomography (CT) era [99]. In a recent study, consolidation was not as common as mucoid impaction [100]. Other findings include tramline shadows, finger-in-glove opacities and tooth paste shadows [101–104]. High-resolution CT (HRCT) of the chest detects abnormalities not apparent on the chest radiograph, allows better assessment of the pattern and distribution of bronchiectasis and is the radiological investigation of choice. The usual findings on CT chest include bronchiectasis, mucoid impaction, mosaic attenuation, centrilobular nodules, tree-in-bud opacities and pleuropulmonary fibrosis suggestive of chronic pulmonary aspergillosis (CPA) [105, 106]. Uncommon radiological manifestations include miliary nodular opacities [107], perihilar opacities simulating hilar lymphadenopathy [103, 108], pleural effusions [109] and pulmonary masses [110, 111].

Bronchiectasis is arbitrarily classified as central if confined to the medial two-thirds or medial half of the lung, at a point midway between the hilum and the chest wall [112]. Central bronchiectasis (CB) with peripheral tapering of bronchi is believed to be a *sine qua non* for the diagnosis of ABPA. However, bronchiectasis in ABPA can extend to the periphery (Fig. 3), and peripheral bronchiectasis has been described in 26–39% of the lobes involved by bronchiectasis [84, 106]. In one study, bronchiectasis extended to the periphery in 33–43% depending on the criteria used for defining CB [100]. The significance of CB as a specific finding for ABPA is uncertain as almost 40% of the involved lobes have bronchiectasis extending to the periphery [84, 106, 113]. Also, the sensitivity of CB was only 37% in diagnosis of ABPA in one study [114]. The expert group also felt that CB should be considered a complication of ABPA and not a diagnostic criterion.

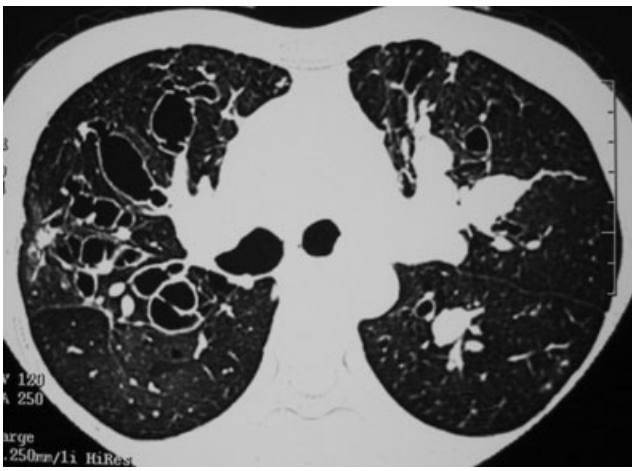

Fig. 3. Lung windows of High-resolution CT (HRCT) chest depicting extensive bronchiectasis extending till the periphery. There is evidence of mucoid impaction within the bronchiectatic cavities of the left lung.

Mucoid 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 [84]. High-attenuation mucus (HAM), defined as mucus visually denser than paraspinal skeletal muscle, is a pathognomonic finding of ABPA (Fig. 4) [32, 115–117]. High-attenuation mucus 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. Some patients with ABPA develop upper lobe fibrosis and shrinkage (Fig. 5) [104]. The rate of cavitation visible on plain chest radiographs varies between 3% and 21% and that of aspergilloma from 0% to 7.2% [106, 118, 119]. The pathophysiology of pleural fibrosis in ABPA is not known, and requires more research.

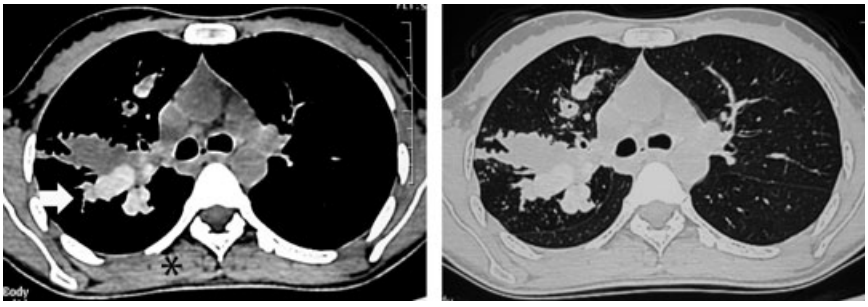

Fig. 4. High-resolution CT (HRCT) chest showing the presence of high-attenuation mucus (bold arrow) in the mediastinal windows with corresponding lung window sections. The mucus is visually denser than the paraspinal skeletal muscle (asterisk).

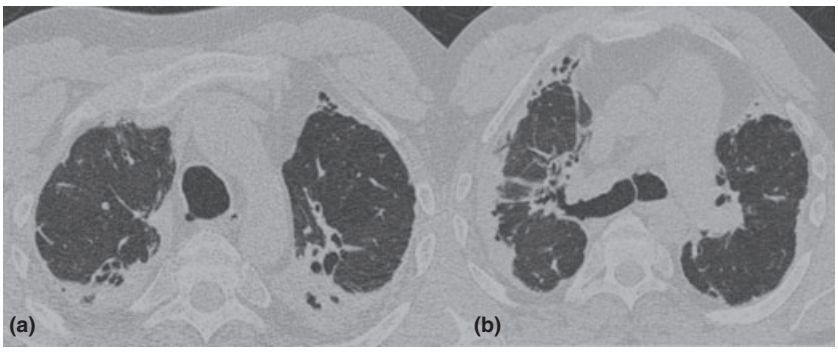

Fig. 5. Computed tomography (CT) scan of a patient with chronic pulmonary aspergillosis complicating allergic bronchopulmonary aspergillosis (ABPA). There is extensive bilateral upper lobe cavitation, pleural fibrosis and left-sided bronchiectasis (2A) and marked right-sided circumferential pleural fibrosis with small cavitation within this fibrosis anteriorly, left lingual pleural fibrosis and right-sided proximal bronchiectasis.

