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REVIEW ARTICLE

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Allergic bronchopulmonary aspergillosis in India

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Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disorder caused by immune-mediated reactions mounted against *Aspergillus fumigatus*. The disorder most commonly complicates the course of patients with asthma and cystic fibrosis. From its first description in 1952, significant advances have been made in understanding the pathogenesis and the diagnosis and treatment of ABPA. In the last two decades, most research on ABPA has been published from India. The prevalence and clinical presentation may differ in India from that reported elsewhere. Herein, we review the epidemiology, clinical and radiological characteristics, and distinctive features of ABPA in the Indian subcontinent. To support the review, we surveyed pulmonologists nationwide to understand the challenges in diagnosing and managing ABPA. The survey has yielded valuable insights into the practices associated with the diagnosis and management of ABPA in India.

KEYWORDS
ABPM, allergic bronchopulmonary mycoses, allergic fungal airway disease, allergic sensitization, fungal asthma, fungal sensitization

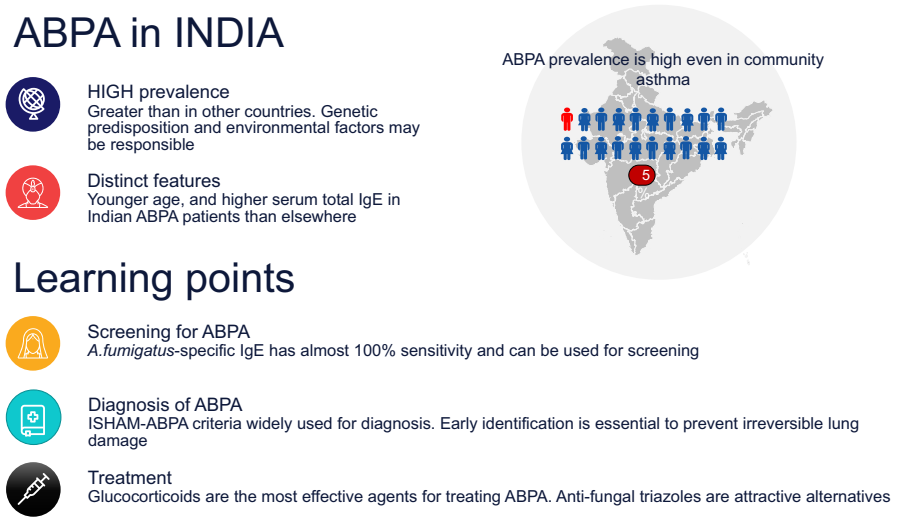
1 | INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is caused by immune responses generated against *Aspergillus fumigatus* colonizing the airways of patients with asthma or cystic fibrosis (CF). A related disorder is allergic bronchopulmonary mycosis (ABPM), an ABPA-like syndrome caused by fungi other than *A. fumigatus*.[1] Patients with ABPA most commonly manifest with difficult-to-treat asthma. Other common symptoms include fleeting pulmonary opacities, expectoration of sputum plugs, hemoptysis, bronchiectasis, and lung collapse. ABPA is a common cause of bronchiectasis in India[2] and is particularly important as it is a treatable cause of bronchiectasis.[3] Early detection and appropriate treatment can prevent the progression of bronchiectasis.

Hinson and colleagues first described ABPA in 1952 from the United Kingdom.[4] The disorder was reported almost two decades later by Shah et al. from India.[5] In the last two decades, several large case series of ABPA have been published from India.[6,7] The frequency and clinical presentation of ABPA may be different in India than that reported elsewhere. For instance, there is little data on CF-ABPA from India.[8] This review summarizes the epidemiology, clinical and imaging characteristics, and distinctive features of ABPA encountered in India. To support the review, we conducted a nationwide survey of pulmonary physicians to understand the current practices in diagnosing and managing ABPA. We contacted chest physicians (3275 members), from the Indian Chest Society and Chest Council of India, on multiple occasions through e-mails to complete the questionnaire (File S1) on the Google Forms platform. We obtained a positive response from 267 (8.2%) pulmonary physicians. The characteristics, practice settings, and diagnosis practices of the physicians included in the Indian ABPA survey compared to the United States[9] are outlined in Table 1.

2 | EPIDEMIOLOGY IN INDIA VS. OTHER COUNTRIES

India is believed to have an ABPA prevalence in asthma of at least twice that reported in other countries.[10] Based on the published literature, we had previously attempted to estimate the burden of ABPA



GRAPHICAL ABSTRACT

ABPA in India has a high community prevalence of 5% in people with asthma. The clinical and radiological features of ABPA differ in India from other countries. *A. fumigatus*-specific IgE has almost 100% sensitivity and can be used for screening asthmatics for ABPA. The ISHAM-ABPA working group criteria are widely used for diagnosis. Early identification is essential to prevent irreversible lung damage. There is an urgent need for increased awareness of ABPA, its diagnosis, and management algorithms.

in Indian asthmatic patients.[11] Using the best guess prevalence of ABPA, we calculated that there would be roughly 1.4 million ABPA cases in India.[11] In a systematic review, we have recently estimated the prevalence of ABPA-complicating asthma.[12] We found 47 studies (9822 asthmatics) reporting the prevalence of ABPA in asthma. Of the 47 studies, the majority were from India ($n=19$).[6,13–30] The prevalence of ABPA in asthmatics (treated in tertiary care asthma or chest clinics) was significantly higher in India than in the rest of the world (788/4703 [16.8%] vs. 409/5119 [7.9%]; $p<.0001$). However, a major caveat of the systematic review was that most studies were reported from tertiary care and, thus, do not represent the population prevalence.

