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Special Article

Allergic bronchopulmonary aspergillosis: Brazilian Association of Allergy and Immunology guidelines for diagnosis and management

Aspergilose Broncopulmonar Alérgica (ABPA): guia da Associação Brasileira de Alergia e Imunologia para o diagnóstico e manejo

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is an immunoallergic lung disease caused by hypersensitivity reactions to antigens of the fungus *Aspergillus fumigatus*. The disease primarily affects individuals with asthma or cystic fibrosis and can lead to irreversible lung damage if not accurately diagnosed and treated. Despite being described nearly 70 years ago, the disease remains underdiagnosed. This may be related to the diagnostic methods used, the lack of standardized tests, and still imprecise diagnostic criteria. Standard therapy involves the use of systemic corticosteroids. Azole antifungals are indicated for the treatment of exacerbations and are the preferred strategy to reduce corticosteroid use. Biologics hold promise for treating ABPA due to their ability to inhibit type 2 inflammation, regulate IgE levels and eosinophil counts, and modulate inflammatory cytokines. Thus, in patients with asthma, especially those with difficulty in achieving disease control, the possibility of ABPA should be considered. Given the variability of diagnostic criteria and the need

RESUMO

A Aspergilose Broncopulmonar Alérgica (ABPA) é uma doença imunoalérgica pulmonar causada por reações de hipersensibilidade aos antígenos do fungo *Aspergillus fumigatus*. A doença afeta principalmente pessoas com asma ou fibrose cística e pode levar a dano pulmonar irreversível se não diagnosticada e adequadamente tratada. Apesar de descrita há quase 70 anos, a doença ainda é subdiagnosticada. Isso pode estar relacionado aos métodos de diagnóstico utilizados, à falta de testes padronizados e a critérios diagnósticos ainda imprecisos. O tratamento principal envolve o uso de corticosteroides sistêmicos. Antifúngicos azólicos são indicados para tratar exacerbações e são a estratégia preferencial para reduzir o uso de corticosteroides. Medicamentos biológicos prometem ser úteis no tratamento da ABPA, devido à sua capacidade de inibir a inflamação tipo 2, regular os níveis de eosinófilos e IgE e modular citocinas inflamatórias. Assim, frente a pacientes com asma, principalmente aqueles que têm dificuldade em alcançar o controle da doença, deve ser considerada a hipóte-

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to validate them in different populations, more studies are needed to better understand the disease, allowing its early detection and appropriate management. In these guidelines, we aim to update the data on ABPA epidemiology, clinical manifestations, diagnosis, differential diagnosis, and treatment.

Keywords: Allergic bronchopulmonary aspergillosis, pulmonary aspergillosis, asthma, bronchiectasis, eosinophilia, immunoglobulin E.

se de ABPA. Devido à variabilidade dos critérios diagnósticos e à necessidade de verificar a sua validação em populações distintas, são necessários mais estudos para um melhor entendimento da doença, possibilitando sua detecção precoce e manejo adequado. Nestas diretrizes procuramos atualizar dados sobre epidemiologia, manifestações clínicas, diagnóstico, diagnóstico diferencial e tratamento desta doença.

Descritores: Aspergilose broncopulmonar alérgica, aspergilose pulmonar, asma, bronquiectasia, eosinofilia, imunoglobulina E.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disease first described in 1952 by Hinson et al. in England in individuals presenting with bronchitis/asthma, peripheral eosinophilia, bronchiectasis, and/or expectoration of mucus plugs containing the fungus *Aspergillus fumigatus*.[1] In 1968, the disease was reported in the United States,[2] and in 1974, França described nine cases in Brazil, eight in adults and one in a child. [3]

ABPA is the most common cause of allergic bronchopulmonary mycosis (ABPM), a noninvasive disease with high potential for lung destruction. It primarily affects individuals with conditions that favor the germination of *A. fumigatus* conidia, particularly patients with asthma or cystic fibrosis (CF).[4]

A. fumigatus is a ubiquitously distributed fungus, mainly found in environments rich in decomposing organic matter, such as dead plants and animals. Its atmospheric concentration, conidia size (2.5–3 µm), mutability, allergenic potential, environmental conditions, thermotolerance (12-52 °C), mycotoxin production, as well as the host's age and immunocompetence, are key determinants of its pathogenicity.[4,5]

Inflammation of bronchial mucosa, as seen in asthma and CF, facilitates conidia retention and germination, leading to the formation of germ tubes and hyphae, which produce the main *A. fumigatus* antigens. Thus, depending on the individual's genetic background and immune status, type I and III hypersensitivity reactions may occur, resulting in ABPA. Clinical manifestations of ABPA range from mild bronchospasm to pulmonary fibrosis.[4-6]

ABPA remains an underrecognized disease, with approximately 30% of patients initially misdiagnosed with tuberculosis, particularly in developing countries such as Brazil.[6]

Given the disease's potential to cause irreversible complications, it is crucial to establish screening policies for ABPA, as early detection is essential for adequate treatment and improved prognosis.

The objective of this study was to provide a comprehensive review of ABPA, including its epidemiology, clinical manifestations, diagnosis, differential diagnoses, and treatment.

Epidemiology

It is estimated that more than 4 million people are affected by ABPA worldwide.[4,7] However, the exact prevalence of the disease remains uncertain and varies depending on the studied region. ABPA affects approximately 2.5% to 15% of patients with asthma and between 7% and 9% of patients with CF.[4,8]

The prevalence of ABPA exceeds 40% in patients with asthma sensitized to *A. fumigatus*, being more common in those with severe asthma.[8] In Brazil, the prevalence among adult asthmatics sensitized to *A. fumigatus* was reported at 20%.[9] In children with CF (median age of 7.3 years), the rate of allergic sensitization detected by skin prick test or specific serum IgE ranged from 12.5% to 23%.[10,11] Globally, the highest prevalence of ABPA has been reported in India.[12]

There is no age or sex predilection for the occurrence of ABPA, but it is more commonly observed in adults.[13] Additionally, genetic predisposition, such as specific *HLA-DR* alleles, may contribute to the development of ABPA in susceptible individuals.[14]

Difficulties in determining the true prevalence of ABPA are related to the lack of standardized diagnostic tests and criteria, as well as variations in the characteristics of study populations.

Aspergillus fumigatus

Aspergillus is a fungus that plays a crucial role in maintaining ecological balance, contributing to the recycling of organic matter and nutrient availability.[15] It is a eukaryotic, heterotrophic organism belonging to the domain *Eukarya*, kingdom *Fungi*, division *Ascomycota*, class *Eurotiomycetes*, order *Eurotiales*, family *Aspergillaceae,* genus *Aspergillus*, and species *A. fumigatus.*[16]

The genus *Aspergillus* is divided into six subgenera (*Circumdati*, *Nidulantes*, *Fumigati*, *Aspergillus*, *Cremei*, and *Polypaecilum*), which include 27 sections and 446 species.[17] Among these, *A. fumigatus* is the most clinically relevant pathogenic species due to its higher capacity to survive and thrive in a wide range of environmental conditions compared with other species.[18,19]

The taxonomy of *Aspergillus* is complex and frequently revised.[20] Traditionally, classification was based on phenotypic characteristics; however, in recent decades, molecular and chemotaxonomic analyses have played a more significant role.[21] These new approaches are necessary due to the large number of species within the genus, making precise identification challenging. A polyphasic methodology, which integrates both biotypic and genotypic characteristics, has proven to be the most effective for species identification. Biotypic analysis includes evaluating the conidia's shape, size, color, and thermotolerance.[18]

Thermotolerance is a key distinguishing feature, as *A. fumigatus* differs from other *Aspergillus* species in its optimal growth temperature. It thrives best at 37 °C but can grow between 20 °C and 52 °C, and it can survive prolonged exposure to temperatures as high as 55 °C. Consequently, *A. fumigatus* can be found worldwide, particularly in self-heating environments such as hay, corn, and compost.[19,21]

Genotypically, different molecular biology techniques can be used for defining species, including ribosomal RNA sequencing, restriction fragment length polymorphism, protein-coding gene sequencing, and multilocus sequence typing.[20] The analysis of gene sequences encoding β-tubulin, calmodulin, or the RNA polymerase II second largest subunit (RPB2) appears to be the most suitable for distinguishing between *Aspergillus* species.[21]

The morphological characteristics of *Aspergillus* were first described in 1729 by Pietro Micheli, an Italian priest and biologist, who compared its structure to a holy water sprinkler, hence the name *Aspergillus*.[19] These fungi are composed of filamentous cells called hyphae, which can grow and form a network called mycelium, classifying them as filamentous fungi. The hyphae are septate and hyaline, varying in diameter, and branch into conidiophores, which are specialized asexual reproductive structures that produce asexual spores called conidia. The conidiophores emerge from the basal cell through the hypha, and terminate in a vesicle, which connects to the basal cell via a stalk (stipe). Phialides, the conidia-producing cells, arise from the vesicle. In *A. fumigatus*, the conidiophores are uniseriate, meaning they emerge directly from the vesicle.[15]

Aspergillus section *Fumigati* species are characterized by smooth conidiophores, balloon-shaped vesicles, columnar conidial heads, greenish globose conidia with textures ranging from smooth to rough, and are uniseriate.[22] Conidiophores are simple, typically aseptate, and have septate hyaline hyphae that vary in diameter[18,20] (Figure 1).