Serum precipitins or specific IgG against A. fumigatus. Serum precipitins (IgG) against *A. fumigatus* are present in 69–90% of patients with ABPA [32, 120–123] but also in 10% of asthmatics with or without SAFS [1]. IgG antibodies (including precipitins) against *A. fumigatus* can be demonstrated either using double gel diffusion techniques [123], enzyme linked immunoassay (ELISA), fluorescent enzyme immunoassay (FEIA) or other methods [16]. Two commercial assays (ImmunoCap and Platelia *Aspergillus* IgG EIA) are sensitive measures of *Aspergillus* IgG antibodies compared with counterimmunoelectrophoresis [124]. ImmunoCap method has better reproducibility and thus may be more apt for monitoring IgG levels following treatment [124]. However, *Aspergillus* IgG may not be specific for ABPA as high levels are encountered in other forms of aspergillosis especially CPA. High titres in ABPA, with evidence of pleural fibrosis or persistent cavitation, may represent the interval development of CPA [125–127].

Peripheral eosinophilia. A peripheral blood eosinophil count > 1000 cells/μL has been considered a major criterion for diagnosis of ABPA. However, a recent study found that only 40% of patients with ABPA presented with an eosinophil count > 1000 cells/μL at diagnosis [128]. In ABPA, the pulmonary eosinophilia is far greater than peripheral blood with little correlation between the two; thus, a low eosinophil count does not exclude ABPA [129, 130]. Highly elevated eosinophil counts are common in many other disorders and so the specificity of this criterion is problematic. Also, patients receiving oral steroids can have lower or normal eosinophil levels.

Sputum cultures for A. fumigatus. Culture of *A. fumigatus* in sputum is supportive but not diagnostic of ABPA because the fungus can also be grown in other pulmonary diseases due to ubiquitous nature of the fungi. In ABPA, the rates of culture positivity range from 39 to 60% depending on the number of specimens examined [12, 122]. Interestingly, a recent study suggested that routine processing procedures for isolating filamentous fungi from respiratory sputum samples may underestimate fungal prevalence [131]. The authors used a different sputum processing method, whereby sputum plugs are separated from saliva and aliquots of approximately 150 mg are inoculated directly onto potato dextrose agar [131]. It is interesting to note that the vast majority of culture-negative ABPA patients have detectable *A. fumigatus* DNA in their sputum [132]. As azole resistance has been documented in *A. fumigatus* [132], it may be valuable obtaining cultures before starting antifungal therapy, and susceptibility testing and/or realtime molecular testing for resistance of any isolates obtained [133].

Pulmonary function tests. Bronchial provocation with *Aspergillus* antigens are not recommended as it can cause fatal bronchospasm [134]. Routine pulmonary function tests are helpful in 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 [84].

Role of recombinant Aspergillus *antigens*. Patients with ABPA are mostly evaluated with crude extracts from *Aspergillus*. These antigens lack reproducibility and consistency, and frequently cross react with other antigens [135]. Recent advances in technology have enabled cloning of several proteins of *A. fumigatus*. The recombinant allergens Asp f1, Asp f2, Asp f3, Asp f4 and Asp f6 have been evaluated for their diagnostic performance in asthma and ABPA [136–140]. Crameri et al. demonstrated excellent correlation between the Immunocap FEIA and in-house ELISA [139]. Antibodies against rAsp f1 and rAsp f3 are elevated in both AS and ABPA while antibodies against rAsp f4 and rAsp f6 are elevated only in ABPA (Table 3) [137, 140].

Table 3. Recombinant *Aspergillus fumigatus* antigens evaluated in allergic bronchopulmonary aspergillosis (ABPA) complicating asthma

	Sensitivity, n/N (%)		Specificity, n/N (%)	
Antigen	ABPA	*Aspergillus* sensitization	Asthma or controls	References
rAsp f1	84/105 (80)	30/60 (50)	0/13 (100)	[137, 139, 261]
rAsp f2	24/25 (96)	Not done	0/20 (100)	[262]
rAsp f3	66/71 (93)	26/48 (54)	0/24 (100)	[137, 263]
rAsp f4	58/72 (81)	0/52 (0)	0/25 (100)	[137, 264]
rAsp f6	38/72 (53)	0/52 (0)	0/25 (100)	[137, 264]
rAsp f34	60/64 (94)	11/24 (46)	0/7 (100)	[265]
rAsp f1 or f3	58/60 (97)	30/40 (75)	0/20 (100)	[137]
rAsp f4 or f6	65/72 (90)	0/52 (0)	0/25 (100)	[137, 264]

However, there was inconsistency in results obtained from different centres [136]. Thus, the expert group felt that although the current data suggest a promising role of recombinant antigens in diagnosis of AS and probably ABPA [141–143], there is need for larger studies from different centres to give a final recommendation on the diagnostic value of these allergens.