Unfortunately, there is little data on the prevalence of ABPA in the community. In an Irish regional hospital respiratory medicine outpatient (population 536,000), 14 patients with ABPM were identified from 1390 new referrals, suggesting a period prevalence of one percent.[31] In a questionnaire-based study conducted in Orange County, California (2.4 million people), there were 143 cases of ABPA under the care of Pulmonary and Allergy specialists.[32] In another analysis carried out in 1991, the ABPA committee of the American Academy of Allergy, Asthma, and Immunology, in a survey among their members (33% respondents), found 703 ABPA patients under current care. Both the surveys carried out in the United States (US) suggest the prevalence of ABPA (11,000 ABPA patients in a 260 million US population in 1991) of under one percent (12 million asthma patients in the US; roughly 4.2 ABPA patients/100,000 population).[32]

Recently, in a community-based survey, we screened 43,261 participants and diagnosed asthma in 361 patients. Of these, 348 asthmatics were further investigated. We found aspergillus sensitization (AS, raised *A. fumigatus*-specific IgE >0.35 kUA/L) and ABPA in 57 (16.4%) and 20 (5.7%) patients, respectively.[30] The community prevalence of ABPA was 46.2 per 100,000 population. The asthma burden in India has been estimated between 27.6 and 37.9 million.[11,33] Assuming an ABPA prevalence of 5% of asthmatics, India would have roughly 1.4–1.9 million ABPA cases. In the National Health and Nutrition Examination Survey conducted in the United States, the prevalence of AS was 17% in asthma,[34] like in the study from India.[30] However, the ABPA prevalence is higher in India than the United States. The similar proportion of AS but a higher proportion of ABPA in India (versus the United States) point towards a possible role of genetic rather than environmental factors in Indian asthmatics.

Key messages

- ABPA in India has high community prevalence of 5% in people with asthma.
- The clinical and radiological features of ABPA may differ in India from other countries.
- There is an urgent need for increased awareness of ABPA, its diagnosis and management algorithms.

While ABPA usually complicates the course of patients with asthma or CF, uncommonly, ABPA can present in those without asthma (ABPA sans asthma).[35] Interestingly, AS and ABPA have been described from India in several pulmonary disorders other than bronchial asthma.[36–38] We first described the occurrence of ABPA in a patient with chronic obstructive pulmonary disease (COPD).[39] Subsequently, we found the prevalence of AS (using skin testing) and ABPA in COPD as 8.5% (17/200) and 1% (2/200), respectively.[40] In another study, the prevalence of AS in COPD was 13% (26/200) and 9% (18/200) using *A. fumigatus*-specific IgE estimation and skin

TABLE 1 Characteristics, practice settings, and the diagnosis practices of the physicians included in the Indian allergic bronchopulmonary aspergillosis (ABPA) survey compared to the United States.

	India	United States [9]
Number of respondents	267/3275 (8.2)	508[a]/5155 (9.8)
Age, years	43 ± 11	–
Male: female	217:50	–
Indian zone		
North	66/265 (24.7)	
South	68/265 (25.5)	
East	52/265 (19.5)	
West	79/265 (29.6)	
Place of practice		
Private clinic	103/265 (38.6)	
Corporate hospital	79/265 (29.6)	
Government hospital	83/265 (31.1)	
Number of asthma cases seen per month		
Less than 10	12/267 (4.5)	–
10–50	130/267 (48.7)	–
51–100	78/267 (29.2)	–
>100	47/267 (17.6)	–
Number of ABPA cases seen per month (Indian survey) or in the past year (US survey)		
None	36/267 (13.1)	–[a]
1–5	189/267 (70.8)	214/245 (87.3)
6–10	30/267 (11.2)	23/245 (9.4)
>10	12/267 (4.1)	1/245 (0.4)
Number of patients with CF-ABPA in the past year	–	40/245 (16.3)
Tests used for ABPA screening		
Serum *A. fumigatus*-specific IgE	141/267 (52.8)	
Serum total IgE	77/267 (28.8)	
Serum *A. fumigatus*-IgG/ chest radiograph/ skin test/eosinophil count/sputum	15/8/3/13/3	
Tests used for diagnosing ABPA		
A. fumigatus-specific IgE[b]	244/267 (91.4)	157/245 (64.1)
Cut-off ≥0.10 kUA/L	24	
Cut-off ≥0.35 kUA/L	178	
Cut-off ≥0.50 kUA/L	42	
Serum total IgE[b]	265/267 (99.3)	
Cut-off ≥417 IU/mL	8	
Cut-off ≥417 IU/mL	11	110/245 (44.9)
Cut-off ≥500 IU/mL	69	–
Cut-off ≥1000 IU/mL	177	103/245 (42.0)
Peripheral blood eosinophil count[b]	257/267 (96.3)	54/245 (22.0)[c]
<500 cells/μL	6	
≥500 cells/μL	176	
≥1000 cells/ μL	75	
A. fumigatus-specific IgG[b]	215/267 (80.5)	99/245 (40.4)
Cut-off ≥27 mgA/L	100	
Cut-off ≥40 mgA/L	67	
Cut-off ≥60 mgA/L	48	
Aspergillus skin test	77/267 (28.8)	205/245 (83.7)
Sputum fungal smear and culture	58/267 (21.7)	–
Aspergilllus precipitins	53/267 (19.9)	127/245 (51.8)
Serum galactomannan	23/267 (8.6)	–
Bronchiectasis	–	122/245 (49.8)

Note: The values are presented as numbers, mean ± standard deviation or number of responses/total numbers (percentage).

[a]Of the 508 respondents, 263 (51.8%) had not attended any patient of ABPA in the past year and were not included further.

[b]The number of physicians using a test for diagnosis and reporting the cut-offs used for interpretation were different. Hence the numbers may not tally.

[c]The cut-off used was peripheral blood eosinophil count ≥400 cells/μL.

testing, respectively.[41] The prevalence of AS was even higher (19% and 25% using skin test and specific IgE estimation) among bidi-smokers without COPD.[41] Bidi is a smoking tobacco made from 0.2–0.5 g of raw, dried, and crushed tobacco flakes rolled by hand in a *Diospyros melanoxylon* leaf and secured by a cotton thread. Although AS has been described in COPD in other countries, the prevalence is far less than reported in India.[42]

3 | ENVIRONMENTAL AND GENETIC FACTORS IN ABPA

The high prevalence of ABPA in India lacks a clear explanation. The possible reasons could be either environmental or genetic. In a questionnaire-based case–control study, we enquired about the exposure to organic matter and living conditions (home environment, presence of dampness in home, and others) in 202 and 101 patients with ABPA and asthma.[43] Interestingly, we found a higher rural residence in ABPA patients than the asthmatics without ABPA.[43] The higher environmental burden of *A. fumigatus* spores in rural areas,[44] and repeated exposure to fungal spores in asthmatic subjects may explain the higher occurrence of ABPA in rural India. In contrast, ABPA has been noted with a higher frequency in the urban population in the United Kingdom.[45] The issue, however, remains that not all asthmatic patients develop ABPA despite being exposed to the same environment. Thus, host susceptibility must contribute to the development of ABPA.