The *Aspergillus* life cycle consists of two phases: a somatic phase, during which it absorbs simple soluble nutrients for sustenance, and a reproductive phase.[16] The genus *Aspergillus* is considered anamorphic, as it predominantly undergoes asexual reproduction in nature by producing chains of phialides and conidia.[20,23]

Once germinated, the hyphae grow and form a colony. In the colony phase, *A. fumigatus* hyphae become embedded in an extracellular matrix and form a biofilm. Its rapid growth rate is a key factor promoting its dissemination.[23]

Conidia detach and become airborne, with environmental concentrations ranging from 0.1 to 3 conidia per m^3. This allows them to reach all levels of the respiratory tract. Additionally, they can remain dormant until they encounter adequate environmental conditions. *A. fumigatus* can grow on a wide variety of substrates and tolerate freezing temperatures or desiccation for prolonged periods.[19]

The first reported case of *Aspergillus* infection in humans was described by Sluyter in 1847.[24] The spectrum of diseases caused by *Aspergillus* includes mycotoxicosis, allergies, asthma, aspergilloma, necrotizing aspergillosis, invasive pulmonary aspergillosis, and ABPA.[25]

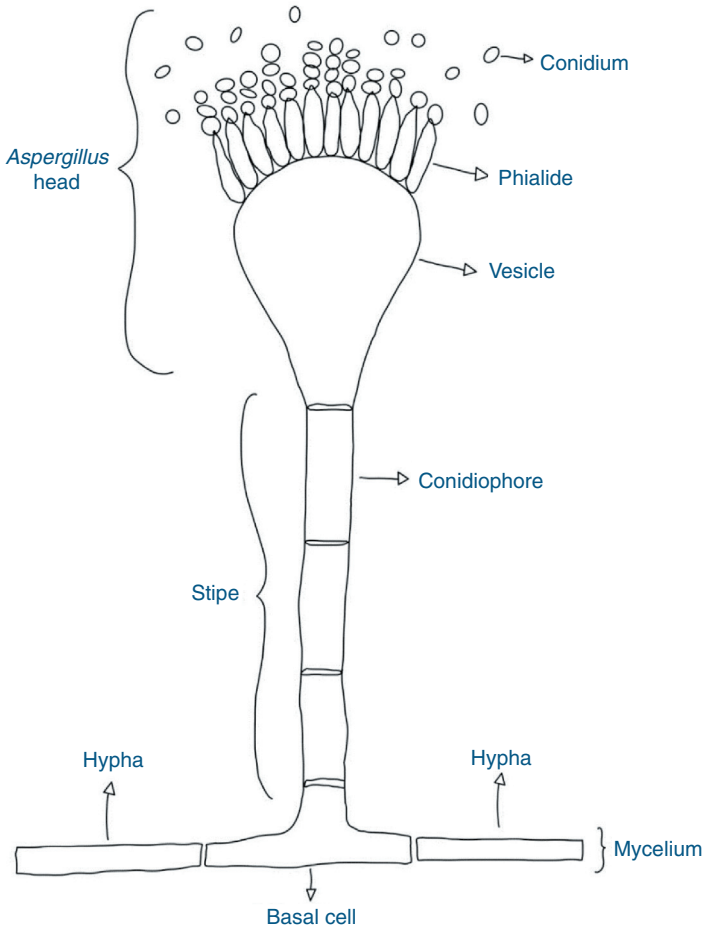


Figure 1
Morphological characteristics of *Aspergillus fumigatus*
Adapted from Souza HG et al.[15].

Pathogenesis

The pathogenesis of ABPA is complex, involving genetic factors, host-pathogen interactions, innate and adaptive immune responses, hypersensitivity reactions, and eosinophilic inflammation.

Genetic factors may contribute to susceptibility to ABPA. Human leukocyte antigen (HLA) genotyping studies have identified specific HLA-DR alleles, such as HLA-DR2 and HLA-DR5, which are associated with an increased risk of developing ABPA in patients with asthma and CF, respectively.[26] Conversely, HLA-DQ2 appears to confer protection against the disease.[27] The *ZNF77* gene variant rs35699176 has been reported to compromise the integrity of respiratory epithelial cells, exposing extracellular matrix proteins and thereby promoting the adhesion, germination, and growth of *A. fumigatus* conidia.[28] Polymorphisms in innate immune response pathways, including surfactant protein A2 and Toll-like receptors 3 and 9, have also been described in patients with ABPA.[29-31]

Aspergillus is a ubiquitous saprophytic fungus found in the air and soil, thriving in decaying vegetation.[23] The small size of *Aspergillus* spores allows deep penetration and deposition in the airways. Inhalation

of these spores can lead to airway colonization and germination in susceptible individuals, particularly those with asthma or CF.[32]

Normally, *A. fumigatus* does not elicit an immune response because its conidia possess a hydrophobic layer composed of RodA protein, which prevents recognition by dendritic cells, rendering the spores immunologically inert.[33] However, if the conidia persist in the respiratory tract, they germinate and produce hyphae, losing their hydrophobic layer. This triggers pathogen-associated molecular patterns, which activate pattern recognition receptors on pulmonary epithelial cells, leading to the release of alarmins such as interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP). These alarmins stimulate type 2 innate lymphoid cells (ILC2), which produce type 2 (T2) cytokines, including IL-4, IL-5, and IL-13, resulting in eosinophilia, mucus production, and bronchial hyperreactivity. Evidence suggests that ILC2s interact with CD4+ T lymphocytes, promoting adaptive immune responses and persistent airway inflammation.[34]

Impaired mucociliary clearance and local immune responses in these individuals facilitate the persistence of *Aspergillus* hyphae in the airways, triggering an exaggerated immune response. The release of several fungal proteins and proteases (catalase, aspartic protease, metalloprotease, elastase, and collagenase) contributes to fungal colonization and perpetuates respiratory epithelial damage.[35-37]

In addition, *A. fumigatus* hyphae produce its key antigens. The World Health Organization (WHO) and the International Union of Immunological Societies (IUIS) have identified 30 *A. fumigatus* allergenic proteins,[38] of which five (Asp f1, Asp f2, Asp f3, Asp f4, and Asp f6) are available as recombinant proteins for testing.[39] Asp f1, described by Arruda LK et al., is a ribotoxin protein specific to *A. fumigatus*, which is expressed and secreted exclusively by germinating spores.[40] Asp f3, Asp f4, and Asp f6 are somatic proteins. Although Asp f1 is considered the most allergenic, all of these antigens have the potential to elicit IgE- and IgG-mediated immune reactions.[39]

Thus, ABPA pathogenesis is characterized by a marked type 2 (T2) inflammatory response involving a combination of type I (immediate) and type III (immune complex-mediated) hypersensitivity reactions.[41] In type I hypersensitivity, *Aspergillus* antigens bind to IgE on the surface of mast cells and basophils, leading to the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins. This results in bronchoconstriction, increased vascular permeability, and mucus production.[42] In type III hypersensitivity, immune complexes formed by *Aspergillus* antigens and IgG are deposited in lung tissue, activating the complement system and attracting inflammatory cells, leading to tissue damage and marked eosinophilic inflammation.[43]

The T2 inflammatory process in ABPA is characterized by massive eosinophilic infiltration of the airways and high levels of polyclonal IgE. Eosinophils play a central role in ABPA pathogenesis, contributing to airway inflammation, mucus production, and bronchial hyperresponsiveness.[41] Cytokines such as IL-4, IL-5, and IL-13, produced by Th2 cells, promote eosinophil recruitment, activation, and survival.[44] Furthermore, IL-4 and IL-13 promote IgE production by B cells and induce goblet cell hyperplasia, increasing mucus secretion. Airway inflammation leads to the formation of dense eosinophilic mucus containing Charcot-Leyden crystals, which obstruct the airways. Variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene may play a role in ABPA, even in the absence of CF, although this is not fully elucidated.[45]

Clinical presentation

The most common clinical findings in ABPA are related to the symptoms of the underlying diseases that predispose to it, as well as those directly caused by ABPA itself. These manifestations can range from mild bronchospasm to pulmonary fibrosis. Patients may experience recurrent and paroxysmal coughing, dyspnea, increased sputum production, wheezing, frequent exacerbations, and exercise intolerance. Depending on the disease stage, symptoms such as the expectoration of brownish mucus plugs, occasional hemoptysis, fever, and general malaise may be present. Digital clubbing is uncommon and typically observed in patients with longstanding bronchiectasis.[44,46]

A subset of patients with ABPA may present without underlying asthma, with chest imaging findings being the key factor leading to the suspicion of the disease.[47] The diagnosis of ABPA may take up to 10 years to be suspected and established, often considered only in cases of severe, treatment-resistant asthma requiring high doses of inhaled corticosteroids combined with long-acting bronchodilators or even oral corticosteroids (corresponding to steps 4 or 5 of the Global Initiative for Asthma [GINA]).[48] Rarely, allergic fungal rhinosinusitis caused by *Aspergillus*

may occur simultaneously, presenting with symptoms such as nasal obstruction and thickened and dark nasal discharge.[49]

Clinical findings are crucial for the diagnosis of ABPA and, when combined with characteristic radiological features on chest computed tomography (such as mucoid impaction and parenchymal opacities), the presence of biomarkers (elevated total IgE, specific serum IgE against *A. fumigatus*, or a positive immediate hypersensitivity skin test), as well as other supporting criteria such as elevated blood eosinophils, specific IgG, or serum precipitins against *A. fumigatus*, they can confirm the diagnosis.[49-50]

Several clinical stages of ABPA have been described, initially proposed by Patterson et al. in 1982[50] and more recently revised by Agarwal et al. in 2024.[49] These are summarized in Table 1.