Diagnosis and diagnostic criteria

The diagnosis of ABPA is currently made on a combination of clinical, radiological and immunological findings using the Patterson criteria [3, 6]. The expert group felt that these criteria need revision as they offer equal importance to all parameters while some components of the criteria are more important than others. For example, the specificity of *Aspergillus* IgG for ABPA as opposed to other forms of aspergillosis remains unknown. Moreover, there is neither any consensus on the number of major or minor criteria required to make the diagnosis, nor receiver operator curve (ROC) analysis of the optimum cut-off values for IgE levels and eosinophil count. From a clinical perspective, it would be helpful to have simpler criteria, if possible. New diagnostic criteria were formulated with an aim to improve the diagnosis and care of patients with ABPA and limit the weaknesses of the previous criteria (Table 4). The refinement in inclusion/exclusion criteria will also benefit clinical research particularly studies planning to evaluate aetiology and/or new therapies. The new criteria will need validation and further refinement. Bronchiectasis was removed from the diagnostic criteria as ABPA may present without CB. The minor criteria of Patterson et al. although sometimes present should not be required for diagnosis, and hence have also been removed. The expert group agreed that a cut-off value of 1000 IU/mL can help in differentiating SAFS from ABPA-S but would require validation. In clinical practice, many patients will fall short of diagnostic criteria for ABPA. These patients may be labelled as 'ABPA- at risk' and require close monitoring and follow-up.

Table 4. Newly proposed diagnostic criteria for allergic bronchopulmonary aspergillosis

Predisposing conditions
Bronchial asthma, cystic fibrosis
Obligatory criteria (both should be present)
Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Aspergillus fumigatus*
Elevated total IgE levels (> 1000 IU/mL)*
Other criteria (at least two of three)
Presence of precipitating or IgG antibodies against *A. fumigatus* in serum
Radiographic pulmonary opacities consistent with ABPA†
Total eosinophil count > 500 cells/μL in steroid naïve patients (may be historical)

*If the patient meets all other criteria, an IgE value < 1000 IU/mL may be acceptable.

†The chest radiographic features consistent with ABPA may be transient (i.e. consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e. parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis).

While investigating a patient with asthma for ABPA, it is recommended to perform an *Aspergillus* skin test and/or *A. fumigatus* specific IgE levels, with the latter being more sensitive [88]. If either is positive, the total serum IgE levels should be measured. If the value is > 1000 IU/mL, other tests for ABPA including a CT of the chest, IgG specific to *A. fumigatus* or serum precipitins to *A. fumigatus* and total eosinophil count should then be performed to fully characterize the disease (Fig. 6). Allergic bronchopulmonary mycosis can be diagnosed in the same way, with sensitization to another fungus being predominant [15].

Natural history

The natural history of ABPA remains unclear because of its variable course in different patients [6, 7, 144–147]. However if untreated, the inexorable inflammatory process can result in bronchiectasis and pulmonary fibrosis, and ultimately respiratory failure and cor pulmonale [83]. Allergic bronchopulmonary aspergillosis generally does not remit but it can remain quiescent for long periods. Given its relapsing nature, with development of serious complications, it is important to provide a clinical framework for staging the disease.

Clinical staging of allergic bronchopulmonary aspergillosis

Although ABPA has been classified into five stages [5]; there is considerable ambiguity in description of these

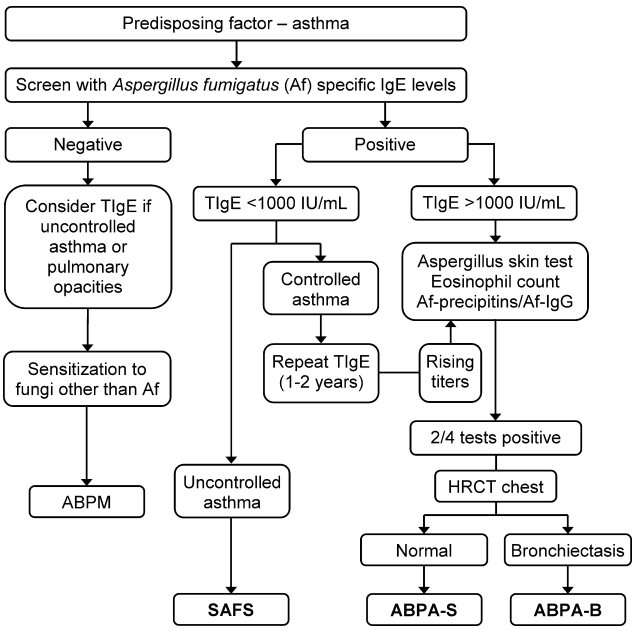

Fig. 6. Protocol for investigating allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma. All asthmatic patients should be investigated for ABPA using *A. fumigatus*-specific IgE levels (some centres employ *Aspergillus* skin test as the first investigation). Further investigations are performed as shown in the algorithm. Once a diagnosis of ABPA is made, the disease is further classified based on high-resolution CT (HRCT) chest as ABPA-S, ABPA-B, ABPA-HAM, ABPA-CPF (see Table 6). The clinical stage of the patient also needs to be ascertained (see Table 5). For example, a patient with ABPA would be finally classified as ABPA-B, stage Ib. In those with severe asthma, also consider the diagnosis of severe asthma with fungal sensitization (SAFS), as an alternative to ABPA as SAFS may also be responsive to oral antifungal therapy. TIgE, total IgE values.

