

## A challenge in diagnosis and treatment in asthma patients with allergic bronchopulmonary aspergillosis: a review

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### ABSTRACT

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Allergic bronchopulmonary aspergillosis (ABPA) is a common form of fungal-related asthma disease mainly caused by *Aspergillus fumigatus*. The increasing prevalence of asthma globally and the characteristic of *Aspergillus* are very easily dispersed in the air to inhale, leading to increased cases of ABPA in asthma patients. Inhalation of conidia *Aspergillus* spp. can trigger asthma exacerbations due to poor mucociliary clearance. However, the exact pathogenesis is still unclear. Clinical features commonly found in ABPA patients are productive cough with dark green or brown mucus or even hemoptysis. Several criteria for establishing the diagnosis of ABPA can be based on clinical features, laboratory examinations, and imaging, but none has become the gold standard. However, the primary laboratory test utilized for ABPA screening is the measurement of serum-specific IgE levels to *A. fumigatus*, owing to its high sensitivity. Despite the challenges in finding the most fitting universal consensus, most clinicians still follow the criteria proposed by Rosenberg *et al.* in 1977. The recommended ABPA treatment is prednisone and/or azole antifungal agents such as itraconazole. In addition, the potential of monoclonal antibodies in ABPA therapy is still under further research. Long-term diagnosis and treatment delays can lead to complications such as bronchiectasis and fibrosis. This review aimed to highlight ABPA in asthma patients, from etiopathogenesis to managing the disease.

### ABSTRACT

Aspergilosis bronkopulmoner alergika (ABPA) adalah salah satu bentuk umum dari penyakit asma yang berkaitan dengan infeksi jamur, utamanya *Aspergillus fumigatus*. Prevalensi asma yang meningkat di seluruh dunia dan karakteristik *Aspergillus* yang sangat mudah tersebar di udara dan mudah terhirup menyebabkan peningkatan kasus ABPA pada pasien asma. Inhalasi konidia *Aspergillus* spp. dapat menyebabkan eksaserbasi asma akibat klirens mukosilier yang buruk, namun patogenesisnya pastinya masih belum jelas. Gambaran klinis yang umumnya ditemukan pada pasien ABPA dengan asma adalah batuk produktif dengan sekret hijau tua atau coklat hingga hemoptisis. Kriteria penegakan diagnosis ABPA dapat didasarkan pada gambaran klinis, pemeriksaan penunjang, dan gambaran radiologi, namun belum ada yang menjadi standar baku emas. Meskipun demikian, pemeriksaan laboratorium yang sering digunakan untuk skrining ABPA adalah kadar IgE spesifik *A. fumigatus* pada serum karena sensitivitasnya yang tinggi. Terlepas dari kesulitan dalam menentukan konsensus universal, kebanyakan klinisi masih mengikuti kriteria yang disusun oleh Rosenberg dkk. pada tahun 1977. Terapi ABPA yang direkomendasikan adalah prednison dan/atau agen antifungal azol seperti itraconazol. Di samping itu, terapi ABPA dengan antibodi monoklonal memiliki potensi namun masih perlu diteliti lebih lanjut. Diagnosis yang terlambat dan terapi yang tertunda dapat menyebabkan komplikasi seperti bronkiektasis dan fibrosis. Kajian pustaka ini membahas ABPA pada pasien asma, mulai dari etiopatogenesis hingga penatalaksanaannya.

### Keywords:

allergic bronchopulmonary aspergillosis;  
*Aspergillus fumigatus*;  
asthma;  
diagnosis;  
treatment

## INTRODUCTION

Asthma is the most common disorder due to chronic airway inflammation. It was estimated that more than 300 million people have asthma globally, and 5 to 10% suffer from severe asthma.<sup>19</sup> Risk factors of asthma such as heredity and various environmental conditions trigger asthma; however, definite identification is still challenging.<sup>10,12</sup> Asthmatic symptoms occur due to airway hyperresponsiveness that causes airway obstruction and phenotypically can be divided into two; allergic and intrinsic asthma. The most common asthma triggers are allergens such as house dust mites, pollen, and mold spores.<sup>13,14,15</sup> In terms of its etiopathogenesis, allergic asthma is characterized by a hypersensitive response involving the activation and increase of Th2 cells and allergen-specific IgE.<sup>1,2,16,17</sup>

Fungal-related allergic asthma has a broad spectrum depending on the host condition and the fungus that causes it. One of the spectra often encountered is allergic bronchopulmonary aspergillosis (ABPA), mainly caused by *Aspergillus fumigatus*.<sup>17,20</sup> From 11-70% of asthmatic patients who are sensitized by fungi, 16-38% are confirmed to be sensitized by *A. fumigatus*.<sup>15,18,19,21,26</sup> ABPA is characterized by a progressive allergic lung disease resulting from a hypersensitive reaction to antigens from *Aspergillus* spp. In contrast, allergic bronchopulmonary mycosis (ABPM) is used when the antigen comes from other fungi.<sup>2,3,18,19,22</sup> The first case of ABPA was reported in 1952; then, there has been an increasing number of cases everywhere over the years.<sup>2,27</sup> Globally, it is reported that more than 4 million people are affected by ABPA, predominantly adults.<sup>22,28,29</sup> Moreover, diagnosing and beginning therapy for asthma patients with ABPA is challenging because there is no universal consensus

on the diagnostic criteria, and they are still being modified due to a lack of a standard. This review focused on ABPA in asthma patients, from etiopathogenesis to managing the disease.