Diagnosis

Diagnosing ABPA is challenging and requires the assessment of clinical, immunological, and radiological criteria to differentiate it from other pulmonary conditions.[51] The first diagnostic criteria for ABPA were proposed by Rosenberg et al. in 1977 (Table 2). These included seven primary components (asthma, peripheral blood eosinophilia, immediate skin reactivity to *Aspergillus* antigen, presence of precipitating antibodies against *Aspergillus* antigen, elevated serum IgE concentrations, history of transient or fixed pulmonary infiltrates, and central bronchiectasis) and three secondary components (*A. fumigatus* culture in sputum, history of expectoration of brown plugs or flecks, and Arthus reactivity).[52] These criteria were the most used for the diagnosis of ABPA. However, in 2013, the ABPA working group of the International Society for Human and Animal Mycology (ISHAM) proposed updated criteria to establish standardized diagnostic guidelines for ABPA.[53]

Subsequently, new evidence emerged regarding the sensitivity and specificity of the ISHAM criteria. A study evaluating the performance of different diagnostic criteria[54] demonstrated that specific serum IgE tests were more sensitive than skin tests in detecting *Aspergillus* sensitization. It also showed that the sensitivity and specificity of the ISHAM criteria improved with a lower total IgE threshold. Additionally, a cutoff level for *A. fumigatus*-specific IgG was proposed, leading ISHAM to modify its diagnostic criteria in 2021.[54] Despite validation, the revised ISHAM criteria still showed low sensitivity in cases of ABPM caused by fungi other than *Aspergillus*. To address this, Asano et al. proposed and validated new diagnostic criteria, which demonstrated higher sensitivity and specificity compared to the Rosenberg-Patterson and ISHAM criteria, even in atypical ABPA cases and other forms of ABPM.[55]

Given these evolving insights and remaining gaps in knowledge, new guidelines have recently been published to aid clinicians and researchers in the management of ABPA.[49]

The currently proposed diagnostic criteria are shown in Table 3, along with their advantages and disadvantages.

Clinical criteria

The clinical criteria for diagnosing ABPA involve the presence of characteristic symptoms and risk factors, particularly asthma and CF, along with warning signs that may indicate ABPA, such as: uncontrolled asthma despite appropriate treatment; (ii) persistent respiratory symptoms, including cough, dyspnea, wheezing, and sputum production; (iii) recurrent acute exacerbations with pulmonary eosinophilia; and (iv) bronchiectasis.[51,55]

Immunological criteria

Immunological markers may help confirm hypersensitivity to *Aspergillus* and provide insights into disease activity.

According to the latest ABPA guidelines, a total serum IgE level of ≥ 500 IU/mL is considered sufficient for an ABPA diagnosis, while a threshold of ≥ 417 IU/mL is used for ABPM.[49,55] An increase of ≥ 50% in total serum IgE levels is indicative of ABPA exacerbation[49] (Table 3).

The detection of specific IgE against *Aspergillus* antigens plays a crucial role in diagnosis. However, variability in test methods and allergen quality can impact the accuracy of results. To address these challenges, the use of recombinant allergens has been proposed. These proteins, produced using genetic engineering techniques, provide more controlled and standardized production compared with natural allergens, enhancing test sensitivity and specificity for ABPA diagnosis. The presence of IgE against rAsp f1 or rAsp f3 has demonstrated high sensitivity, while rAsp f4 and rAsp f6 showed high specificity for diagnosing ABPA in patients with asthma and CF.[39] The presence of IgE against rAsp (f1, f2, and f4) was considered specific for ABPA in two studies.[56,57]

Table 1
Clinical classification of ABPA/ABPM

Stage	Definition	Findings
1	Acute ABPA	***New diagnosis*** - Previously undiagnosed ABPA that meets diagnostic criteria. ***Exacerbation*** - In a patient with diagnosed ABPA: – Sustained clinical worsening (> 14 days); **OR** – Radiological deterioration; **AND** – Increase in total serum IgE by ≥ 50% compared to the last recorded IgE value during clinical stability; **AND** – Exclusion of other causes of worsening. ***Asthma exacerbation*** - Worsening of respiratory symptoms for at least 48 hours without immunological or radiological deterioration of ABPA. ***Infectious exacerbation/bronchiectasis*** - Clinical deterioration for at least 48 hours with increased cough, dyspnea, sputum volume or consistency, sputum purulence, fatigue, malaise, fever, or hemoptysis, without immunological or radiological worsening of ABPA.
2	Responsive	Symptomatic improvement of at least 50% (on a Likert scale or visual analog scale) after 8 weeks; **AND** Significant radiological improvement (> 50% reduction in radiological opacities) or a ≥ 20% decrease in total serum IgE after 8 weeks of treatment.
3	Remission	Clinical and radiological improvement for > 6 months without the use of systemic corticosteroids. No increase in total serum IgE ≥ 50% compared to the last recorded IgE value during clinical stability. *Patients on long-term biologic agents or antifungal therapy may also be considered in remission if they meet the above criteria.*
4	Treatment-dependent ABPA	≥ 2 consecutive exacerbations within 3 months after discontinuation of systemic corticosteroids. Worsening of respiratory symptoms **AND** worsening in imaging findings or a 50% increase in total serum IgE within 4 weeks of stopping oral corticosteroids on two separate occasions.
5	Advanced ABPA	Extensive bronchiectasis (≥ 10 segments) on imaging due to ABPA. *Cor pulmonale* or chronic type 2 respiratory failure.

ABPA = allergic bronchopulmonary aspergillosis, ABPM = allergic bronchopulmonary mycosis.
Adapted from Agarwal R et al.[49]

The European Academy of Allergy & Clinical Immunology ABPA Task Force proposed changes to the diagnostic algorithm, incorporating the research of recombinant allergens, while emphasizing the need for appropriate recommendations for countries with limited resources.[58] However, a Brazilian study found no advantages in using recombinant allergens (rAsp f1, rAsp f2, rAsp f3, rAsp f4, and rAsp f6) over conventional immunological tests, highlighting persistent challenges in ABPA diagnosis.[59]

Skin testing for immediate hypersensitivity using *Aspergillus* extracts can assess immune response to fungal antigens, serving as an alternative to specific IgE testing.[6,49,53]

The detection of specific IgG antibodies through serological tests, such as double immunodiffusion or enzyme immunoassay, is another key criterion for ABPA diagnosis. A study conducted in the Indian population proposed a specific IgG threshold for *Aspergillus* of > 27 mgA/L.[60] However, this cutoff varies depending on assay methodology and population, with thresholds of > 60 mgA/L in Japan and > 40 mgA/L in the United Kingdom.[61,62]

Peripheral blood eosinophilia is common in ABPA, but its presence alone is not sufficient to differentiate it from eosinophilic asthma or other eosinophilic lung diseases. An eosinophil count >500 cells/μL is considered an additional diagnostic marker for ABPA.[6,49,53,55] Eosinophilia in sputum may also be observed; however, recent guidelines emphasize that sputum eosinophil count remains an unmet need in ABPA diagnostics.[49]

Additionally, direct visualization of the fungus (using Gram or Grocott–Gömöri staining), as well as fungal culture can be performed on sputum, induced sputum, or bronchoalveolar lavage (BAL) samples. The presence of *Aspergillus spp.* in culture can support the diagnosis.[49]

Table 2
Differential diagnoses of ABPA[71]

Diseases associated with bronchiectasis
– Asthma without ABPA
– Cystic fibrosis without ABPA
– Post-infectious (mycobacteria, pertussis, adenovirus)
– Immunodeficiencies
– Ciliary dyskinesia
– Yellow nail syndrome
– Tracheobronchomegaly (Mounier-Kuhn syndrome)
– Collagen diseases (rheumatoid arthritis, Sjögren's syndrome)
Diseases associated with eosinophilia
– Asthma without ABPA
– Eosinophilic pneumonia
– Drug hypersensitivity
– Eosinophilic granulomatosis with polyangiitis (EGPA)
– Hypersensitivity pneumonitis
– Primary or secondary malignancy
– Granulomatous lung disease
– Parasitic infections (Löffler's syndrome)

ABPA = allergic bronchopulmonary aspergillosis.