stages with lack of precise definitions. Hence, a new staging with more accurate definitions has been recommended (Table 5). These amendments would be especially beneficial in clinical trials evaluating new therapies. Importantly, a patient does not necessarily progress from one stage to the other in a sequential fashion. Asthmatic patients are generally investigated for ABPA only if they are symptomatic. However, routinely investigating every asthmatic for ABPA would help in early diagnosis of the disorder before the onset of bronchiectasis. Hence, a new stage has been proposed. Patients in stage 0 are asymptomatic with controlled asthma and are diagnosed on routinely investigating asthmatic patients for ABPA. Patients who present with acute to subacute symptoms of ABPA are classified as stage 1. Patients in stages 0 or 1 meet all the criteria for diagnosis of ABPA as defined in Table 4. With treatment, there is improvement in symptoms, clearing of radiographic opacities and at least 25% decline in IgE levels by 8 weeks and this is stage 2. The aim of therapy is not normalization of IgE levels but a 25–50% decline associated with clinical and radiological improvement [34, 98]. About 25–50% of the patients suffer an exacerbation of the disease (stage 3) usually within 1–2 years [5, 6, 84], which is defined as increase in IgE levels by 50% of baseline associated with clinico-radiological worsening. The presentation of ABPA with aspergilloma, and/or HAM predicts a patient likely to experience recurrent exacerbations [148, 149]. If there are no ABPA exacerbations over the next 6 months after stopping therapy, an additional label of remission (stage 4) should be used. Even in patients with remission, the IgE levels do not return to normal values [145]. Patients in remission are followed up by measurement of IgE levels every 3–6 months for the first year and then annually, depending on the clinical status of the patient. Some patients in stage 4 may enter into prolonged remission. However, it does not imply a cure as exacerbations of the disease have been documented several years after remission [147]. Patients in stage 5 are those with difficult to control ABPA and/or asthma, and can be classified into two subtypes. The first group (treatment-dependent ABPA) includes patients requiring repeated courses of steroids or azoles for control of ABPA activity. The other group (glucocorticoid-dependent asthma) requires glucocorticoids for control of asthma. Patients in stage 6 are those with widespread bronchiectasis and/or fibrosis with type II respiratory failure and/or cor pulmonale. Even in advanced stages, the disease can be clinically as well as immunologically active requiring therapy [7, 150].

Radiological classification of allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis has been classified radiologically as ABPA with central bronchiectasis (ABPA-CB) or serological ABPA (ABPA-S) on the presence or absence of bronchiectasis respectively [6, 151]. Greenberger et al. proposed ABPA-S as the earliest stage of ABPA with less severe immunological findings compared to ABPA-CB [9]. However, in their study only *A. fumigatus*-specific IgG levels were higher in ABPA-CB, while the other immunological parameters (total and *A. fumigatus* specific IgE) were similar in the two groups [9]. Thereafter, Kumar et al. classified ABPA into three groups namely ABPA-S, ABPA-CB and ABPA-CB with other radiological findings (ABPA-CB-ORF) [152]. Unfortunately, this study included only 18 patients (six in each group), and the CT manifestations of ORF included findings representing the end-stage fibrotic, probably immunologically quiescent disease. In a study involving 234 patients with ABPA, Agarwal et al. categorized ABPA into ABPA-S, ABPA-CB and ABPA-CB with HAM (ABPA-CB-HAM) [148]. The HAM-based classification scheme was consistently associated with immunological severity from ABPA-S

Table 5. Newly proposed clinical staging of ABPA in asthma

Stage	Definition	Features
0	Asymptomatic	• GINA definition of controlled asthma • On investigation fulfils the diagnostic criteria of ABPA (Table 4) • Has not been previously diagnosed to have ABPA
1	Acute	• Patient has uncontrolled asthma/constitutional symptoms • Fulfils diagnostic criteria for ABPA • Not previously diagnosed to have ABPA
1a	With mucoid impaction	Meets all the criteria and there is documented mucoid impaction on chest radiograph, CT chest or bronchoscopy
1b	Without mucoid impaction	Meets all the criteria and there is no documented mucoid impaction on CT chest or bronchoscopy
2	Response	• Clinical improvement (resolution of constitutional symptoms, improvement in asthma control) • Major radiological improvement* • IgE decline by ≥ 25% of baseline at 8 weeks
3	Exacerbation	Clinical and/or radiological deterioration associated with an increase in IgE by ≥ 50%
4	Remission	Sustained clinicoradiological improvement with IgE levels remaining at or below baseline (or increase by < 50%) for ≥ 6 months on or off therapy other than systemic glucocorticoids
5a	Treatment-dependent ABPA	If patient has relapse on two or more consecutive occasions within 6 months of stopping treatment or has worsening of clinical, radiological or immunological parameters on tapering oral steroids/azoles
5b	Glucocorticoid-dependent asthma	If the patient requires oral or parenteral glucocorticoids for control of asthma while the activity of ABPA is controlled as reflected by IgE levels and chest radiograph
6	Advanced ABPA	Presence of type II respiratory failure and/or cor pulmonale with radiological evidence of fibrotic findings consistent with ABPA on HRCT of the chest after excluding reversible causes of acute respiratory failure

*Permanent changes like cystic opacities/fibrosis should not be considered in radiological remission.
CT, computed tomography; HRCT, high-resolution CT; GINA, global initiative for asthma.

(mild), ABPA-CB (moderate) to ABPA-CB-HAM (severe). They also observed that the classification scheme of Greenberger et al. was associated with immunological severity in some parameters only while in the Kumar classification, the immunological markers were most severe in the ABPA-CB group and not ABPA-CB-ORF suggesting that ORF does not relate directly to immunological severity [148].

The expert group laid down a new radiological classification that incorporates all the current evidence on the radiological findings in ABPA. Radiologically, ABPA has been classified into four major categories (Table 6), namely serological ABPA (ABPA-S), ABPA with bronchiectasis (ABPA-B), ABPA with high-attenuation mucus (ABPA-HAM), and ABPA with chronic pleuropulmonary fibrosis (ABPA-CPF).