## METHODS

A comprehensive data-based literature search was conducted from PubMed, Web of Science, Scopus, and Google Scholar on topic-related articles using the keywords “asthma”, “allergic bronchopulmonary aspergillosis”, “etiology”, “pathogenesis”, “diagnosis”, and “treatment”. No time limits were applied. Articles of all types such as research, guidelines, systematic reviews and meta-analyses, and other narrative reviews are included. All authors are responsible for conducting a literature review and compiling the results into this review.

## DISCUSSION

### Etiopathogenesis

#### *Characteristics of fungi*

*Aspergillus* is a saprophytic fungus that is thermophilic and thermotolerant to grow at a temperature of 37 to 75°C. The conidia of *Aspergillus* wind-dispersed easily in the atmosphere so that they can be found in the environment outdoors; soil, plant, decaying vegetation, and indoor air.<sup>30</sup> *Aspergillus fumigatus* is the most common cause of ABPA, but other *Aspergillus* fungi such as *A. niger*, *A. flavus*, *A. nidulans*, and *A. terreus* can also be the cause.<sup>15,20,23,30,33</sup> Although not yet standardized, isolated fungal on cultures media such as sabouraud dextrose agar (SDA), potato dextrose agar (PDA), or malt extract agar (MEA) media can be carried out to identify species based on a variety of colors colony *Aspergillus* spp.<sup>28,30,34,39</sup>

This saprophytic fungus has a bilayer cell wall dominated by polysaccharides synthesized by transmembrane synthase, transglycosidase, and glycosyl hydrolase. The cell wall is also composed of proteins generally associated with polysaccharides, forming glycoproteins. The central core comprises an  $\alpha$ -1,3-glucan polymer,  $\beta$ -1,3-glucan, galactomannan, galactosaminogalactan, and chitin. The outer cell wall consists of rodlet layers followed by melanin. Macroscopically, *A. fumigatus* exhibits a velvety, woolly, or powdery surface texture with colors ranging from blue-green to gray, often with a narrow white border. (FIGURE 1A).<sup>40</sup> Microscopic morphological structure of *Aspergillus* is constructed from hyaline septate hyphae and conidiophore consisting of conidia chains, phialides, metulae, and vesicles derived from foot cells (FIGURE 1B). However, in *A. fumigatus* there is no metulae.<sup>30,33,41,42</sup>

### Factors contributing to the failure of *Aspergillus* clearance in asthmatic patients

*Aspergillus* is an opportunistic pathogen and rarely causes disease if inhaled by an immunocompetent individual. Therefore, it is known that ABPA commonly occurs in patients with previous pulmonary disease as a predisposing factor, including a history of asthma or cystic fibrosis. In asthmatic patients, inhalation of conidia *Aspergillus* spp. can not be eliminated as well as in healthy people.<sup>2,17</sup> The defect in conidia elimination is caused by goblet cell hyperplasia, damage to the ciliary structure, and function that interferes with mucociliary clearance. These hyperplastic goblet cells secrete excessive mucus but fail to eliminate it due to damaged cilia.<sup>17,43</sup> Besides host immune status and structural defect, genetic factors also increase the risk of developing conidia in the host, leading to asthma aspergillosis (TABLE 1).<sup>2,17,19,23,44-49</sup>