Table 3
Evolution of ABPA diagnostic criteria

	ABPA diagnostic criteria	Advantages and disadvantages
Rosenberg-Patterson (1977)	**Primary criteria** 1. Asthma. 2. Peripheral eosinophilia. 3. Immediate skin hypersensitivity to *Aspergillus* antigens. 4. Presence of precipitins to *Aspergillus* antigens. 5. Elevated total serum IgE. 6. History of pulmonary infiltrates (transient or fixed). 7. Central bronchiectasis. **Secondary criteria** – *Aspergillus fumigatus* in sputum. – History of expectoration of brownish mucus plugs. – Delayed skin reactivity to *Aspergillus* antigens (Arthus reaction). **Definitive ABPA diagnosis:** Presence of all primary criteria.	**Advantages:** Facilitated diagnosis when the disease was largely unknown. Flexible and easy-to-use criteria. **Disadvantages:** Not applicable for ABPA-CF. Not applicable for patients with ABPM.
ISHAM criteria (2013)	**Predisposing conditions** – Asthma or CF. **Mandatory criteria** – Total serum IgE (> 1000 IU/mL).* – Specific IgE for *Aspergillus fumigatus* > 0.35 kUA/L or positive skin test. **Additional criteria** – Peripheral eosinophilia > 500 cells/μL.** – Positive precipitins or specific IgG for *Aspergillus*. – Bronchiectasis on CT scan. – Mucoid impaction on CT scan. **Definitive ABPA diagnosis:** At least two mandatory criteria and at least two additional criteria. * If all other criteria are met, total IgE < 1000 IU/mL is acceptable. ** Without systemic corticosteroid use.	**Advantages:** More clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. Applicable to ABPA-CF. **Disadvantages:** Not applicable for patients with ABPM.

[a] Or clinical-radiological presentation consistent with ABPA.
[b] Total serum IgE < 500 IU/mL is acceptable if all other criteria are met.
[c] In the absence of a population-specific cutoff, follow manufacturer recommendations.
[d] High-attenuation mucus confirms ABPA even if other criteria are not met.
Specific IgE for rAsp f1, f2, and f4 confirms ABPA diagnosis and can be used as a diagnostic criterion.

ABPA = allergic bronchopulmonary aspergillosis; ABPA-CF = ABPA in cystic fibrosis; ABPM = allergic bronchopulmonary mycosis; CT = computed tomography; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease.

Adapted from Agarwal R et al.[75], Valle SOR et al.[67] and Agarwal R et al.[49].

Table 3 *(continuation)*
Evolution of ABPA diagnostic criteria

	ABPA diagnostic criteria	Advantages and disadvantages
Modified ISHAM criteria (2021)	**Predisposing condition** – Asthma. **Mandatory criteria** – Total serum IgE > 500 IU/mL. – Specific IgE for *Aspergillus fumigatus* > 0.35 kUA/L or positive skin test. **Additional criteria** – Peripheral eosinophilia > 500 cells/μL. – Positive precipitins or IgG for *Aspergillus* > 27 mgA/L. – Bronchiectasis on CT scan. – Mucoid impaction on CT scan. **Definitive ABPA diagnosis:** At least two mandatory criteria and at least two additional criteria.	**Advantages:** Clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. **Disadvantages:** Not applicable for ABPA-CF. Not applicable for patients with ABPM. Requires evaluation across different geographic regions.
Modified ISHAM criteria (2024)	**Predisposing condition**[a] – Asthma, CF, COPD, or bronchiectasis. **Mandatory criteria** – Total serum IgE ≥ 500 UI/mL[b] – Specific IgE for *Aspergillus fumigatus* ≥ 0.35 kUA/L or positive skin test. **Additional criteria** – Positive IgG for *Aspergillus fumigatus*[c] – Peripheral eosinophilia > 500 cells/μL. – Chest CT with findings suggestive of ABPA (bronchiectasis, mucoid impaction, and high-attenuation mucusd) or transient infiltrates on chest X-ray. **Definitive ABPA diagnosis:** At least two mandatory criteria and at least two additional criteria.	**Advantages:** More clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. Applicable for diagnosing ABPA in various predisposing conditions. Considers regional differences. **Disadvantages:** Not applicable for patients with ABPM.

[a] Or clinical-radiological presentation consistent with ABPA.
[b] Total serum IgE < 500 IU/mL is acceptable if all other criteria are met.
[c] In the absence of a population-specific cutoff, follow manufacturer recommendations.
[d] High-attenuation mucus confirms ABPA even if other criteria are not met. Specific IgE for rAsp f1, f2, and f4 confirms ABPA diagnosis and can be used as a diagnostic criterion.

ABPA = allergic bronchopulmonary aspergillosis; ABPA-CF = ABPA in cystic fibrosis; ABPM = allergic bronchopulmonary mycosis; CT = computed tomography; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease.
Adapted from Agarwal R et al.[75], Valle SOR et al.[67] and Agarwal R et al.[49].

Molecular biology techniques, such as polymerase chain reaction (PCR) on different clinical samples (sputum, lung tissue), may be particularly useful in cases of ABPA with negative cultures or for early diagnosis.[51,55]

The sensitivity of sputum cultures for detecting *Aspergillus* in ABPA is low, as is the accuracy of serum galactomannan antigen testing. However, in suspected cases of ABPM, current guidelines recommend performing fungal cultures on sputum samples collected before initiating treatment to characterize the fungal species and later assess treatment failure.[49]

Radiological criteria

The characteristic radiological findings of ABPA may vary according to the disease stage and can help differentiate it from other pulmonary conditions.[6,49,51,53] High-resolution computed tomography (HRCT) is the gold standard for detecting the broad spectrum of lung alterations associated with ABPA. One of the hallmark findings is the presence of recurrent and migratory pulmonary infiltrates, which may appear in different lung lobes and can be either unifocal or multifocal. Ground-glass opacities, defined as areas of increased lung attenuation without complete obscuration of blood vessels, are frequently observed and may indicate alveolar inflammation with or without eosinophilic and mucoid exudate. Bronchiectasis, characterized by permanent and irreversible bronchial dilation, is another key radiological feature of ABPA. In ABPA, bronchiectasis predominantly affects central airways, especially in the proximal segments of the upper and middle lobes.[6,49,52,53]

High-attenuation mucus (HAM) in the bronchi, often associated with bronchial dilations resembling a "finger-in-glove" pattern, is another characteristic finding.[53] HAM is defined as mucus visually denser than paraspinal skeletal muscle and may be associated with the presence of calcium salts and metal ions (manganese or iron)[63] or dehydrated mucus.[64] Other common findings include bronchial wall thickening and parenchymal scarring, indicative of long-term inflammation and tissue damage.[46,65]

Centrilobular nodules with a "tree-in-bud" pattern, suggestive of small airway inflammation and often associated with chronic inflammation, are frequently seen in ABPA.[66]

The final stage of ABPA is characterized by fibrosis, which can be recognized by the presence of architectural distortion predominantly affecting the upper lobes. Pulmonary fibrosis may appear on HRCT as traction bronchiectasis, honeycombing, and volume loss.[65,66]

Early recognition and treatment of ABPA are crucial to prevent disease progression, including the development of bronchiectasis, pulmonary fibrosis, and advanced lung disease. In its initial stages, when only serological markers are present, ABPA is referred to as serologic ABPA. Unfortunately, ABPA is often diagnosed only after years of disease progression, when fibrosis and airway remodeling become evident. The diagnosis of ABPA is challenging for several reasons, such as[68]:

- There is no single biomarker for diagnosing and monitoring the disease. Several criteria have been proposed based on clinical, immunological, and radiological parameters (Table 3).
- Some criteria are not specific to ABPA and may not always be present simultaneously.
- ABPA symptoms are characterized by periods of remission and exacerbation.
- The lack of standardization in allergens used for diagnosis affects the reproducibility of test results.
- Treatment of patients with asthma with corticosteroids and other anti-inflammatory medications may mask several diagnostic criteria.
- Other fungi can colonize the lower airways and induce a disease similar to ABPA, termed ABPM.

In this context, following a diagnostic flowchart is recommended to improve diagnostic accuracy (Figure 2).