Management

The management of ABPA consists of anti-inflammatory therapy (systemic glucocorticoids) to suppress the immune activity, and use of antifungal agents to attenuate the fungal load in the airways [153]. The goals of therapy include control of asthma, prevention and

Table 6. Newly proposed radiological classification of ABPA based on computed tomographic (CT) chest findings

Classification	Features
ABPA-S (Serological ABPA)	All the diagnostic features of ABPA (Table 4) but no abnormality resulting from ABPA on HRCT chest*
ABPA-B (ABPA with bronchiectasis)	All the diagnostic features of ABPA including bronchiectasis on HRCT chest
ABPA-HAM (ABPA with high-attenuation mucus)	All the diagnostic features of ABPA including presence of high-attenuation mucus
ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)	ABPA with at least two to three other radiological features such as pulmonary fibrosis, parenchymal scarring, fibro-cavitary lesions, aspergilloma and pleural thickening without presence of mucoid impaction or high-attenuation mucus

*Findings resulting from co-existent disease, bullae from asthma, tracheomalacia, etc. should not be considered while labelling the patients as ABPA-S.
HRCT, high-resolution CT; ABPA, allergic bronchopulmonary aspergillosis.

treatment of acute exacerbations, and arresting the development of bronchiectasis and CPA.

Systemic glucocorticoid therapy

Oral corticosteroids are currently the treatment of choice for ABPA although there are no well-designed trials of steroids in ABPA. Glucocorticoids are anti-inflammatory and suppress immune hyperreactivity of both asthma and ABPA. There is no data to guide the dose and duration of glucocorticoids, and different regimens of glucocorticoids have been used (Table 7). The use of lower doses of glucocorticoids (regime 1 in Table 7) without antifungal therapy is associated with higher occurrence of recurrent relapses or glucocorticoid dependence (45%) [6]. A higher dosage of glucocorticoids (regime 2 in Table 7) was shown to be associated with higher remission rates and a lower prevalence of glucocorticoid-dependent ABPA (13.5%) [84]. Whether a higher dose or prolonged duration of corticosteroids is associated with better outcomes remains unclear in the absence of direct comparisons between the two regimens. A randomized controlled trial on the efficacy and safety of two different glucocorticoid dose regimens in ABPA has been completed (clinical trials.gov; NCT00974766). Hopefully, the results of this trial will help in answering the question regarding dose of glucocorticoids in ABPA.

Table 7. Treatment protocols for the management of ABPA

Oral glucocorticoids
Regimen 1 [93]
Prednisolone 0.5 mg/kg/day for one to two weeks, then on alternate days for six to eight weeks. Then taper by 5–10 mg every 2 weeks and discontinue
Regimen 2 [84, 92]
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
Oral itraconazole
Dose: 200 mg twice a day, with therapeutic drug monitoring for at least 16 weeks. Response often takes longer than 16 weeks
Approaches: Recurrent short courses or long-term therapy
Which agent to use
Oral steroids
ABPA with mucoid impaction
ABPA with significant deterioration of lung function attributed to worsening asthma or ABPA (and not intercurrent infection) would require treatment with glucocorticoids.
In those with mucoid impaction and proximal collapse, assessment should be made at 3 weeks and if the collapse has not resolved, therapeutic bronchoscopy should be performed
Azoles (with or without concomitant steroids)
ABPA with recurrent exacerbations (to prevent exacerbations after controlling the exacerbation with glucocorticoids)
Glucocorticoid-dependent ABPA
Inhaled steroids
Single agent ICS therapy should not be used as first-line in the management of ABPA
Can be used for the control of asthma once the oral prednisolone dose is < 10 mg/day
Follow-up and monitoring
The patients are followed up with a history and physical examination, chest radiograph, total IgE levels and quality of life questionnaire every 8 weeks
A ≥ 25% decline in IgE level along with clinicoradiological improvement signifies satisfactory response to therapy
If the patient cannot be tapered off prednisolone/azole then the disease has evolved into stage 4. Management should be attempted with alternate-day prednisone/azole in the least possible dose
Monitor for adverse effects of treatment

Inhaled corticosteroids (ICS)

Inhaled corticosteroids achieve high concentrations in the tracheobronchial tree with minimal systemic side-effects. Numerous small case studies have reported the use of ICS in ABPA [154–160]. These studies utilized varying doses of ICS and many patients continued to receive oral steroids while receiving ICS. Also in many studies, clinical or radiological and spirometric criteria were used to define response, and IgE levels were not measured. This makes it difficult to analyse whether the beneficial effects were solely due to ICS.

Oral azoles

Although systemic steroids are highly efficacious in the management of ABPA [32, 34, 84, 148, 151], almost 50% of patients relapse when they are tapered and 20–45% become glucocorticoid dependent [6, 84]. Many patients also develop adverse effects related to chronic steroid therapy [161, 162]. The use of specific antifungal agents in ABPA can decrease the immune response by reducing the antigenic stimulus consequent to a decreased fungal burden, and can thus obviate/reduce the need for glucocorticoids [163]. Ketoconazole has been used in ABPA [164, 165], but has been replaced by the less toxic and more active agent, itraconazole [166–172]. Two randomized controlled studies (84 patients) have evaluated the role of itraconazole in ABPA [171, 172]. In one study, 55 patients with 'glucocorticoid dependent' ABPA were randomized to receive either itraconazole 200 mg twice daily or placebo. The difference between the two groups was in favour of itraconazole in terms of a composite end-point (reduction in steroid dose by ≥ 50%; and, decrease in total IgE by ≥ 25%; and, at least one of the following: increase in exercise tolerance by ≥ 25%, improvement of ≥ 25% in results of spirometry, resolution of pulmonary opacities) but failed to reach statistical