Familial occurrence of ABPA has been documented in almost 5% of Indian ABPA patients.[46] Several genetic polymorphisms in innate and adaptive immunity have been described in asthmatic ABPA patients.[47] However, only a few studies have evaluated genetic association in Indian ABPA patients (Table 2).[48–50] Not only are these studies limited by their small sample size, but also they have evaluated the association between polymorphisms in surfactant protein A2, mannose-binding lectin, and CFTR gene only. Large studies are needed to explore the host susceptibility factors in Indian ABPA patients.

4 | CLINICAL PRESENTATION

Most patients with ABPA present with difficult-to-treat asthma.[17,51,52] The other common manifestations include fever, hemoptysis, fleeting pulmonary opacities, and bronchiectasis. Interestingly, we found that nearly 19% of patients with ABPA had well-controlled asthma.[17] Thus, symptoms alone are a poor guide to diagnose ABPA. Interestingly, in the Indian survey, a majority (152/267, 57%) of the physicians indicated that they did not routinely screen their asthmatic patients for ABPA. The common indications for screening included severe asthma, bronchiectasis, or other pulmonary opacities on imaging, and raised serum total IgE or peripheral blood eosinophilia. Thus, we believe there is a significant time lag before asthmatic patients are diagnosed with ABPA in India. This could be a reason for the high prevalence of bronchiectasis in Indian ABPA patients.

We compared the clinical presentation in Indian patients with ABPA to those in Japan, China, and France (Table 3).[7,53–55] The Indian ABPA patients were younger, with high total IgE and extensive bronchiectasis. One of the reasons for the extensive bronchiectasis and high total IgE could be delayed recognition and more severe disease, as almost a third of Indian ABPA patients are misdiagnosed as pulmonary tuberculosis.[7] High-attenuation mucus, an immunologically severe disease,[56] was more common in India and Japan than in France or China. The Japanese patients had higher eosinophil counts than the Indian patients and other countries. The high eosinophil count may account for Japan's higher frequency of high-attenuation mucus.

5 | DIAGNOSIS OF ABPA

The common investigations used for diagnosing ABPA include skin tests (prick or intradermal) for *Aspergillus* sensitization, serum *A. fumigatus*-specific IgE, serum precipitins or IgG against *A. fumigatus*, serum total IgE, peripheral blood eosinophil count, chest radiograph, computed tomography (CT) of the chest, sputum cultures, and spirometry.

5.1 | *A. fumigatus*-specific IgE

A. fumigatus-specific IgE is the preferred investigation for screening asthmatic patients for ABPA, with a sensitivity and specificity of 100% and 72% at a cut-off of 0.35 kUA/L (using the Phadia platform).[23,57] Studies for the cut-off values with the other commercial platforms are lacking. In our survey, 53% (141/267) of physicians used *A. fumigatus*-specific IgE as a screening test for ABPA; however, only 67% considered a value >0.35 kUA/L as positive.

5.2 | Aspergillus skin test

The sensitivity of skin testing in the diagnosis of ABPA ranges from 88%–94%, thus can potentially miss 6%–12% of ABPA.[23,58] Moreover, skin testing can be affected by the quality of the antigen,[59] the competence of the technical staff performing the test, and the potential risk of anaphylaxis. Hence, skin testing is not favoured for screening asthmatic patients for ABPA. Notably, less than two percent of the practitioners across India used skin tests as a screening tool for ABPA.

TABLE 2 Genetic susceptibility in asthmatic allergic bronchopulmonary aspergillosis (ABPA) patients in India.

Author/reference	Mutations/polymorphisms	Number of ABPA patients	Control population	Significance OR (95% confidence intervals)
Surfactant Protein A2 (10q22.3)				
Saxena (2003)[48]	G1649C in exon 4	32	34 controls	2.6 (1.2–5.7), $p = .01$
Saxena (2003)[48]	T1492C in intron 3	32	34 controls	4.8 (1.1–21.6), $p = .03$
Saxena (2003)[48]	A1660G in exon 4	27	–	5.3 (1.7–16.9), $p = .002$
Mannose-binding lectin (10q11.2-q21)				
Kaur (2006)[49]	G1011A in intron 1	11	49 allergic individuals; 84 controls	Allergy: 1.2 (0.5–3.3), $p = .7$ Control: 8.2 (2.8–23.4), $p < .0001$
CFTR mutations (7q31.2)				
Kanaujia (2022)[50]	CFTR gene sequencing	18	12 asthmatics, 8 controls	Asthma: 0.52 (0.07–3.27), $p = .47$ Control: 5.0 (0.52–52.53), $p = .31$

Abbreviation: CFTR, cystic fibrosis transmembrane conductance regulator.

TABLE 3 Clinical characteristics of patients with allergic bronchopulmonary aspergillosis (ABPA) across three countries.