Differential diagnoses

The differential diagnoses of ABPA include conditions associated with elevated peripheral blood eosinophil counts, recurrent pulmonary infiltrates, increased total serum IgE levels, or bronchiectasis.[69] In this context, the primary differential diagnoses are CF, pulmonary tuberculosis, sarcoidosis, infectious pneumonia, acute and chronic eosinophilic pneumonia, *Aspergillus*-induced asthma, eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome), bronchocentric granulomatosis, tropical pulmonary eosinophilia, and parasitic infections with pulmonary involvement (Löffler's syndrome).[12,70] Table 2 lists the main differential diagnoses of ABPA related to the presence of bronchiectasis or eosinophilia.[71]

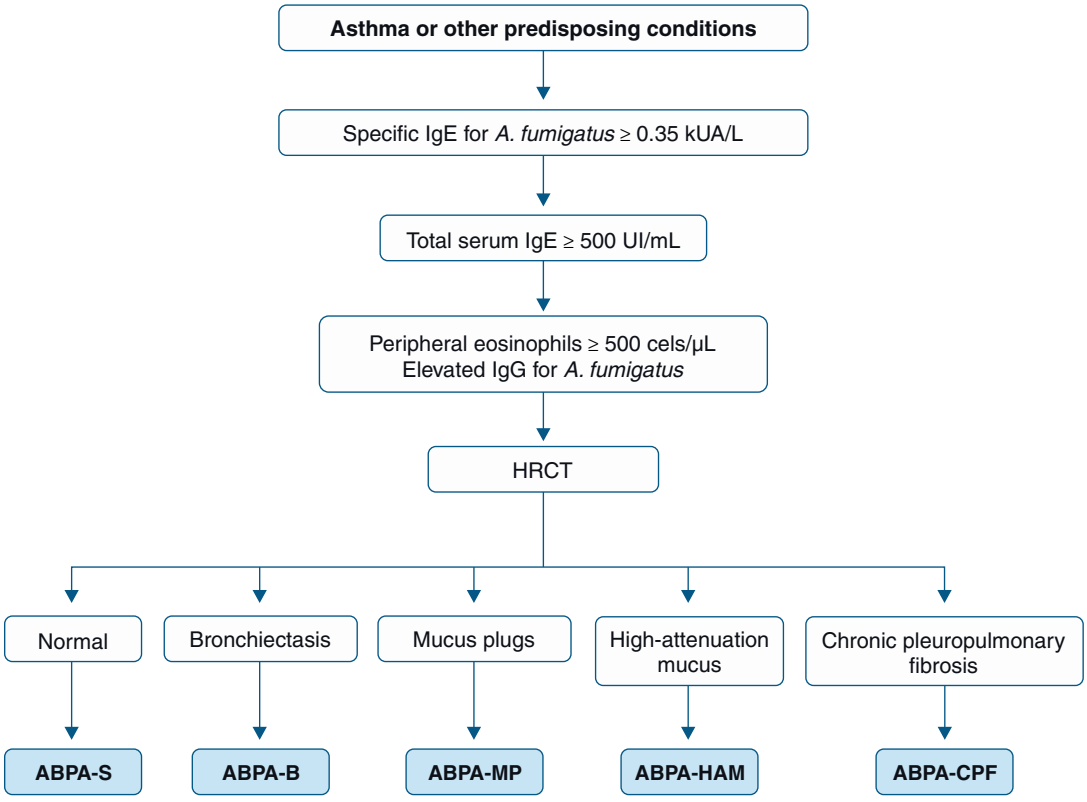
Due to the frequent involvement of the posterior segments of the upper lung lobes in ABPA and the high prevalence of tuberculosis in Brazil, ABPA cases are often misdiagnosed as tuberculosis.[72]

EGPA typically presents with uncontrolled asthma associated with purpura (cutaneous vasculitis), commonly on the hands or legs, and, in some cases, with sensory or motor neuropathy. It may also manifest with pulmonary infiltrates, extravascular granulomas, small vessel vasculitis on lung biopsies, and peripheral blood eosinophilia.[69]

Other pulmonary diseases caused by *Aspergillus* should also be considered in the differential diagnosis of ABPA, including[73]:

- *Aspergillus*-induced asthma.
- Hypersensitivity pneumonitis.
- Aspergilloma.
- Chronic cavitary and fibrotic pulmonary aspergillosis.
- Acute and subacute invasive aspergillosis (chronic and necrotizing).

Among these, *Aspergillus*-induced asthma is particularly notable. This condition involves asthma with an IgE-mediated hypersensitivity reaction to *Aspergillus* antigens but without other ABPA manifestations, particularly without bronchiectasis, mucoid impaction, or specific IgG for the fungus.[73]



ABPA = allergic bronchopulmonary aspergillosis; *A. fumigatus* = *Aspergillus fumigatus*; HRCT = high-resolution chest computed tomography; ABPA-S = ABPA with positive serology; ABPA-B = ABPA with bronchiectasis; ABPA-MP = ABPA with mucus plugs; ABPA-HAM = ABPA with high-attenuation mucus; ABPA-CPF = ABPA with chronic pleuropulmonary fibrosis.

Figure 2
ABPA diagnosis flowchart
Adapted from Agarwal R et al.[49]

Aspergillus sensitization may also occur in severe fungal asthma, which affects a subgroup of asthmatic patients sensitized to *Aspergillus* or other fungal antigens. These patients experience frequent exacerbations requiring recurrent hospitalizations. Diagnostic criteria for severe fungal asthma include[73]:

– Severe (or poorly controlled) asthma.
– Positive skin tests for fungi or elevated specific IgE ≥ 0.4 kU/L.

Treatment

The goals of ABPA treatment are to prevent permanent lung damage, improve prognosis, and enhance the patient's quality of life.[74] Treatment varies according to disease stage and involves systemic corticosteroids, antifungal therapy, biologic agents, and respiratory physiotherapy tailored to individual patient needs (Table 4). In patients with asthma or CF, management should also include treatment of the underlying disease. Inhaled corticosteroids and bronchodilators should be maintained and/or optimized in patients with asthma.

Systemic corticosteroids

Oral corticosteroids are the first-line treatment for ABPA.[49,50] However, several treatment regimens exist, differing in dosage and duration.[75] The most commonly used regimen starts with a daily dose of 0.5 mg/kg of prednisolone for 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, with a subsequent taper of 5 mg every 2 weeks until completing 3 to 5 months of treatment.[5]

Although disease remission is achieved in most cases treated with systemic corticosteroids, relapse occurs in a significant proportion of patients (13.5% to 45%), and some may become corticosteroid-dependent.[6,50]

Pulse corticosteroid therapy may be used as an alternative to oral administration. Methylprednisolone at 15 mg/kg/day (not exceeding 1 g) for 3 days has been used in children to minimize the side effects of daily corticosteroid therapy[76] and in cases of exacerbations refractory to oral treatment.[77]

Antifungal therapy

Antifungal agents reduce fungal load in the airways, decrease antigenic stimulation, and mitigate the inflammatory response, potentially reducing the need for systemic corticosteroids. The use of azole antifungals, either alone or in combination with corticosteroids, is an option for ABPA treatment.[78] Azoles such as itraconazole are typically prescribed at a dose of 200 mg twice daily for 16 weeks.[75] The combination of itraconazole with prednisolone results in a greater reduction in exacerbation rates over 1 year compared to monotherapy with either agent.[78]

Other azoles, including voriconazole, posaconazole, and isavuconazole, have also demonstrated efficacy in treating ABPA, particularly in cases of intolerance or resistance to itraconazole.[49,79] However, drug interactions, hepatotoxicity, and variable bioavailability can limit their use.[80]

The efficacy of nebulized amphotericin B for treating ABPA exacerbations appears to be limited and should only be considered when other therapeutic options have been exhausted.[49,81]

Biologic therapy

Post-treatment recurrences are common, regardless of whether corticosteroids, antifungal therapy, or a combination of both is used. In addition, prolonged treatment can lead to adverse effects, underscoring the need for new, safe, and effective therapeutic strategies. Given ABPA pathogenesis, biologic agents developed for severe asthma targeting T2 inflammation are considered potential treatment alternatives for ABPA.[82] Although evidence remains limited, recent case reports and series have demonstrated their efficacy.[82-85]

The monoclonal anti-IgE antibody omalizumab has shown promise in reducing corticosteroid use, improving lung function, and preventing exacerbations.[84] It is administered subcutaneously every 2–4 weeks, with the dosage determined based on patient weight and total serum IgE levels.[84] However, due to the high IgE levels observed in ABPA, the doses used may be suboptimal.

The two biologics targeting IL-5, mepolizumab and reslizumab, along with the anti-IL-5Rα monoclonal antibody (MAB) benralizumab, have demonstrated efficacy in treating eosinophilic lung diseases, including ABPA. These anti-IL-5/IL-5Rα MABs have been successful in reducing exacerbation frequency, minimizing oral corticosteroid requirements, and improving lung function, even in patients unresponsive to omalizumab.[82]

Table 4
Medications used in the treatment of ABPA

Medication		Indication
Oral corticosteroids[a]	– Prednisolone: 0.5 mg/kg/day for 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, then taper by 5 mg every 2 weeks until completing 3 to 5 months. **OR** – Prednisolone: 0.5, 0.25, and 0.125 mg/kg/day for 4 weeks each, then taper by 4 mg/week until completing 4 months. **OR** – Deflazacort: 0.75 mg/kg/day for 4 weeks, reduce by half every 4 weeks for the next 2 months, then taper gradually by 6 mg every 2 weeks until discontinuation at 4 months.	– Acute or exacerbated ABPA.
Intravenous corticosteroids	– Methylprednisolone: 15 mg/kg/day (max 1 g) intravenously for 3 consecutive days	– To minimize side effects of daily corticosteroid use.
Antifungal therapy	Oral antifungals[b]: – Itraconazole 200 mg twice daily for 16 weeks. **OR** – Voriconazole 200 mg twice daily for at least 24 weeks. Nebulized antifungals[c]: – Liposomal Amphotericin B 25–50 mg once or twice per week. – Deoxycholate Amphotericin B 10 mg twice daily 3–6 times per week	– Acute or exacerbated ABPA.
Biologic therapy[d]	– Omalizumab: 150 mg, approved for patients ≥ 6 years, administered SC. Dose and frequency depend on weight and total IgE levels. Max IgE level: 1500 UI/mL. **OR** – Mepolizumab: 40 mg or 100 mg, approved for patients ≥ 6 years. For children (6–11 years): 40 mg SC every 4 weeks and for patients ≥ 12 years: 100 mg SC every 4 weeks. **OR** – Benralizumab: 30 mg, approved for patients ≥ 12 years, administered SC every 4 weeks for the first 3 doses, then every 8 weeks. **OR** – Dupilumab: 200 mg or 300 mg, approved for patients ≥ 6 years, administered SC every 2 weeks. For children (6–11 years): dose and frequency depend on weight. For patients ≥ 12 years: 300 mg for corticosteroid-dependent severe asthma. **OR** – Tezepelumab: 210 mg, approved for patients ≥ 12 years, administered SC every 4 weeks.	– Treatment-dependent ABPA. – Adverse events of contraindication to the use of corticosteroids or antifungals.