significance when each outcome was examined separately [171]. The other study included 29 'clinically stable' ABPA patients randomized to receive itraconazole or placebo. There was significant decline in sputum inflammatory markers, serum IgE levels and the number of exacerbations [172]. A major limitation was that neither study reported outcomes longer than 8 months in terms of relapses of ABPA. Itraconazole therapy should generally be monitored by drug levels to ensure adequate bioavailability [173]. Toxicity can be minimized if the blood levels are maintained in a therapeutic range [174]. Recent data also suggest that lower blood levels may be associated with clinical failure and possible development of azole resistance in *A. fumigatus* [173, 175]. Itraconazole has also used been used as monotherapy in acute stages of ABPA [169, 172]. However, more trials are required to confirm the efficacy of itraconazole monotherapy. A randomized controlled trial comparing monotherapy of itraconazole vs. prednisolone in ABPA (MIPA study; clinical trials.gov; NCT01321827) is underway, which aims to answer this question.

Which therapy to use? Glucocorticoids or itraconazole or both

Many patients with ABPA require long-term treatment, and both steroids and itraconazole are associated with numerous adverse effects. The side-effects of glucocorticoid therapy are well known, and azole therapy also has numerous side-effects including skin cancer with long-term voriconazole therapy [161, 162, 176–183]. It is also not known whether treatment with steroids or itraconazole will improve long-term outcomes, in particular prevent or reverse bronchiectasis and CPA. Moreover, it is not clear whether ABPA patients in stage 0 should be treated or can be followed without any treatment. However, all experts agreed that if a decision is made not to treat the patient, then he/she should be closely followed. Any significant deterioration in clinical, radiological or immunological status should prompt treatment. All experts also agreed that ABPA with mucoid impaction and/or significant deterioration of lung function attributed to worsening asthma or ABPA (and not intercurrent infection) would benefit from treatment with glucocorticoids (Table 7). In those with mucoid impaction and proximal collapse, assessment should be made at 3 weeks and if the collapse has not resolved despite adequate therapy, therapeutic bronchoscopy should be performed. In those with recurrent exacerbations, one should consider itraconazole therapy. Azoles are effective in preventing ABPA exacerbations but more trials are required for the role of azoles in managing acute exacerbations of ABPA. There are two approaches to the use of azole therapy: recurrent short courses (4–6 months) or long-term therapy with azoles. A major limitation of long-term treatment with azoles is the development of resistance in *A. fumigatus* [132, 184]. Whatever the treatment approach used, it should provide maximum benefit to the patient with least propensity for adverse reactions. High doses of ICS alone have no role in the management of ABPA. Inhaled corticosteroids can be used for the control of asthma once the oral prednisolone dose is reduced to below 10 mg/day. Clinicians should also be aware of the profound interaction between ICS and itraconazole in some patients leading to cushingoid effects and long-term adrenal failure, if dose of ICS is not significantly reduced.

Follow-up of patients on treatment

Patients on treatment should initially be followed every 6–8 weeks with serum IgE levels, chest radiograph, lung function test and quality of life questionnaire (Table 7). Chest radiographs need not be performed once there is normalization (or return to baseline) of the radiographic opacities. The clinical effectiveness of therapy is reflected by decrease in the patient's total serum IgE levels along with symptomatic and radiological improvements. The goal of therapy is not to attempt normalization of IgE levels but to decrease the IgE levels by 25–50% which in most cases leads to clinical and radiographic improvement [34]. One should also aim to establish a stable serum level of total IgE which serves as a baseline to future detection of exacerbation and helps in follow-up of the patient.

Other therapies

There are reports of ABPA complicating CF treated with nebulized amphotericin and inhaled steroids [185–188]. Omalizumab, a humanized monoclonal antibody against IgE, could be a potential therapeutic approach since ABPA is associated with elevated IgE levels. The use of omalizumab in ABPA has been associated with improvement in symptoms, reduction in exacerbations and asthma hospitalizations, improvement in lung function and reduction in dose of oral steroids [189–205]. However, most of these studies are either single patient case-reports or small case-series. Also, the dose required in ABPA may be very high and prohibitively expensive. More data are required before any recommendation regarding the use of omalizumab can be made. Currently, it may be tried in those with steroid-dependent ABPA or in patients who develop treatment-related adverse reactions. Pulse doses of intravenous methylprednisolone have also been used for treatment of severe exacerbations of ABPA [198, 206–210]. Newer antifungal agents including voriconazole [202, 211–218], and posaconazole [183, 210] are also efficacious

in ABPA, if tolerated. Without more data, these drugs are indicated in those intolerant to itraconazole or in itraconazole failures [219].

Adjunct therapies

Nebulized hypertonic saline (7%, 4–5 mL) can be used to reduce the viscosity of sputum to ease expectoration of mucus plugs. However, the first dose should be administered under supervision and preceded by salbutamol because of risk of bronchospasm; one should avoid its use in those with $FEV_1 < 1$ L [2, 220]. Long-term azithromycin therapy can be used to decrease cough and expectoration in patients with bronchiectasis and frequent exacerbations [221, 222]. However, if the patients do not show improvement in 2–3 months, treatment should be stopped. Therapeutic bronchoscopy should be considered in patients who have proximal collapse, which persists after 3–4 weeks of oral steroid therapy in patients compliant with therapy. The removal of mucus plugs can cause significant improvement in symptoms and lung function [223].