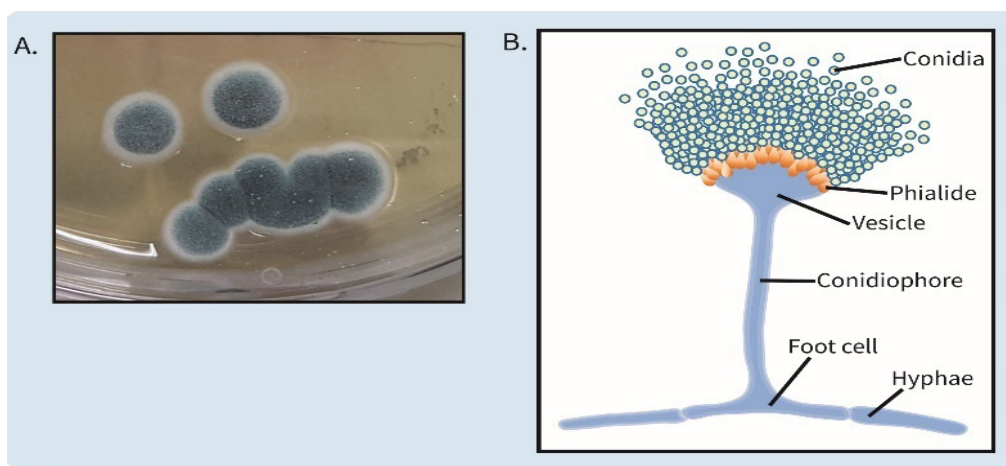


FIGURE 1. Morphology of *A. fumigatus*. A. Colony in SDA media.<sup>40</sup> B. Microscopical illustration.

TABLE 1. Host genetic factors related to the pathogenesis of aspergillosis asthma.<sup>2,17,49,18,19,23,44-48</sup>

PRRs	Cytokines
<ul style="list-style-type: none"> <li>• TLR-9 gene polymorphism</li> <li>• TLR-3 gene polymorphism</li> </ul>	<ul style="list-style-type: none"> <li>• IL-10-1082GA promoter polymorphism</li> <li>• IL-4 alpha receptor polymorphism</li> <li>• IL-13 polymorphism</li> <li>• IL-15 polymorphism</li> <li>• TNF-<math>\alpha</math> polymorphism</li> <li>• TGF- <math>\beta</math> polymorphism</li> </ul>
Others	
<ul style="list-style-type: none"> <li>• EEA-1 gene mutations</li> <li>• CHIT-1 gene mutations</li> <li>• Mannose-binding lectin gene mutations</li> <li>• Surfactant protein A2 gene polymorphism</li> <li>• CARD9 gene polymorphism</li> <li>• ZNF77 gene polymorphism</li> </ul>	<ul style="list-style-type: none"> <li>• HLA-DR2</li> <li>• HLA-DR5</li> <li>• HLA-DQ</li> </ul>

CHIT: chitotriosidase; EEA: early endosome antigen; TLR: toll-like receptor; CARD: caspase recruitment domain-containing protein; IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor; HLA: human leukocyte antigen; PRRs: pattern recognition receptors.

### Immune evasion mechanisms of *Aspergillus*

Asthmatic patients inhale the conidia of *Aspergillus* spp., leading to exacerbations. The conidia of *Aspergillus* are very small, around 3-5  $\mu\text{m}$ , which allows them to reach the lower respiratory tract very easily. The cell wall of *A. fumigatus*, the most common cause of ABPA, plays an essential role in the activation host immune system.<sup>17,50,52</sup> However, the exact pathogenesis of asthma aspergillosis is still in debate.

The cell wall of the conidia and hyphae of *A. fumigatus* has different components. The conidia have a rodlet layer and melanin at the outer. Meanwhile, the hyphal cell wall has an extracellular polysaccharide galactosaminogalactan, a component essential for fungal adherence and virulence. These differences in components affect the activation mechanism of the host immune system.<sup>19,44,50,52</sup>

Conidia have a rodlet and melanin layer on the outside initially, which causes pathogen-associated molecular patterns (PAMPs) not to be recognized by pattern recognition receptors (PRRs) of host cells; thus, the activation of the immune system is inhibited. The rodlet layers outer have been shown to inhibit

the activation of dendritic cells, alveolar macrophages, and T cells. Therefore, the rodlet layer is crucial for preventing the activation of the immune system. Later the rodlet layer will be degraded at the beginning of germination so that the PRRs of host cells will recognize the conidia: dectin-1, toll-like receptor (TLR)-2, TLR-4, C-type lectin receptors (CTLs), complement receptor 3 (CR3). On the contrary, hyphae of *A. fumigatus* do not have an outer protective layer, so PRRs can directly recognize PAMPs to activate the host immune system.<sup>19,42,51,53,54</sup>

The inhaled conidia can be completely cleared by professional phagocytic cells (macrophages) and non-professional phagocytes (bronchial epithelial cells/ alveoli) in individuals without prior pulmonary impairment. However, professional phagocytic cell function is impaired in individuals with chronic lung diseases such as asthma; thus, conidia can colonize bronchial/ alveolar epithelial cells. Clearance of conidia begins with adhesion to phagocytic cells, which then enter to form vesicle sacs (phagosomes) and combine with lysosomal enzymes to form phagolysosomes; then, some will be lysed and eliminated. Meanwhile, the non-eliminated conidia will swell, germinate, and grow hyphae.<sup>19,31,54,56</sup>