[a] First-line treatment. For the first exacerbation, corticosteroids can be used alone, while subsequent exacerbations may require combination therapy with azoles.
[b] Itraconazole can be used alone in patients with contraindications to corticosteroids. Combining it with prednisolone may reduce the risk of exacerbation.
[c] Nebulized Amphotericin B may be considered when systemic corticosteroids and/or azoles are required.
[d] Clinical studies are needed to clarify the role of biologics in ABPA treatment.

ABPA = allergic bronchopulmonary aspergillosis; SC = subcutaneously.
Adapted from Valle SOR et al.[67] and Agarwal R et al.[49]

Dupilumab, an anti-IL-4Rα MAB, has shown beneficial therapeutic effects on symptoms and lung function in ABPA.[83,86] Some patients with ABPA refractory to omalizumab or mepolizumab have responded favorably to dupilumab.[83,87]

Tezepelumab, a human IgG2 MAB targeting TSLP, has proven effective in improving asthma control.[88] A recent case report described a patient using tezepelumab who experienced symptom improvement, reduced mucus plugs, and resolution of pulmonary opacities associated with ABPA.[85]

Respiratory physiotherapy techniques and positive expiratory pressure devices can benefit patients with ABPA, especially those with CF.[80] These techniques help remove mucus plugs, improve lung function, and reduce the risk of recurrent infections.

The treatment of ABPA in CF is largely similar to that in asthma. However, patients with CF often experience concomitant malabsorption, making treatment more complex. Oral medications, particularly itraconazole capsules, may have reduced absorption.[80]

Remission is defined as the absence of asthma and ABPA exacerbations, no dependence on systemic corticosteroids, and optimal lung function. This goal can be achieved through a combination of corticosteroids, antifungals, and biologic agents.[49]

Figure 3 presents the currently recommended treatment algorithm for ABPA.[49]

Treatment monitoring

Treatment response should be monitored using clinical parameters, chest radiography, and total serum IgE measurements every 8 weeks. A successful response is indicated by the resolution of radiographic opacities and a minimum 25% reduction in total serum IgE levels, establishing a new baseline. Clinical and/or radiological worsening, along with a 50% increase in IgE levels, suggests an exacerbation.[80] For patients receiving omalizumab, monitoring total IgE levels is unreliable, as IgE concentrations increase during therapy.

ABPA and CF

CF is an autosomal recessive genetic disorder characterized by reduced or absent function of the CFTR protein. CF affects approximately 89,000 individuals worldwide, including more than 6,000 Brazilians registered in the Brazilian CF Registry (REBRAFC).[89]

The CFTR protein is located in the apical portion of the cell membrane and functions as an ion channel that facilitates chloride ion transport into the epithelial lumen. The dysregulation of CFTR-mediated ion transport results in depletion of the periciliary liquid layer and hyperconcentration of mucin. This severely impairs ciliary movement and mucus clearance, resulting in secretion buildup and recurrent infections. Over time, these infections damage the epithelium and airway structures, particularly the bronchi and bronchioles. This process leads to the formation of sac-like dilations (bronchiectasis) and initiates a vicious cycle of mucus accumulation, infections, structural damage, pulmonary function decline, and disease progression.[90]

CF-related respiratory symptoms include chronic productive cough, recurrent infections (*Staphylococcus aureus*, non-encapsulated *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*), airway obstruction symptoms, recurrent sinusitis and otitis, and digital clubbing. Radiological findings commonly include small airway disease, bronchiectasis, and sinusitis. Infection and colonization by *P. aeruginosa* are typically associated with more rapid disease progression.[90]

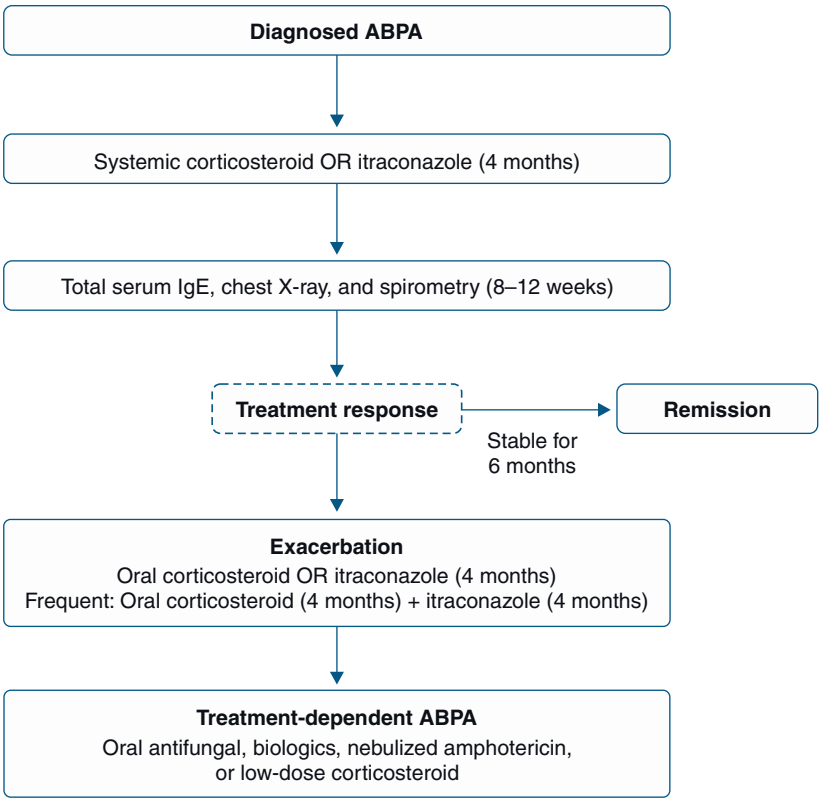
Due to the altered airway physiology in CF, fungal species are frequently found in sputum samples, with *A. fumigatus* being the most common. However, unlike *P. aeruginosa* colonization, the impact of *A. fumigatus* on CF disease progression remains uncertain. In some cases, inhaled *A. fumigatus* conidia may colonize the respiratory tract, leading to ABPA, which significantly increases morbidity, accelerates lung function decline, and worsens bronchiectasis and pulmonary fibrosis.[90]

Diagnosis of ABPA in patients with CF

The diagnostic criteria for ABPA in patients with CF, as proposed by the CF Foundation Consensus Conference (CFFCC) in 2003,[91,92] are similar to the 2024 ISHAM criteria[49] (Table 5). Fungal colonization, especially of *A. fumigatus*, in sputum is common and does not necessarily indicate disease unless clinical deterioration occurs, in which case the criteria in Table 3 should be applied.

CFFCC recommendations include[91,92]:

– Screening for ABPA in patients with CF aged > 6 years old with clinical deterioration.
– Measure total serum IgE annually:



ABPA = allergic bronchopulmonary aspergillosis.

Figure 3
ABPA treatment flowchart
Adapted from Agarwal R et al.[49].

– If IgE > 500 IU/mL – Test for specific IgE against *A. fumigatus* or perform skin test for immediate hypersensitivity. If positive, consider ABPA and conduct further diagnostic testing (specific IgG for *A. fumigatus* or serum precipitins, chest CT).
– If IgE between 200 and 500 IU/mL – Repeat testing. If levels increase, conduct additional diagnostic tests (specific IgE or skin test, specific IgG for *A. fumigatus* or serum precipitins, chest CT).

Treatment of ABPA in patients with CF

The treatment suggested by the Brazilian Guidelines for the Diagnosis and Treatment of Cystic Fibrosis follows a structured approach, although the level of evidence is considered low.[93] The treatment strategy aligns with the recommendations in Table 4[93]:

– *Prednisone:* 0.5–2.0 mg/kg/day (max 60 mg/day) for 1–2 weeks, followed by gradual tapering to alternate-day dosing, with withdrawal over 2–3 months.
– *Itraconazole:* 5 mg/kg/day (max 400 mg/day), administered every 12 hours if the dose exceeds 200 mg, for 3–6 months; alternatively, *Voriconazole:* 4 mg/kg every 12 hours (max 400 mg/day) for 3–6 months.