Environmental control

Anecdotal patient evidence suggests that some exacerbations are driven by large environmental exposures [39–43]. We therefore recommend avoidance of activities that could result in inhalation of large numbers of *Aspergillus* conidia, such as gardening, agricultural and farm-related activities, exposure to home or other building renovations, housing close to a composting site and cleaning old dusty environments (such as cellars, loft spaces, old books and other archives). If activities are unavoidable, use of surgical masks may minimize spore inhalation.

Complications

The complications of ABPA include recurrent exacerbations, acute respiratory failure due to proximal collapse, bronchiectasis, and if untreated development of bronchiectasis and CPA with occurrence of pulmonary hypertension and type 2 respiratory failure.

Recurrent exacerbations

Recurrent exacerbations in ABPA can either be due to recurrent episodes of mucoid impaction or recurrent episodes of worsening of airflow limitation. In the acute setting, most patients will require treatment with glucocorticoids. However, the aim should be to prevent these recurrent exacerbations by judicious use of either glucocorticoids or azoles.

Large airway collapse

Mucus impaction is a common finding in ABPA [224], although lobar and main bronchial collapse is less common [223]. Patients with large airway collapse can present with acute hypoxemic respiratory failure. In these patients, therapeutic bronchoscopy (either fiberoptic or rigid) is indicated depending on the severity of respiratory failure.

Bronchiectasis

It can be considered the most dreaded complication of ABPA. Currently, most patients are diagnosed with bronchiectasis especially in developing countries [84]. The occurrence of bronchiectasis not only denotes permanent lung damage but also predisposition for recurrent relapses [148]. Hence, routinely investigating asthmatics to diagnose ABPA before development of lung damage is recommended.

Chronic pulmonary aspergillosis

The early descriptions of ABPA included some patients with pulmonary fibrosis and shrinkage, usually of the upper lobe [104, 119]. Pulmonary cavitation has been documented in 3–21% of patients [99, 104, 106, 118, 119]. Likewise lobe shrinkage was documented in 40–42% of patients, usually surrounded by fibrosis [99, 104]. Pleural fibrosis was found in 18–43% of patients [104, 106]. These findings are consistent with CPA, which can complicate the course of numerous pulmonary diseases, including ABPA [225]. CPA progresses at a variable rate, but may be arrested by successful therapy with azoles [226].

Cor pulmonale and/or type 2 respiratory failure

If ABPA is not treated appropriately, widespread bronchiectasis and pulmonary fibrosis can develop, with eventual manifestation of cor pulmonale and chronic type 2 respiratory failure. Some patients can even present with pulmonary hypertension due to missed diagnosis of ABPA [85]. Apart from the anti-inflammatory therapy, long-term oxygen therapy is indicated as in other pulmonary disorders [227].

Allergic bronchopulmonary aspergillosis in special situations

Allergic bronchopulmonary aspergillosis complicating other conditions

Allergic bronchopulmonary aspergillosis can rarely complicate other lung diseases like chronic obstructive

pulmonary disease [228–230], idiopathic bronchiectasis [231], post-tubercular bronchiectasis [232], bronchiectasis secondary to Kartagener's syndrome [233], chronic granulomatous disease and hyper-IgE syndrome [234]. However, more data are required to confirm these associations.

Allergic bronchopulmonary aspergillosis without bronchial asthma

Allergic bronchopulmonary aspergillosis may occasionally develop in those without pre-existing asthma [235]. These cases are often mistaken for other pulmonary disorders like bronchogenic carcinoma or pulmonary tuberculosis because of the absence of asthma [107].

Simultaneous presentation of allergic bronchopulmonary aspergillosis and aspergilloma

The concurrent presentation of ABPA and aspergilloma in the initial stages of the disease represents an immunologically severe form of ABPA with chances of recurrent relapses [149]. In this situation, glucocorticoids are not harmful, and administration of glucocorticoids alleviates the asthma thus decreasing sputum production [236]. In the later stages, aspergilloma could represent a manifestation of CPA with progressive loss of lung function, and risk of massive hemoptysis [237–241]. Antifungal therapy (with or without steroids) is beneficial as it may help in stabilizing the disease, and decrease the occurrence of relapses. However, as many patients would require long-term therapy with azoles, there is an increased potential for adverse drug reactions. Aspergilloma can also antedate the diagnosis of ABPA [236, 242]. Continuous release of *Aspergillus* antigens leads to immunological activation culminating in serological manifestations of ABPA. In fact, serological findings of ABPA can be demonstrated in some cases of aspergilloma complicating long-standing pulmonary cavities, which could represent true hypersensitivity reaction consequent to the *Aspergillus* colonization [236, 238].

Allergic bronchopulmonary mycosis

Allergic bronchopulmonary mycosis is a rare disease with less than 150 cases reported globally [15]. It is an ABPA-like syndrome caused by fungi other than *A. fumigatus*. The diagnostic criteria are essentially similar to ABPA except sensitization to the specific fungi needs to be documented. Numerous fungi have been reported to cause this syndrome, but the frequency is far less when compared to ABPA [1, 15, 86].