Parameters	India ($n=810$)[7]	Japan ($n=358$)[54]	France ($n=139$)[53]	China ($n=232$)[55]
Age, years	35 ± 13	64 (51–72)	60 ± 11	42 ± 18
M:F	410:400	154:204	67:72	112:120
Age of onset				
Asthma	–	37 (10–55)	–	–
ABPA	–	57 (44–68)	–	
Duration of asthma, y	12 ± 10		29 ± 21.5	–
Hemoptysis	258/810 (31.9%)	–	–	18/232 (17.8%)
Expectoration of mucus plugs	211/810 (26.1%)	–	–	45/232 (19.4%)
History of inappropriate anti-tuberculosis therapy	258/810 (31.9%)	–		19/232 (14.4%)
Serum *A. fumigatus*-IgE, kUA/L	21.6 (7.3–40.8)	–	10.2 (1.9–31.8)	–
Serum *A. fumigatus*-IgG, mgA/L	89 (49–172)	–	–	–
Serum total IgE, IU/mL	7113 (3300–11,800)	1913 (758–5555)	492 (299–1855)	4174 ± 1345
Peripheral blood eosinophil count, cells/μL	800 (400–1400)	1075 (640–1797)	165 (65–360)	630 ± 120
Sputum culture				
Aspergillus spp.	–	118/210 (56%)	–	
Schizophyllum commune	–	8/210 (4%)	–	
Bronchiectasis	704/810 (86.9%)	358/487 (73.5%)	120 (86.3%)	174/232 (75%)
Number of lobes involved	4 (2–5)			–
Number of segments involved	7 (4–11)	–	–	–
High-attenuation mucus	286 (35.3%)	148 (41.3%)	12 (8.6)	–

Note: All the values are represented as either *n/N* (percentage), median (25–75 percentile), or mean ± standard deviation.

5.3 | Serum total IgE levels

The serum total IgE is an essential test for diagnosing and monitoring treatment in patients with ABPA. A normal serum IgE level almost completely excludes active ABPA as the cause of the patient's current symptoms. The sensitivity and specificity of serum total IgE (at cut-off 500 IU/mL) as a screening test for ABPA is less than *A. fumigatus*-specific IgE (98% and 49% vs. 100% and 72%).[29] Thus, serum total IgE is inferior to *A. fumigatus*-IgE as it will pick up more false positives. In the survey, almost one-third of the practitioners still used serum total IgE as a screening test. Serum total IgE is helpful for monitoring therapy.[60] A fall by >25% of the baseline IgE levels suggests a response to treatment, while a 50% increase in serum IgE levels, along with clinical or radiological worsening, signifies an ABPA exacerbation.

5.4 | *A. fumigatus*-specific IgG

A. fumigatus-specific IgG antibodies can be detected by either immunoprecipitation methods (double gel diffusion and counter immunoassay techniques) or commercial enzyme immunoassays. In a systematic review, the pooled sensitivity was 69% (95% CI, 48–84) and 85% (95% CI, 73–92) for immunoprecipitation and immunoassay methods, respectively. One additional ABPA case was detected for every six (95% CI, 5–7) tests performed with immunoassay (versus immunoprecipitation).[61] Hence, enzyme immunoassay methods should be used in preference to the traditional immunoprecipitation methods.

The optimal cut-off for *A. fumigatus*-specific IgG varies between different ethnicities.[62] In the Japanese population, the cut-off value for *A. fumigatus*-specific IgG in diagnosing ABPA is 60 mgA/L using the Phadia fluorescent enzyme immunoassay platform.[63] In contrast, we found a cut-off value of 27 mgA/L in India.[64] Despite India-specific cut-off values, only 37% used the 27 mgA/L cut-off. The remaining used cut-offs of 40 mgA/L (manufacturer recommended) and 60 mgA/L (Table 1). Recently, a point-of-care lateral flow assay (LFA) for detecting *A. fumigatus*-IgG was found to have sensitivity and specificity of 89% and 96%, respectively, in chronic aspergillosis.[65] However, more evidence is needed in ABPA.

5.5 | Peripheral blood total eosinophil count (TEC)

A TEC >500 cells/μL is considered a major criterion for diagnosing ABPA.[66] We had previously shown that 76% of ABPA patients had TEC above 500 cells/μL, while only 41% had a count greater than

1000 cells/μL.[67] The sensitivity of total eosinophil count is only 74% for diagnosing ABPA.[29] In the survey, 5% of the physicians used TEC as a screening test. However, one-third of the physicians still used 1000 cells/μL cut-off for diagnosing ABPA.

5.6 | Chest radiograph

Chest radiograph has limited utility in diagnosing ABPA as normal radiograph may be encountered despite the patient having bronchiectasis on CT thorax.[68] In the survey, only 1% of the physicians used chest radiographs for screening asthmatic patients for ABPA. A chest radiograph is helpful in follow-up, as transient abnormalities clear after the institution of therapy for ABPA.

5.7 | CT of the chest

CT of the chest is the preferred imaging modality for ABPA.[69] The most common finding is bronchiectasis (Figure 1). Other findings include mucus impaction, centrilobular nodules, consolidation, mosaic attenuation, and others. Apart from high-attenuation mucus (HAM), none of the CT findings are pathognomonic of ABPA. HAM is defined as mucus visually denser than the paraspinal skeletal muscle (Figure 2).[17,56,70–72] The presence of HAM can be used as a rule-in test for ABPA.[29,71] Other uncommon imaging findings include miliary nodular opacities,[73] perihilar opacities simulating hilar lymphadenopathy,[74,75] pleural effusions,[76] complete lung collapse,[77] and pulmonary masses.[78] Notably, ABPA can present without any radiological manifestations (serologic ABPA).[68] Thus, diagnosis of ABPA should be based on immunological findings and not imaging alone. Most chest physicians (99%) from India use CT chest to detect bronchiectasis in ABPA.

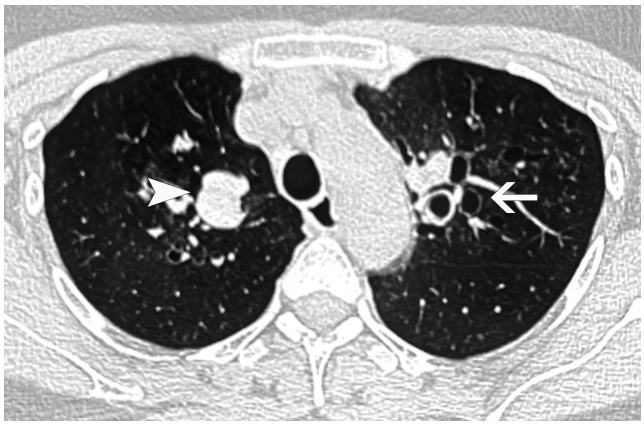


FIGURE 1 Computed tomography of the chest (lung windows) showing bronchiectasis in the left lung (arrows). The right lung shows mucus-filled dilated bronchi, which are called bronchocele (arrowhead).