The PRRs function to recognize PAMPs in dendritic cells will induce the release of C-C motif chemokine ligand 17 (CCL17), which will regulate the differentiation of T cells into Th2 cells and activate regulatory T cells, which will suppress Th1 cell and macrophage response.<sup>19,31,54,57</sup> In addition, the protease enzyme (Alp-1/ Asp f13 (alkaline serine protease), which is secreted by hyphae at the beginning of its growth, can also induce epithelial cells to release pro-inflammatory cytokines: interleukin (IL)-33, IL-25, dan thymic stromal lymphopietin (TSLP).<sup>19,42,44,58</sup> The secretion of these cytokines cause inflammation and ultimately cause damage to epithelial cells. On the contrary, these cytokines can also

activate type 2 lymphoid cells (ILC2) and regulate the differentiation of T cells into Th2 cells, reducing the inflammatory response. Type helper 2 cells will then produce IL-4, IL-5, and IL-13. Activation of ILC2 will cause the release of type 2 cytokines, such as IL-5, IL-13, IL-9, and amphiregulin, in large quantities. Later, cytokines produced by ILC2 and Th2 cells will regulate the differentiation of B cells into plasma cells, produce IgE, and stimulate eosinophils. Moreover, the IgE will sensitize the mast cells and basophils, triggering hypersensitivity reaction type I. Furthermore, plasma cells will produce IgG-mediated immune complexes associated with types III hypersensitivity reactions (FIGURE 2).<sup>19,57</sup>

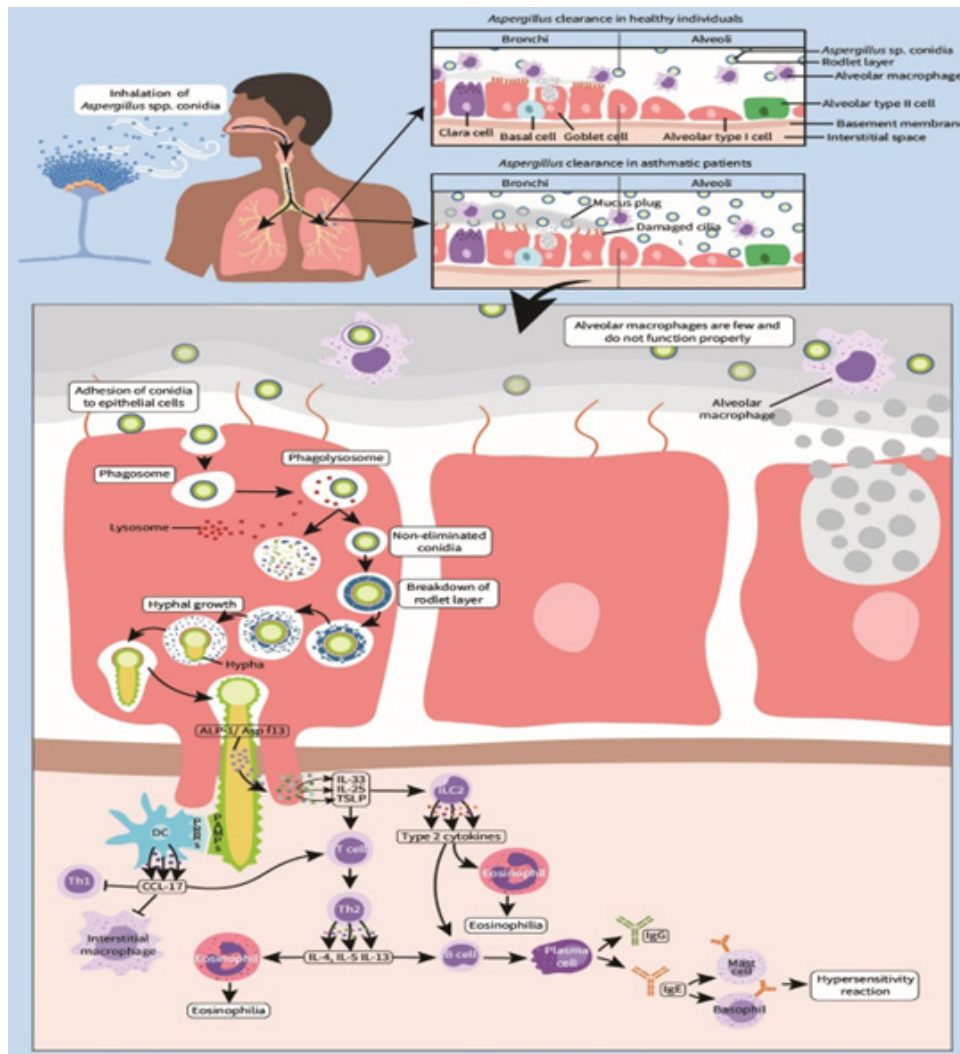


FIGURE 2. Asthma aspergillosis immunopathogenesis. Inhaled conidia in healthy individuals are mostly entirely cleared by phagocytic cells, but in asthmatic patients, conidia can persist and develop within bronchial/alveolar epithelial cells.