Alternative/adjunctive treatments include pulse corticosteroid therapy, biologic agents, and inhaled amphotericin B.[93]

The role of CFTR modulators in ABPA treatment remains unclear, as does their interaction with antifungal therapies.[94]

A recent retrospective study of 65 patients with CF treated for ABPA found that a regimen of decreasing doses of prednisone over 18 days combined with itraconazole for 1 year (with serum monitoring) successfully prevented lung function decline associated with ABPA, without corticosteroid-related adverse effects.[95]

Allergic Bronchopulmonary Mycosis (ABPM)

ABPA was the first ABPM described and remains the most commonly reported in the literature. However, several other airborne fungi have been identified as capable of inducing chronic inflammatory responses in the lungs, causing cough, dyspnea, and excessive mucus production. Due to the overlapping antigenic repertoire among *Aspergillus* species, the term ABPA is recommended when any *Aspergillus spp.* (not just *A. fumigatus*) is involved. The broader term ABPM is used when other fungal species are responsible for the disease.

Although detailed information on ABPM remains limited, it is known that if left undiagnosed and untreated, the condition can lead to bronchiectasis, lung function decline, and pulmonary fibrosis.[96]

The prevalence of ABPM is increasing in several regions, particularly in countries with hot and humid climates such as Brazil, India, Australia, and parts of Europe.[73] Similar to ABPA, ABPM primarily affects young and middle-aged adults with asthma, CF, or

Table 5
Criteria for diagnosing ABPA in patients with cystic fibrosis

CFFCC diagnostic criteria[91,92]
– Diagnosed CF with acute or subacute deterioration.
– Total serum IgE > 1000 IU/mL (unless the patient is on systemic corticosteroids).
– Positive specific IgE or positive skin prick test for *A. fumigatus*.
– Positive precipitins or serum IgG for *A. fumigatus*.
– New or recent infiltrates on chest X-ray or CT that do not respond to antibiotics and conventional physiotherapy.
2024 ISHAM diagnostic criteria[49]
– Diagnosed CF.
Mandatory criteria - Both criteria must be present:
– Total serum IgE > 500 IU/mL.[a]
– Specific IgE for *Aspergillus fumigatus* > 0.35 kUA/L or positive skin test.
Additional criteria - At least two of the following must be present:
– Peripheral eosinophilia > 500 cells/μL.[b]
– Elevated specific IgG for *A. fumigatus*.[c]
– Chest CT findings suggestive of ABPA (bronchiectasis, mucoid impaction, or high-attenuation mucus) or transient infiltrates on chest X-ray.

[a] If all other criteria are met, total IgE < 500 IU/mL is acceptable.
[b] Without systemic corticosteroid use.
[c] In the absence of a population-specific cutoff, follow manufacturer recommendations.

ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; CT = computed tomography.
CFFCC = Cystic Fibrosis Foundation Consensus Conference. ISHAM = International Society for Human and Animal Mycology.

other underlying lung disease, with no significant sex preference. Since these fungi are airborne, their growth and distribution depend on local environmental conditions, leading to regional variations in ABPM incidence.[55]

Causative agents

Several fungi in addition to *A. fumigatus* are known to cause ABPM (Table 6). *Candida albicans* is the most frequently identified non-*Aspergillus* agent, but other fungi can colonize the respiratory tract, proliferate, trigger immune-mediated inflammation, and promote airway damage.[96]

Disease mechanisms

The pathogenesis of ABPM is essentially the same as ABPA, involving genetic factors, host-pathogen interactions, and innate and adaptive immune responses. Genetic variants contribute to ABPM susceptibility.[26-31] Fungi colonize the airways in susceptible individuals, triggering a T2 inflammatory response, type I and III hypersensitivity reactions, eosinophilia, and mucus hypersecretion.[34-44] This inflammatory process is exacerbated by factors such as mucociliary clearance impairment and fungal protein secretion, which perpetuate damage to the respiratory epithelium.

The resulting inflammatory process leads to the destruction of the bronchial walls, resulting in the development of bronchiectasis, a hallmark feature of ABPM. The local anatomical changes caused by bronchiectasis predispose patients to recurrent infections, persistent inflammation, progressive lung damage, and fibrosis.[97]

Clinical presentation

Allergic fungal diseases present a heterogeneous spectrum of symptoms and clinical manifestations.98 Clinical characteristics of ABPM are similar to those of uncontrolled asthma. Patients typically experience cough, dyspnea, and expectoration of mucus plugs. Other nonspecific symptoms include fever, malaise, chest pain, and hemoptysis. A detailed medical history may reveal the chronic nature of symptoms and a history of radiological tests showing images consistent with past pneumonia. Studies have shown an association between ABPM and asthma (32% of cases) as well as other allergic conditions, such as rhinosinusitis, atopic dermatitis, and urticaria (41%).[96]

Physical examination is often normal, although auscultation of the lungs may reveal coarse crackles during periods of acute exacerbation or in patients with fibrosis, and digital clubbing may be present in some cases.

Imaging studies may reveal atelectasis due to mucus plugging and bronchiectasis. Laboratory investigations often provide crucial diagnostic information.[96,97]

The new clinical classification for ABPA/ABPM describes five clinical stages: acute ABPA, response to therapy, remission, treatment-dependent ABPA, and advanced ABPA (Table 1).

Laboratory investigation

After a thorough evaluation of the patient's clinical history, laboratory and imaging tests may play a decisive role in confirming ABPM.

The laboratory assessment of ABPM follows the same approach as ABPA and includes total IgE and specific IgE for fungi, specific IgG or serum precipitins for fungi, and HRCT. In addition, fungal culture from sputum or BAL may be helpful in identifying the causative fungus.[96,97]

Diagnosis

Accurate diagnosis of ABPM is as challenging as ABPA. Given the variability in clinical presentation, antifungal treatment response, and disease prognosis depending on the causative agent, accurate identification of the fungus (not *Aspergillus*) is crucial for optimal management.[99] The presence of specific IgE for certain allergenic components confirms sensitization and can help identify the causative fungus. However, cross-reactivity with crude fungal extracts makes the accuracy of the etiological diagnosis more difficult.[99] Repeated microbiological isolation from respiratory samples is another important resource, but obtaining high-quality biological specimens remains a challenge.[100]

Tests assessing cellular immune response, such as basophil and lymphocyte activation tests, have been studied and are considered a promising alternative to currently used diagnostic tests for ABPM in patients with underlying lung disease.[101]

The identification of new biomarkers for ABPM is of great interest, particularly since traditional clinical diagnostic criteria are more specific for ABPA,[102] and molecular fungal diagnostics are only available for *A. fumigatus*.[100]

Table 6
Fungi recognized as causative agents of ABPM

Causative agents of allergic bronchopulmonary mycosis
Candida albicans[a]
Bipolaris spp.[a]
Schizophyllum commune[a]
Curvularia spp.[a]
Alternaria alternata
Cladosporium spp.
Penicillium spp.
Fusarium vasinfectum spp.
Mucor spp.
Rhizopus spp.
Trichosporon spp.
Saccharomyces cerevisae
Bipolaris spp.
Pseudallescheria boydii
Stemphylium spp.
Paecilomyces spp.
Geotrichum spp.

ABPM = allergic bronchopulmonary mycosis.
[a] More frequently described causative agents.[49]

A study published in 2021 demonstrated improved sensitivity and specificity using new diagnostic criteria for ABPM compared with conventional methods.[55] These criteria were recently revised in 2024[49] and are summarized in Table 7.

Treatment

The treatment principles for ABPM are similar to those for ABPA, with the difference being that identifying the causative fungus can help guide the choice of antifungal therapy.[49]

The goals of ABPM treatment are:

– Inflammation control.
– Eradication of fungal colonization from the airways.
– Removal of bronchial mucus plugs.
– Identification and elimination of the causative agent from the patient's environment.

Systemic corticosteroids remain the cornerstone of ABPM treatment but may be less effective in preventing exacerbations and lung function decline, similar to ABPA. The recommended dosage is 0.5 mg/kg for the first 2 weeks, followed by a gradual taper over 3 months, with complete withdrawal if the patient remains stable without complications. The treatment goal is to reduce total IgE levels by 35% to 50% within 6 to 8 months and achieve complete resolution of pulmonary infiltrates.

Antifungal therapy may be necessary to eradicate fungal colonization from the airways. The choice of antifungal agent and treatment duration depend on effectiveness and availability.