5.8 | Sputum cultures

A. fumigatus can be cultured in various pulmonary diseases other than ABPA due to its ubiquitous nature.[79] Moreover, the culture positivity for *A. fumigatus* varies between 34 and 60%.[80–82] Importantly, patients with ABPA are colonized not only by the causative fungi but also by other fungi and bacteria. Sputum cultures can provide clues to other pathogenic fungi (especially in ABPM), especially if the organism is repeatedly isolated.[82] Another important advantage is documenting antifungal drug resistance prior to or during treatment.[83,84] We routinely obtain bacterial cultures of sputum to rule out and treat infection with *Pseudomonas aeruginosa* and other organisms before starting ABPA treatment.[85,86]

5.9 | Spirometry

Spirometry is useful in categorizing the severity of the underlying lung disease (asthma and bronchiectasis) and shows an obstructive defect of varying severity.[87–90] Serial measurement of forced expiratory volume in the first second (FEV1) can be used as an objective criterion for assessing treatment response in ABPA.[91] Recently, we found a minimally significant difference for FEV1 in acute stage ABPA of 158 mL (or 17%).[91]

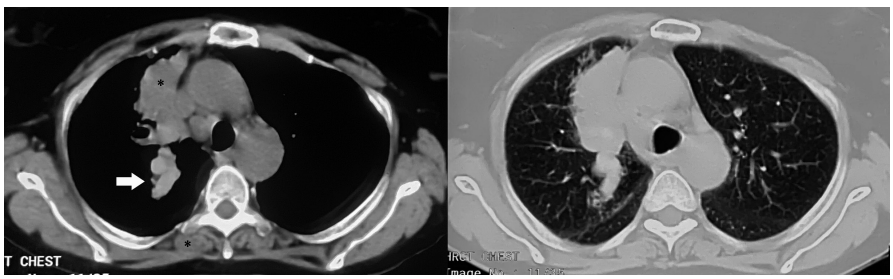


FIGURE 2 Computed tomography of the chest (mediastinal windows, right panel) showing high-attenuation mucus (broad arrow). The mucus is visually denser than the paraspinal skeletal muscle (asterisk). There is also mucus plugging (isodense or hypodense, asterisk) and collapse of the anterior segment of the right upper lobe. The corresponding lung window is shown in the left panel.

6 | OTHER INVESTIGATIONS

6.1 | Galactomannan detection

Galactomannan is a polysaccharide component of the *Aspergillus* cell wall and is released during fungal growth. Serum galactomannan helps diagnose invasive pulmonary aspergillosis.[92] However, the estimation of serum galactomannan has a poor sensitivity (27% at a cut-off of 0.5) to diagnose ABPA (25.7%) and is not recommended.[93] In the survey, 6% of the physicians used GM to diagnose ABPA.

6.2 | Recombinant Aspergillus antigens

Presently, the antigens used to diagnose ABPA are non-specific and frequently cross-react with other fungi.[94,95] The World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee recognizes 23 specific antigens of *A. fumigatus*.[96] Three commercially available recombinant antigens (rAsp f1, rAsp f2, and rAsp f4) are specific to *A. fumigatus*.[97] In a recent study, rAsp f1 at a cut-off value of 4.47 kUA/L had a sensitivity and specificity of 89% and 100%, respectively, for diagnosing ABPA in asthmatic subjects from India.[98] Unfortunately, recombinant antigens are not widely available in India.

6.3 | Basophil activation test

Basophil activation test (BAT) is an in vitro flow cytometry-based cellular assay that measures the activation of basophils upon allergen stimulation with the aid of surface markers (CD63, CD193, and CD203c). While several studies suggest a promising role of BAT in diagnosing ABPA-complicating CF, we found a limited utility of BAT in diagnosing ABPA-complicating asthma.[99] Moreover, the test has two significant limitations: the requirement of a flow cytometer and performance of the test within a few hours of blood sample collection. Thus, BAT is unlikely to be widely used in India.

7 | DIAGNOSTIC CRITERIA

The diagnosis of ABPA is made on a composite of clinical, radiological, and immunological findings (Table 4).[23,29,66,100–103] The Rosenberg-Patterson criteria (8 major, 3 minor) were the earliest criteria framed for diagnosing ABPA.[104] The Patterson criteria had a few limitations, including disagreement on the number of components to diagnose ABPA, offering equal weightage to all the components, and the absence of cut-off values for the various immunological tests.[100,105] The International Society for Human and Animal Mycology (ISHAM) formed an ABPA working group to improve the diagnosis and management of ABPA in asthma. The working group proposed new criteria for diagnosing ABPA that are now widely used.[106] The ISHAM ABPA working group criteria were

TABLE 4 Diagnostic criteria for ABPA.

Rosenberg-Patterson criteria (1977)[104]	ISHAM-ABPA working group criteria (2013)[66]	Modified-ISHAM-ABPA working group criteria (2021)[29]	Japan ABPM Research Program criteria (2021)[108]
Primary • Asthma • Peripheral blood eosinophilia • Immediate skin reactivity to aspergillus antigen • Precipitating antibodies against aspergillus antigens • Increased serum total IgE • Pulmonary infiltrates (transient or fixed) • Central bronchiectasis Secondary • *Aspergillus fumigatus* in sputum (by repeated culture or microscopic examination) • History of expectoration of brown plugs or flecks • Late skin reactivity (Arthus reactivity) to *Aspergillus* antigen	Predisposing condition • Asthma or CF Obligatory • Positive type 1 skin test or elevated serum *A. fumigatus*-specific IgE • Total IgE >1000 IU/mL Any 2 of following • Precipitating antibodies or IgG against *A. fumigatus* • Imaging features consistent with ABPA • Peripheral blood eosinophils >500 cell/μL	All should be present • *A. fumigatus*-specific IgE >0.35 kUA/L • Serum total IgE >500 IU/mL And ≥2 of the following • *A. fumigatus*-specific IgG >27 mgA/L (Phadia platform) • Bronchiectasis on CT thorax • Peripheral blood eosinophil count >500 cells/μL	Presence of ≥6 criteria • Asthma • Peripheral blood eosinophil count >500 cells/μL • Serum total IgE >417 IU/L • Immediate cutaneous hypersensitivity or elevated serum fungi-specific IgE • Presence of precipitins or specific IgG for filamentous fungi • Filamentous fungus growth in sputum cultures or bronchial lavage fluid • Presence of fungal hyphae in bronchial mucus plugs • Central bronchiectasis on CT thorax • Presence of mucus plugs in central bronchi, based on CT/ bronchoscopy or mucus plug expectoration history • High attenuation mucus on CT chest