In asthmatic patients, a series of host immune responses fail to eliminate the fungus and cause an acute and persistent inflammatory reaction. The inflammatory reaction causes molecular to tissue damage that will increase mucus production and chronic inflammation and trigger airway hyperresponsiveness. If this continues uninterrupted, it can lead to bronchiectasis and pulmonary fibrosis.<sup>19,44</sup>

## Diagnosis

### *Clinical features*

Although most ABPA patients are asymptomatic, it can trigger exacerbations and worsen asthma symptoms in asthmatic patients.<sup>18</sup> Productive cough with dark green or brownish mucus, or even hemoptysis, is commonly observed in asthma patients. Other common features are dyspnea, chest pain, wheezing, clubbing fingers, and coarse crackles.<sup>18,44,59</sup> A more advanced ABPA may trigger a more severe manifestation, such as low-grade fever, headache, anorexia, and weight loss, that can hinder the patient's daily activities.<sup>60</sup> These manifestations may lead to complications such as bronchiectasis and fibrosis in the longer term.<sup>18,44,60,61</sup> The conventional progression staging of ABPA disease may be divided from acute (stage 1), remission (stage 2), exacerbation (stage 3), corticosteroid-dependent asthma (stage 4), to fibrosis (stage 5).<sup>62</sup> Meanwhile, the International Society for Human and Animal Mycology proposed a new staging, which consists of asymptomatic (stage 0), acute (stage 1), exacerbation (stage 2), remission (stage 4), treatment-dependent ABPA or glucocorticoid-dependent asthma (stage 5), and complicated ABPA (stage 6).<sup>28</sup>

### *Laboratory investigations*

There has been no agreed laboratory test as the gold standard of ABPA, so a combination of tests is needed to

establish the diagnosis. The primary laboratory test used for screening is the serum-specific IgE level of *A. fumigatus* due to its high sensitivity.<sup>63</sup> *Aspergillus fumigatus* IgE levels of more than 0.35 kUA/l are supposed to be associated with the incidence of ABPA in asthmatic patients.<sup>44</sup> The sensitivity of this method is up to 100%, and the specificity is 70% (TABLE 2).<sup>63</sup> Contrary to the previous test, total serum IgE levels are preferred in post-treatment follow-up ABPA patients because they tend to decrease promptly as therapy progresses but must be done several times to determine the various baseline between individuals. Moreover, there is a minimum total IgE level of 1000 IU/mL to prevent overdiagnosis due to its high sensitivity but very low specificity (TABLE 2).<sup>18,44,63</sup>

A positive *Aspergillus* skin test can help diagnose ABPA patients, but the sensitivity and specificity are not satisfactory<sup>63</sup> (TABLE 2), so it needs to be supported by an increase in total serum IgE levels for diagnosis. If both of these tests lead to a diagnosis of ABPA, additional tests, such as the precipitin test for *A. fumigatus*, may be performed to rule out other diagnoses because of their high specificity.<sup>64</sup> Unfortunately, this test has low sensitivity and variable cut-off, making it unreliable in the initial diagnosis (TABLE 2).<sup>63</sup> In addition, there is a test of specific IgG levels against *A. fumigatus* with good sensitivity and specificity for the diagnosis of ABPA, but it is not recommended for monitoring therapy (TABLE 2).<sup>65</sup> Various commercial IgG *A. fumigatus* assays may yield varying sensitivity results in the diagnosis of chronic pulmonary aspergillosis. However, this study utilized only one commercial test for ABPA.<sup>65,66</sup> Furthermore, an increased number of eosinophils in the peripheral blood is also one of the examination criteria for diagnosing ABPA. Nevertheless, the test is unreliable because it can lead to misdiagnosis due to very low sensitivity (TABLE 2).<sup>28,44,64</sup>

TABLE 2. Sensitivity and specificity of laboratory investigation in diagnosis ABPA.<sup>63,66</sup>

Methods	Sensitivity (%)	Specificity (%)
Specific IgE against <i>A. fumigatus</i>	100	70
Total serum IgE level	92-97	24-40
Skin test against <i>A. fumigatus</i>	88-95	80-87
<i>A. fumigatus</i> precipitins	33-43	97-98
Specific IgG against <i>A. fumigatus</i>	75-90	97-99
Peripheral blood eosinophils	30-36	93

Other tests, such as sputum culture, can identify species other than *A. fumigatus* that cause ABPA and determine the antifungal susceptibility test. Pulmonary function tests can also determine the severity of ABPA and the patient's progress in therapy. However, these two types of tests are rarely used by clinicians for both diagnosis and follow-up therapy.<sup>18,44,64</sup>