Allergic bronchopulmonary aspergillosis and allergic Aspergillus *sinusitis*

Allergic *Aspergillus* sinusitis (AAS) is a form of allergic fungal sinusitis (AFS) in which allergic hypersensitivity to *Aspergillus* (similar to ABPA) occurs in the paranasal sinuses [243]. AAS/AFS may co-exist with ABPA. The diagnosis is primarily based on demonstration of eosinophilic mucin and fungal hyphae in the specimens obtained from the paranasal sinuses [244]. In clinical practice, it may not be possible to confirm the diagnosis of AAS as many patients are reluctant to undergo biopsy required for the diagnosis of AAS [245, 246]. In the absence of histopathological evidence, the expert group suggested that demonstration of hyperattenuating mucus and/or bony erosion on a paranasal CT scan may help in suspecting a case of AFS. Treatment for ABPA should be given with the addition of intranasal glucocorticoids for AFS. Azoles may be required, if the symptoms persist or disease progresses. Surgical clearance of the sinuses is required in patients refractory to medical management.

Severe asthma with fungal sensitization

Severe asthma with fungal sensitization is a specific type of asthma phenotype characterized by all the following: (a) severe asthma, (b) evidence of fungal sensitization and (c) exclusion of ABPA [20, 21]. The crucial and the most difficult step in diagnosis of SAFS is differentiation from ABPA especially ABPA-S [86, 87]. As SAFS has only recently been described, there is need for more data regarding its prevalence, natural history and clinical relevance as a specific subtype of asthma [247]. Patients with SAFS often respond to antifungal therapy [21, 248]. Like ABPA, SAFS can also occur in children [249].

Allergic bronchopulmonary aspergillosis in cystic fibrosis

The prevalence of AS in CF ranges from 27 to 41%, while the ABPA prevalence varies between 2 and 15% [1, 250]. It is important to recognize ABPA in CF because the deterioration of lung function is profound in ABPA with CF compared to a control group of CF not sensitized to *A. fumigatus* [169, 251]. Also, patients with ABPA and CF have higher rates of microbial colonization, pneumothorax, hemoptysis and poorer nutritional status [252]. The recognition of ABPA in CF may be difficult as poorly controlled CF lung disease and ABPA share many clinical characteristics [253]. Wheezing, fleeting pulmonary opacities, bronchiectasis and mucus plugging are common manifestations of CF-related pulmonary disease. The diagnosis of ABPA in CF cannot be based solely on

serology and skin test results, as patients with CF may demonstrate variable responses to *A. fumigatus* and prolonged testing might be required to make a definite diagnosis [254]. To overcome these difficulties, an international consensus conference has made recommendations for diagnosis and management of ABPA in CF [143]. The treatment of ABPA in CF is not very different from that of ABPA in asthma. The treatment issues are further complicated by the fact that pulmonary exacerbations in a patient with ABPA and CF could be related to ABPA or pulmonary infection, and hence continuous assessment may be required before a decision to treat an individual case is made [143]. Treatment is more complex as itraconazole capsules are poorly absorbed. Itraconazole solution may be absorbed, but often requires a dose of 500–600 mg daily. Voriconazole may be more successful but often leads to photosensitivity in Caucasians with the risk of skin cancer, and corticosteroids often induce diabetes mellitus, with its serious consequences in CF.

Future directions

The cut-off values of various investigations such as IgE levels and *A. fumigatus* specific IgE levels could vary by ethnicity or underlying disease (asthma or CF), and these need to be defined by a ROC analysis. The role of novel assays such as recombinant *Aspergillus* antigens, thymus-and activation-regulated cytokine (TARC) and the FACS basophil CD203c assay also requires to be clarified [255–257]. The formation of new diagnostic and staging criteria with precise definitions would go a long way in not only strengthening the diagnosis and management of this chronic pulmonary disorder but would also allow better stratification of disease for genome-wide association studies and drug trials. Newer treatment modalities need to be formalized preferably by a multi-institutional collaboration [258]. For example, vitamin D has recently been shown to down-regulate the Th2 pathway via an OX40 ligand-dependent process in ABPA complicating CF [81]. Vitamin D supplementation may prove beneficial in treatment of ABPA, and is the focus of a recent trial in patients with CF and ABPA (clinicaltrials.gov; NCT01222273). Trials of monoclonal antibodies directed against the Th2 cytokine IL-5 have shown clinical benefit in patients with severe asthma and sputum eosinophilia [259], while a monoclonal antibody against IL-13 has been found effective in asthma patients with a high Th2 endotype [260]. These 'anti-Th2' therapies may also be investigated for their efficacy in patients with ABPA.

Conclusions

In conclusion, the expert group emphasized that a high index of suspicion for ABPA should be maintained while managing any patient with bronchial asthma whatever the severity or the level of control. As patients with ABPA can be minimally symptomatic or asymptomatic, all asthmatic patients should be routinely investigated for ABPA in secondary care. Host immunological responses are central to the pathogenesis and are the primary determinants of the clinical, biological, pathological and radiological features of this disorder. Finally, there is an urgent need for standardization of oral antifungal therapy and immunomodulatory drugs for efficient management of this chronic and debilitating condition.

Conflicts of interest

JFM has acted as a paid consultant/speaker to Astellas, Basilea and Merck and has received funding from Astellas, Basilea, Merck and Schering-Plough. No funding was received related to this work. RA is current recipient of grant support from Cipla, India on research on allergic bronchopulmonary aspergillosis. No funding was received related to this work. DWD holds founder shares in F2G Ltd a University of Manchester spin-out company and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, the European Union and AstraZeneca. He acts as an advisor/consultant to F2G and Myconostica (now part of Lab21 group) and T2Biosystems as well as other companies over the last 5 years including Pfizer, Schering Plough (now Merck), Nektar, Astellas and Gilead. He has been paid for talks on behalf of Merck, Astellas, GSK, Novartis, Merck, Dainippon and Pfizer. RBM is current recipient of grant support from Genentech for research on immunopathogenesis on ABPA. All other authors declare no conflict of interest.

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Appendix

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