proposed in 2013 (Table 4). Subsequently, evidence has emerged which indicates that *A. fumigatus*-IgE is better than skin tests,[23,29] *A. fumigatus*-IgG is superior to precipitation tests,[61,64] CT imaging performs better than chest radiographs,[29] and the serum total IgE cut-off of 500 IU/mL is more sensitive than 1000 IU/mL.[93] We modified the ISHAM-ABPA working group criteria (Table 4) by incorporating these changes and found better sensitivity of the modified (100%) than the original criteria (89%). In another study, we investigated the diagnostic performance of different criteria when one or more formal investigations have not been performed in ABPA diagnosis.[107] This study is relevant in India and other resource-constrained settings where all investigations are unavailable or cannot be performed. Elsewhere, Asano et al. found the Japan ABPM Research Program criteria more sensitive than the Rosenberg-Patterson and the ISHAM-working group criteria in asthmatic subjects.[108] Subjects meeting at least six of the 10 components are labelled as definite ABPA/ABPM, while those meeting five are categorized as probable ABPA/ABPM (Table 4). Our survey found that most physicians used either the ISHAM (67%) or the Rosenberg-Patterson (17%) criteria for diagnosing ABPA. Fifteen percent of the respondents did not specify any criteria for ABPA diagnosis.

8 | TREATMENT OF ABPA

Early diagnosis and appropriate treatment of ABPA are essential to prevent irreversible damage due to bronchiectasis.[109] Notably, a few of our asthmatic patients have presented with pulmonary hypertension due to undiagnosed ABPA.[110] The optimal treatment regimen for ABPA should achieve early control of symptoms, prevent the progression of bronchiectasis, and reduce the risk of future exacerbation with the least possible adverse events. The current treatment options are directed either against the inciting fungus (antifungal agents) or the immune response to the fungus (e.g., glucocorticoids).[105] A consensus guideline[66] published a decade earlier found only three randomized controlled trials in the treatment of ABPA.[111–113] Subsequently, eight more RCTs have been conducted in the last decade.[53,85,114–119] The RCTs have confirmed the efficacy of prednisolone, itraconazole, and voriconazole monotherapy for inducing a response in acute-stage ABPA.[111,112,115,117,118]

Despite being the best-studied agent, only 130 (48.7%) of the 267 survey respondents preferred prednisolone as the initial treatment of choice. The dose and duration varied from 0.5 to 1 mg/kg/day of prednisolone for a median of six months (range, 0.5 to 24 months). The prescribed regimen often deviated from the currently suggested prednisolone dose, 0.5, 0.25, 0.125 mg/kg/day for 4 weeks each, then tapered over the next month for an overall duration of 4 months. An additional 14.2% of respondents used methylprednisolone, frequently at doses and duration greater than the current recommendations. Although relapses are of concern in patients with ABPA (with nearly a third of the patients experiencing frequent exacerbations),[35] a higher dose of prednisolone has not been shown to delay or prevent exacerbations.[115]

Azole monotherapy was used by only 7.4% of the survey respondents. Itraconazole and voriconazole effectively induce treatment response and are reasonable alternatives to prednisolone.[117,118] RCTs have also shown that the exacerbation rate at one and two

TABLE 5 Doses of commonly used therapies in the management of allergic bronchopulmonary aspergillosis.

Oral glucocorticoids
Prednisolone (or equivalent) 0.5 mg/kg/day for 4 weeks, 0.25 mg/kg/day for 4 weeks, 0.125 mg/kg/day for 4 weeks, tapered over the next month; total duration: 4 months
Oral azoles (with therapeutic drug level monitoring)
Oral itraconazole 200 mg twice a day for 16–24 weeks (trough level target 0.5–1 μg/mL)
Oral voriconazole 200 mg twice a day for 16–24 weeks (trough level target ≥1 μg/mL)
Nebulized amphotericin B
Amphotericin B deoxycholate Daily: 5–40 mg twice daily Intermittent: 20 mg (10 mg twice daily) thrice weekly
Liposomal amphotericin B Intermittent: 25 mg twice weekly
Amphotericin B lipid complex[a] Intermittent: 50 mg twice weekly
Pulse methylprednisolone[a]
15 mg/kg/day (maximum 1 g) intravenous infusion for three consecutive days
Omalizumab
375 mg subcutaneously every 2 weeks for 4–6 months
Mepolizumab[a]
100 mg subcutaneously every 4 weeks
Benralizumab[a]
30 mg subcutaneously every 4 weeks for 3 doses, then every 8 weeks
Dupilumab[a]
400–600 mg subcutaneously once (given as 2 or 3200 mg injections), followed by 200–300 mg every other week
Tezepelumab[a]
210 mg subcutaneously every 4 weeks
Follow-up and monitoring • Clinical symptoms (cough, dyspnea), chest radiograph, and total IgE levels monitored every 8 weeks • Satisfactory response to therapy is suggested when there is clinical and radiological improvement along with at least a 25% decline in IgE levels • Monitor IgE frequently to establish the 'new' baseline level for an individual patient • Monitor for treatment-related adverse effects and drug interactions • Clinical or radiological worsening, along with a >50% increase in IgE levels, suggests an ABPA exacerbation

[a]There are no published randomized trials in ABPA.