#### Radiologic findings

The modality used in ABPA imaging is a CT scan with infiltrates on the upper lobes as the most common finding.<sup>18</sup> In addition, the feature of bronchiectasis (especially central bronchiectasis with bronchus walls thickening), mucus-filled bronchus, high-attenuating mucus (HAM), centrilobular nodules consolidation, tree-in-bud opacities, and mosaic attenuation may be found.<sup>19,44</sup> Subsequently, the imaging results are classified as transient or fixed. Nonetheless, ABPA patients often do not show any abnormalities in imaging results. On the contrary, another modality, MRI, is not recommended for diagnosis.<sup>18,19,44,63,64</sup>

#### Diagnostic criteria for ABPA

Asthma-related ABPA can be diagnosed through clinical features, laboratory examinations, and imaging. The first ABPA diagnostic criteria were made by Rosenberg *et al.*<sup>67</sup> in 1977, consisting of seven major and three minor items. It is also the most widely

used criterion in diagnosing ABPA. In 1988, Greenberger and Patterson suggested an additional item, elevated *A. fumigatus*-specific IgE and IgG levels in the serum.<sup>68</sup> In 2002, Greenberger suggested minimal essential criteria that consisted of 5 items.<sup>69</sup> Greenberger then simplified this criterion in 2013 into truly minimal diagnostic criteria consisting of four items.<sup>70</sup> Eventually, in 2013, the International Society for Human and Animal Mycology (ISHAM) suggested diagnostic criteria for asthma or cystic fibrosis patients as a predisposing factor. The criteria consisted of two major and three minor items. Both major items and at least two minor items should be present.<sup>28</sup>

Agarwal *et al.*<sup>71</sup> proposed seven types of simplified criteria for comparison with the modified ISHAM-AWG criteria. Of the seven criteria, criteria 5, with the combination of IgE result (total and *A. fumigatus*-specific) and an increase in *A. fumigatus*-specific IgG or bronchiectasis, can be alternative criteria for diagnosing ABPA. In addition, criteria three based on a specific IgE examination can be another alternative, especially in places with limited resources, because it comprises only three components. Criteria 4 with based skin tests can also be used to confirm ABPA due to its high specificity in settings without access to *A. fumigatus* immunoassays.<sup>71</sup>

Asano *et al.*<sup>72</sup> proposed ten new criteria that can be used for diagnosing ABPM and ABPA from the modified Rosenberg and ISHAM criteria. If the patient meets six or more of these

criteria, they can be diagnosed with ABPM. This study result shows more excellent sensitivity than the previous criteria with fairly good specificity. However, this criterion has limitations due to the variable cut-off values of some laboratory tests, and the patient

sample includes only Japanese cases.<sup>72</sup> Therefore, these new criteria still require international multicenter investigation to be validated. All criteria for ABPA diagnostics that have been used and proposed are shown in TABLE 3.

TABLE 3. ABPA Diagnostic Criteria.<sup>61,65,67-71</sup>

References	• Major	• Minor
Rosenberg <i>et al.</i> <sup>61,65</sup>	<ul style="list-style-type: none"> <li>• History of asthma</li> <li>• Peripheral eosinophilia</li> <li>• Positive skin hypersensitivity test against <i>Aspergillus</i> antigen</li> <li>• Elevated total IgE level in serum</li> <li>• Fixed or transient opacity in the lung</li> <li>• Central bronchiectasis</li> </ul>	<ul style="list-style-type: none"> <li>• Presence of <i>A. fumigatus</i> found in the sputum</li> <li>• History of brownish mucus</li> <li>• Arthus-type reactivity against <i>Aspergillus</i> antigen</li> </ul>
ISHAM <sup>71</sup>	<ul style="list-style-type: none"> <li>• Positive skin test against type 1 <i>Aspergillus</i> or increased IgE level against <i>A. fumigatus</i></li> <li>• Increased total IgE level (&gt;1000 IU/ mL)</li> </ul>	<ul style="list-style-type: none"> <li>• Presence of antibody or IgG serum against <i>A. fumigatus</i></li> <li>• Thorax imaging support the presence of ABPA</li> <li>• Total eosinophil count over 500 cells/<math>\mu</math>L in patients who never used steroid therapy</li> </ul>
Minimal Essential Criteria <sup>67</sup>	<ul style="list-style-type: none"> <li>• History of asthma</li> <li>• Positive skin test against <i>A. fumigatus</i></li> <li>• Total IgE level in serum higher than 1000 ng/mL</li> <li>• Elevated <i>A. fumigatus</i> specific IgE or IgG level</li> <li>• Central bronchiectasis without distal bronchiectasis</li> </ul>	
Truly Minimal Criteria <sup>68</sup>	<ul style="list-style-type: none"> <li>• Same as Minimal Essential Criteria but without elevated <i>A. fumigatus</i> specific IgE or IgG level</li> </ul>	
Agarwal <i>et al.</i> <sup>69</sup> (from modified ISHAM-AWG)	<p>Any of the criteria listed below:</p> <ul style="list-style-type: none"> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and either <i>A. fumigatus</i> specific IgG serum &gt; 27 mgA/L or bronchiectasis (criteria 1)</li> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and either bronchiectasis or peripheral eosinophilia (&gt;500 cells/mL) (criteria 2)</li> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and bronchiectasis (criteria 3)</li> <li>• Positive skin test against type 1 <i>Aspergillus</i>, total IgE serum &gt; 500 IU/mL, and bronchiectasis (criteria 4)</li> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and either <i>A. fumigatus</i> specific IgG serum &gt; 27 mgA/L or bronchiectasis (criteria 5)</li> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and either bronchiectasis or peripheral eosinophilia (&gt; 500 cells/mL) (criteria 6)</li> <li>• <i>A. fumigatus</i> specific IgE serum &gt; 0.5 kUA/L, total IgE serum &gt; 500 IU/mL and either <i>A. fumigatus</i> specific IgG serum &gt; 27 mgA/L or peripheral eosinophilia (&gt; 500 cells/mL) (criteria 7)</li> </ul>	
Asano <i>et al.</i> <sup>70</sup>	<ul style="list-style-type: none"> <li>• History of asthma or symptoms of asthma</li> <li>• Peripheral eosinophilia (higher than 500 cells/mm<sup>3</sup>)</li> <li>• Increased total IgE in serum (higher than 417 IU/mL)</li> <li>• Positive skin hypersensitivity or specific IgE against filamentous fungi</li> <li>• Presence of precipitins or specific IgG against filamentous fungi</li> <li>• Presence of filamentous fungal in sputum or bronchial lavage fluid</li> <li>• Fungal hyphae in bronchial mucus plug</li> <li>• Central bronchiectasis</li> <li>• Mucus plug in central bronchi</li> <li>• High attenuation mucus in bronchi</li> </ul>	