years is similar to prednisolone or antifungal monotherapy.[115,117] Unfortunately, most physicians were either using a subtherapeutic dose (100 mg BD) of itraconazole or were unclear about the dosing regimen of itraconazole (Table 5 provides suggested doses). In addition, therapeutic drug level monitoring was used only by 15% of the respondents. To be effective, antifungal azoles (particularly itraconazole) should be administered in appropriate doses (itraconazole 200 mg twice daily administered with meals), and therapeutic drug monitoring is essential.[120] Lack of awareness and inadequate laboratory facilities were major deterrents for therapeutic drug monitoring. Suboptimal drug levels can lead to poor disease control and the subsequent use of multiple, prolonged, or unproven treatment regimens. The judicious use of antifungal azoles is also essential to avoid the emergence of azole-resistant *A. fumigatus*.[121,122] We have found that poor drug quality could be a significant reason for therapeutic failure with itraconazole in chronic pulmonary aspergillosis.[123] The generic itraconazole formulations available in the Indian market with questionable drug availability could thus compound the existing problem of managing ABPA.[124,125] Significant drug interactions of itraconazole with other drugs, including inhaled and systemic glucocorticoids, should be considered, especially when used over prolonged periods.

Nearly 27% of the physicians in the survey reported using a combination of prednisolone with an antifungal azole for acute-stage ABPA, a practice that is not supported by strong evidence. The data suggest that prednisolone monotherapy and combination therapy are equally effective in inducing remission.[85] Although a recent RCT suggested a non-significant trend in decreasing ABPA exacerbations at one year with the combination of prednisolone-itraconazole than prednisolone monotherapy, more data is required.[85] Further,

TABLE 6 Clinical staging of allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma.

Stage	Definition	Features	Management
0	Asymptomatic	• No previous diagnosis of ABPA • Controlled asthma (according to standard asthma guidelines) • Fulfilling the diagnostic criteria of ABPA	• Management of underlying bronchial asthma and observation • ABPA therapy may not be required
1	Acute	• No previous diagnosis of ABPA • Uncontrolled asthma or symptoms consistent with ABPA • Meeting the diagnostic criteria of ABPA	• Prednisolone for 4 months. Alternatively, itraconazole or voriconazole for 4–6 months
	1a, with mucoid impaction	Mucoid impaction observed on chest imaging or bronchoscopy	May consider adjunctive bronchoscopic therapy
	1b, Without mucoid impaction	Absence of mucoid impaction on chest imaging or bronchoscopy	
2	Response	• Clinical or radiological improvement AND • Decline in serum total IgE by ≥25% of baseline at eight weeks	• Management of underlying bronchial asthma • Monitoring treatment with serum total IgE, spirometry, quality-of-life questionnaires, and chest radiograph
3	Exacerbation	• Clinical or radiological worsening AND • Increase in serum total IgE by ≥50% from the new baseline established during response/remission Asthma exacerbation: worsening cough and dyspnea, no radiological deterioration, and < 50% increase in serum total IgE	Prednisolone, itraconazole, or a combination of prednisolone and itraconazole
4	Remission	• Sustained clinicoradiological improvement AND • Serum total IgE at or below baseline (or increase by <50%) for ≥6 months off treatment	• Management of underlying bronchial asthma • Monitoring treatment with serum total IgE, spirometry, quality-of-life questionnaires, and chest radiograph
5a	Treatment-dependent ABPA	• ≥2 exacerbations within 6 months of stopping therapy OR • Worsening of symptoms or imaging and rise in serum total IgE on tapering oral steroids/azoles	Control of exacerbation with prednisolone, itraconazole, or their combination followed by any of the following: itraconazole, low-dose glucocorticoids, omalizumab, monthly pulses of methylprednisolone or nebulized amphotericin B
5b	Glucocorticoid-dependent asthma	Systemic glucocorticoids required for the control of asthma, while the ABPA activity is controlled (as indicated by IgE levels and thoracic imaging)	
6	Advanced ABPA	• Extensive bronchiectasis due to ABPA on chest imaging AND • Cor pulmonale or chronic type 2 respiratory failure	• Pharmacological control of asthma, glucocorticoids or azoles or their combination, depending on the disease activity. • Pulmonary rehabilitation, long-term oxygen therapy, domiciliary non-invasive ventilation, and lung transplantation, as indicated

most subjects with ABPA do not exacerbate frequently, and the subset of patients who might benefit from a combination therapy is unknown. Hence, the routine prescription of a prednisolone-itraconazole combination for ABPA as the initial therapy should be avoided. Itraconazole is a potent inhibitor of the enzyme cytochrome P450 (particularly CYP3A4) and can thus increase the drug levels of glucocorticoids. Notably, itraconazole increased the concentration of methylprednisolone but not prednisolone.[126] This fact is particularly relevant and concerning since a significant proportion of chest specialists in our survey preferred methylprednisolone over prednisolone.

Of the few adjunctive therapies for ABPA, nebulized amphotericin B (NAB) has been evaluated in two clinical trials.[53,116] While NAB did not reduce the proportion of subjects experiencing an exacerbation, it could delay the occurrence of ABPA exacerbations and requires further evaluation.[53] A small randomized cross-over trial of 13 patients found omalizumab as an effective therapy for patients with chronic ABPA.[114]

Potential treatment options that require randomized trials include targeted therapies such as biological agents against serum total IgE, interleukin (IL)-5 or its receptor, IL-4 receptor, thymic stromal lymphopoietin, IL-25, and IL-33. Thirty-four percent of our survey respondents had experience using biologicals for ABPA, the most common being omalizumab (78%), followed by mepolizumab (14%), and others. The indications for using biological agents and the ideal treatment duration in ABPA must be better defined. The survey also points towards the need for regulation and formal guidance to prevent the misuse of biological agents. ABPA registries and recording information on the use of biologicals can provide interim guidance till more robust evidence from clinical trials are available. Most treatment options discussed above are freely available in India. Indeed, the unregulated use of these medications is a challenge while managing ABPA.