In addition, there are comparison diagnosis criteria by Saxena *et al.*<sup>73</sup> between existing criteria such as Patterson and ISHAM with three other modified criteria but with the same patients from Agarwal *et al.*<sup>71</sup> respectively, on an MDT evaluation. Results: We analyzed data from 543 asthmatic subjects (58.8% women; mean age, 36.8 years). The results of this study showed that the sensitivity and specificity of the diagnostic criteria of ISHAM were slightly better than Patterson's. Moreover, of the three modified ISHAM criteria, the best one is the presence of asthma, *A. fumigatus* specific IgE >0.35 KUA/L, total serum IgE level >500 IU/mL; and meets 2 of the following: *A. fumigatus* specific IgG >27 mgA/L, bronchiectasis on chest CT, and eosinophil count >500 cells/mL.<sup>73</sup>

Despite the mentioned criteria above, there is still no standardized universal consensus. Rosenberg's criteria have a high specificity yet low sensitivity. The one proposed by ISHAM has better sensitivity and is still quite specific but too complicated to use. In recent years, there have been new criteria proposed by Agarwal *et al.*<sup>71</sup> with patients from a single tertiary care referral center in India and Asano *et al.*<sup>72</sup> from two health institutes in Japan. Thus, the two newer criteria still require multicenter studies to be validated to be used in varied populations.

In the ISHAM's diagnosis criteria, the cut-off total serum IgE levels >1000 IU/mL still has no clear reason. In addition, there is also no receiver-operating characteristic/ ROC analysis regarding IgE levels with ABPA, SAFS, and Aspergillus-sensitized asthma. Aspergillus IgG may also not be specific for ABPA because high levels are also found in other forms of aspergillosis, such as chronic pulmonary aspergillosis/CPA. Finally, a peripheral eosinophil count of >500 cells/ $\mu$ L is very common in many other diseases and the specificity of

this criterion is questionable. Therefore, further research is needed to validate this diagnostic criterion.

The newly proposed simplified criteria by Asano *et al.*,<sup>72</sup> state that the diagnostic accuracy of the newer criteria should be considered acceptable if the efficiency exceeds 95% and the false-negative rate is less than 5%. Although several criteria qualify for acceptance, there are some criteria (criteria 3, 4, and 7) that shows false-negative rate was >5%. The study is also a single-center study conducted at a tertiary care hospital, with large proportion of patients had bronchiectasis. It is also mentioned that the diagnostic performance of the criteria might be different in the milder asthmatics seen in the community or those with serological ABPA. Thus, the criteria still need prospective multicenter investigation for validation.

## Treatment

Treatment of ABPA aims to treat inflammation in the lung, prevent asthma exacerbations, overcome acute symptoms of ABPA, and delay complications. Glucocorticoids, such as prednisone, and antifungals like itraconazole, are utilized in conservative therapy (TABLE 4).<sup>43,44</sup> The administration of oral glucocorticoid remains the first line of ABPA in all stages.<sup>18,19,44,69</sup> The glucocorticoid that is widely used as an anti-inflammatory is prednisone or prednisolone. Clinicians must be careful if there is an indication of an increase in serum IgE  $\geq$  100% of the initial value because this indicates an exacerbation. Other routine evaluations are required for ABPA patients, such as CXR and eosinophil count, based on the patient's ABPA stage at diagnosis.<sup>18,19,44,69</sup> In addition to reducing the patient's symptoms, mucolytic drugs can be given.<sup>43</sup> Other novel treatments, such as monoclonal antibodies, on the other hand, are still under further study.<sup>74</sup>

TABLE 4. Recommendation therapy for ABPA

Stage	Therapy recommendation	Notes
Stage 1: Acute	<i>First line</i> Prednisone 0.5-0.75mg/kg/d for 6 wk; then TO 5-10 mg every 2 wk	<i>Glucocorticoid therapy follows up:</i> <ul style="list-style-type: none"> <li>Evaluate total serum IgE after 6-8 wk of therapy (the expected result is a decrease more than 35%); CXR and eosinophil count evaluation every 3 m.o.</li> </ul>
Stage 2: Remission	<i>Second line</i> Itraconazole 200-400 mg p.o. 2x1 for 16 wk	
Stage 3: Exacerbation	<i>Combination therapy</i> Prednisone 0.5-0.75mg/kg/d for 6 wk; then TO 5-10mg every 2 wk and Itraconazole 200-400mg PO 2x1; for 16 wk	<ul style="list-style-type: none"> <li>To decide the normal range of total serum IgE, evaluations can be done every 8 wk for a yr</li> <li>In discontinuing corticosteroid therapy, evaluate the remission status of the patient every 6-8 wk</li> <li><i>Antifungal administration:</i></li> <li>Susceptibility test (confirm that the patient is not resistant)</li> <li>Evaluate liver enzyme, triglyceride, potassium, drugs level in blood</li> </ul>
Stage 4 Corticosteroid-dependent asthma	<i>First line</i> Prednisone 10-40mg AD, for a few yr  <i>Second line</i> Itraconazole 200-400mg PO 2x1; for 16 wk	
Stage 5 : Fibrosis	Prednisone 10-40mg AD	<ul style="list-style-type: none"> <li>Must be combined with cor pulmonale and hypoxemia therapy</li> </ul>

- TO: taper off; p.o.:per oral; CXR: chest X-ray; AD: on alternate days

Inhalation and intravenous routes are alternative routes of glucocorticoid administration in ABPA patients. For inhaled glucocorticoid, it is known to improve asthma symptoms and increase total serum IgE when used in combination with a long-acting beta agonist. However, the combination of inhaled glucocorticoids and itraconazole is associated with increased risk of adrenal insufficiency. Pulse steroid therapy or intravenous glucocorticoid used in ABPA is methylprednisolone (10-20mg/kg/d), given for three consecutive days every four weeks and reported in most cases

that intravenous glucocorticoid therapy is showing improvement to ABPA symptoms with minimal side effects.<sup>19,75</sup>

Antifungal therapy in ABPA treatment has multiple roles as an alternative therapy (second line) and combination therapy. Itraconazole is widely used antifungal, with an orally recommended dosage of 200-400 mg/d divided into two doses for 16 wk. Nevertheless, it is necessary to periodically evaluate liver enzymes, triglycerides, blood potassium, and blood drug levels in patients receiving these antifungals until their administration is

discontinued. Administration of other azole alternatives with voriconazole, 400-600 mg/d, divided into two doses for 16 wk, or posaconazole, in patients with treatment failure or intolerance of itraconazole shows clinical improvement. The side effects of itraconazole and posaconazole are better tolerated than voriconazole. However, these alternative newer azoles still need further evidence from randomized controlled trials to be considered the first-line antifungal therapy for ABPA.<sup>18,19,44,76</sup> Although antifungal therapy is more effective and has fewer side effects than glucocorticoid therapy, a susceptibility test against various species of *Aspergillus* is still necessary.

Despite the mentioned therapies, there is also a novel treatment: monoclonal antibodies such as omalizumab, mepolizumab, tezepelumab, and dupilumab.<sup>74</sup> Some of these antibodies are known to have fewer side effects than conventional therapy and have been proven effective in reducing clinical manifestations and the number of exacerbations. Nonetheless, most of these monoclonal antibodies still require further studies.<sup>43,74</sup>

## CONCLUSION

Despite aspergillosis and asthma having long been acknowledged, the diagnosis and treatment approaches are still a challenge for clinicians. Several ABPA overlapping diagnostic criteria without universal consensus are one of the causes. The laboratory test mainly used in screening is the serum-specific IgE level of *A. fumigatus* because of its high sensitivity. Hence, physicians should be vigilant in screening asthmatic patients for this infection to prevent long-term complications such as bronchiectasis and fibrosis.

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