8.1 | Monitoring treatment in ABPA

Given the chronic nature of the disease, the ISHAM-ABPA working group has proposed a clinical framework for staging ABPA (stages 0–6, Table 6),[66] which can also be used in patients undergoing treatment. Response to treatment (stage 2) is characterized by a decline in the serum total IgE by at least 25% (usually performed after eight weeks of treatment), along with clinical or radiological improvement. With successful treatment, the serum total IgE falls progressively. After clinical and radiological stabilization, the nadir of IgE is defined as the 'new' baseline. Exacerbation is diagnosed in the presence of either clinical or radiologic worsening and an increase in the serum total IgE by at least 50% from the 'new' baseline (stage 3). ABPA remission (stage 4) is categorized if there is clinical, immunologic (<50% increase from 'new' baseline), and radiologic stability for at least six months without any ABPA-specific therapy. Patients continuing to require glucocorticoids for controlling ABPA or asthma are classified as treatment-dependent ABPA (stage 5a) or glucocorticoid-dependent asthma (stage 5b), respectively.

In our survey, most respondents (192/267, 71.9%) relied on a combination of clinical, immunological, and radiological criteria to identify ABPA exacerbation, while a small (3%) proportion relied on clinical symptoms only. Poorly controlled asthma resembles ABPA,[127] and distinguishing between the two requires immunological tests and imaging. Also, the reliance on only clinical and radiological criteria (10% of the respondents) is fraught with the risk

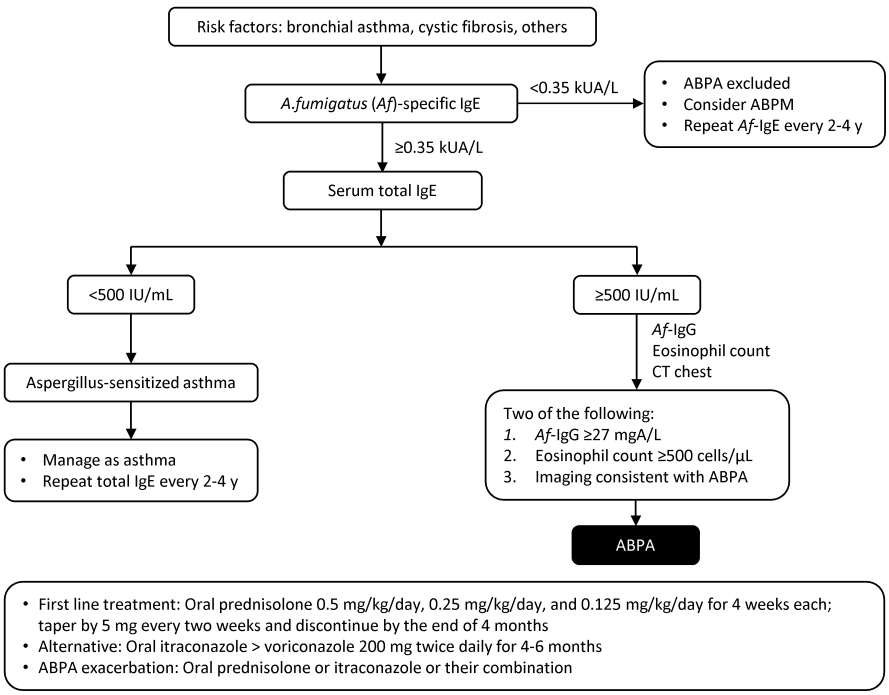


FIGURE 3 Simplified algorithm for diagnosing and treating allergic bronchopulmonary aspergillosis.

of overdiagnosing exacerbation since certain radiological changes are persistent (e.g., bronchiectasis). Poor inhaler technique, nonadherence to inhaled glucocorticoids, and unaddressed comorbid conditions are common causes of poorly controlled asthma in India. They can result in an erroneous diagnosis of ABPA exacerbation. Interlaboratory variation in IgE measurement and unreliable markers during monitoring (*A. fumigatus*-specific IgE, IgG) are also possible sources of error.[60,64,128] *A. fumigatus*-specific IgE or IgG has no role in monitoring treatment response. We found that *A. fumigatus*-specific IgE and IgG may also increase (instead of decrease) following treatment and decline during an exacerbation.[60,64]

On the contrary, the dynamic nature of several monitoring parameters (including serum total IgE and peripheral blood eosinophil count)[57,67] coupled with the over-the-counter use of systemic glucocorticoids can result in underdiagnosis. Hence, a reliable diagnosis of an ABPA exacerbation requires clinical judgement, serial imaging, and serum total IgE (an increase of >50% from the previously available value).

9 | FUTURE DIRECTIONS

Despite the high prevalence of ABPA in India, almost one-third of the cases are still misdiagnosed as pulmonary tuberculosis. Although the response rate of the survey was low, it has still yielded valuable insights into the practices associated with the diagnosis and management of ABPA. There is an urgent need to increase awareness of ABPA and the algorithms for its diagnosis and management (Figure 3). Given the high prevalence of ABPA in Indian asthma patients, all patients with persistent asthma should be routinely screened for ABPA. Although commercial laboratory facilities have now allowed increased accessibility of investigations for diagnosing ABPA, the tests are expensive, and the cost of these tests needs to be reduced. Most data on the prevalence of ABPA in India is from the north; hence, more studies are required from other parts of the country to know the true prevalence across the country. There is also a need to form a nationwide ABPA registry for multicentric collaboration and research. Finally, an unmet demand exists to understand the causes behind the high prevalence. Multifaceted studies combining environmental causes and host susceptibility would provide an answer to this perplexing question.

AUTHOR CONTRIBUTIONS

RA: conceived the idea, drafted and revised the manuscript. ISS: drafted and revised the manuscript. VM: drafted and revised the manuscript. RD: revised the manuscript. DAJ: revised the manuscript.

CONFLICT OF INTEREST STATEMENT

RA: grant support for conducting research in ABPA from Cipla Pharmaceuticals, Mumbai, India. ISS: conflicts of interest–none; financial disclosures–none. VM: conflicts of interest–none; financial disclosures–none. RD: conflicts of interest–none; financial disclosures–none. DAJ: DAJ holds share options in Pulmocide Ltd.

DATA AVAILABILITY STATEMENT

Data statement not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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