Mucus impaction can be relieved via bronchoscopy.[96]

For patients with asthma, chronic obstructive pulmonary disease (DPOC), or CF, management should also include treatment of the underlying

Table 7
Evolution of ABPM diagnostic criteria

Criteria for allergic bronchopulmonary mycosis
Criteria (2021) 1. Current or past history of asthma or asthma-like symptoms. 2. Peripheral blood eosinophilia (≥ 500 cells/μL). 3. Elevated total serum IgE (≥ 417 IU/mL). 4. Positive skin test or specific IgE > 0.35 kUA/L for filamentous fungi. 5. Presence of precipitins or specific IgG for filamentous fungi. 6. Growth of filamentous fungi in sputum or bronchoalveolar lavage. 7. Presence of fungal hyphae in mucus plugs. 8. Central bronchiectasis on CT. 9. Presence of mucus plugs on CT, bronchoscopy, or history of mucus plug expectoration. 10. High-attenuation mucus on CT. **Definitive ABPM diagnosis:** At least 6 criteria present. **Probable ABPM diagnosis:** At least 5 of the 10 criteria.
Criteria (2024) **Predisposing condition[a]** – Asthma, CF, COPD, bronchiectasis, or clinical-radiological presentation consistent with ABPM. **Mandatory criteria** – Specific IgE or positive skin test for the fungus. – Total serum IgE > 500 UI/mL.[b] **Additional criteria** – Specific IgG or positive precipitins for the fungus.[c] – Peripheral eosinophilia > 500 cells/μL (previous test result acceptable). – Two sputum cultures or one bronchoalveolar lavage with a positive fungal culture. – Chest CT showing findings suggestive of ABPA (bronchiectasis, mucoid impaction, or high-attenuation mucus[d]) or transient infiltrates on chest X-ray. **Definitive ABPM diagnosis:** At least two mandatory criteria and at least two additional criteria.

[a] Mucus plug expectoration, finger-in-glove sign, transient infiltrates on radiography, pulmonary collapse, among others.
[b] Total serum IgE < 500 IU/mL is acceptable if all other criteria are met.
[c] IgG cutoff values should be established for each population. If unavailable, follow manufacturer recommendations.
[d] High-attenuation mucus is pathognomonic for allergic bronchopulmonary fungal disease and confirms the diagnosis even if othe criteria are not met.

The absence of specific IgE for rAsp f1, f2, and f4 excludes ABPA and supports an ABPM diagnosis.

ABPM = allergic bronchopulmonary mycosis; ABPA = allergic bronchopulmonary aspergillosis; *A. fumigatus* = *Aspergillus fumigatus*, rAsp = recombinant *A. fumigatus*; COPD = chronic obstructive pulmonary disease.

disease. Inhaled corticosteroids and bronchodilators should be maintained and/or optimized in patients with asthma and in some cases of DPOC.

Biologic therapy, particularly omalizumab and anti-IL-5 agents, appears promising in ABPM treatment, as demonstrated in recent studies.[49]

Broad-spectrum antibiotics may be necessary in cases of pulmonary infection, especially in patients with bronchiectasis or underlying lung diseases.

Additionally, complementary therapeutic measures, such as pulmonary rehabilitation and physiotherapy, should be part of the treatment plan for patients with ABPM.[97]

Conclusion

ABPA occurs in genetically predisposed individuals, primarily those with asthma or CF, although its exact prevalence remains unknown. The diagnostic criteria involve clinical, serological, and radiological parameters, which have evolved since the disease was first described. However, widespread awareness of these criteria remains limited, contributing to underdiagnosis. Moreover, ABPA can mimic common pulmonary diseases such as tuberculosis. Regarding treatment, multiple therapeutic protocols have been proposed, with oral corticosteroids as the first-line therapy, either alone or in combination with azole antifungals. Biologic agents targeting T2 inflammation have shown benefits in some cases. Further research is needed to establish diagnostic criteria for different populations, as well as clinical trials of targeted therapeutic agents for patients with ABPM.

References

1. Hinson KFW, Moon AJ, Plummer NS. Bronchopulmonary aspergillosis: a review and report of eight new cases. Thorax. 1952;7:317-33.
2. Patterson R, Golbert TM. Hypersensitivity disease of the lung. Univ Mich Med Cent J. 1968;34:8-11.
3. França AT. Asma Brônquica: importância do *Aspergillus fumigatus* [thesis]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 1974.
4. Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol. 2013;51(4):361-70.
5. Greenberger PA. Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 2002 Nov;110(5):685-92.
6. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in North India. Chest. 2006;130(2):442-8.
7. Gago S, Denning DW, Bowyer P. Pathophysiological aspects of Aspergillus colonization in disease. Med Mycol. 2019;57(Supplement_2):S219-S227.
8. Agarwal R, Nath A, Aggarwal NA, Gupta D, Chakrabarti A. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India. Mycoses. 2010;53:138-43.
9. Serpa FS. Aspergilose Broncopulmonar Alérgica: critérios diagnósticos em pacientes sensíveis ao *Aspergillus fumigatus* [dissertation]. Rio de Janeiro: UFRJ; 1997.
10. Valle SOR. Identificação de aspergilose broncopulmonar alérgica em pacientes com fibrose cística e reatividade cutânea aos antígenos do *Aspergillus fumigatus* [dissertation]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 1998.
11. Rosario NA, Riedi CA. Cystic fibrosis and atopy. Allergol Immunopathol (Madr). 2013;41(2):137-9.
12. Agarwal R, Sehgal IS, Dhooria S, Muthu V, Prasad KT, Bal A, et al. Allergic Bronchopulmonary aspergillosis. Indian J Med Res. 2020;151:529-49.
13. Muthu V, Sehgal IS, Prasad KT, Dhooria S, Aggarwal AN, Garg M, et al. Allergic bronchopulmonary aspergillosis (ABPA) sans asthma: A distinct subset of ABPA with a lesser risk of exacerbation. Med Mycol. 2020;58:260-3.
14. Chauhan B, Santiago L, Hutcheson PS, Schwartz HJ, Spitznagel E, Castro M, et al. Evidence for the involvement of two different MHC class II regions in susceptibility or protection in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 2000;106(4):723-9.
15. Souza HG, Sales LS, Figueiredo CN, Santana Neto D, Cruz-Magalhães V, Souza JT, et al. Diversidade taxonômica e identificação de Aspergillus. In: Soares ACF, Evangelista-Barreto NS, Santos PA, orgs. Tópicos em Microbiologia Agrícola. Cruz das Almas, BA: EDUFRB; 2020. p. 219-46.
16. Moraes AML, Paes RA, Holanda VL. Micologia. In: Molinaro EM, Caputo LFG, Amendoeira MRR, orgs. Conceitos e Métodos para formação de profissionais em laboratórios de saúde: volume 4. Rio de Janeiro: EPSJV, IOC; 2009. p. 399-496 p. ISBN:978-85-98768-41-0.
17. Houbraken J, Kocsubé S, Visagie CM, Yilmaz N, Wang XC, Meijer M, et al. Classification of Aspergillus, Penicillium, Talaromyces and related genera (Eurotiales): An overview of families, genera, subgenera, sections, series and species. Stud Mycol. 2020;95:5-169.
18. Sugui JA, Kwon-Chung KJ, Juvvadi PR, Latgé JP, Steinbach WJ. *Aspergillus fumigatus* and related species. Cold Spring Harb Perspect Med. 2014;5(2):a019786.
19. Gugnani HC. Ecology and taxonomy of pathogenic aspergilli. Front Biosci. 2003;8:s346-57.
20. Silva FC, Chalfoun SM, Batista LR, Santos C, Lima N. Taxonomia polifásica para identificação de Aspergillus flavi: uma revisão. Revista Ifes Ciência. 2015;1(1). doi: https://doi.org/10.36524/ric.v1i1.235.
21. Samson RA, Visagie CM, Houbraken J, Hong SB, Hubka V, Klaassen CHW, et al. Phylogeny, identification and nomenclature of the genus Aspergillus. Studies in mycology. 2014:78:141-73.
22. Mesquita-Rocha S. *Aspergillus fumigatus*: aspectos gerais e importância na medicina contemporânea. J Health Sci Inst. 2019;37(2):169-73.
23. van de Veerdonk FL, Gresnigt MS, Romani L, Netea MG, Latgé J. *Aspergillus fumigatus* morphology and dynamic host interactions. Nat Rev Microbiol. 2017;15(11):661-74.
24. Bodey GP, Vartivarian S. Aspergillosis. Eur J Clin Microbiol Infect Dis. 1989;8:413-37.

25. Simões D, Caetano LA, Cristina Viegas VC, Sabino R. Aspergillus collected in specific indoor settings: their molecular identification and susceptibility pattern. International Journal of Environmental Health Research. 2021;31(3):248-57.
26. Chauhan B, Santiago L, Kirschmann DA, Hauptfeld V, Knutsen AP, Hutcheson PS, et al. The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. J Immunol. 1997;159:4072-6.
27. Chauhan B, Santiago L, Hutcheson PS, Schwartz HJ, Spitznagel E, Castro M, et al. Evidence for the involvement of two different MHC class II regions in susceptibility or protection in allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 2000;106(4):723-9.
28. Gago S, Overton NLD, Ben-Ghazzi N, Muralidhar K, Sarma PU. Lung colonization by *Aspergillus fumigatus* is controlled by ZNF77. Nat Commun. 2018;9(1):3835.
29. Saxena S, Madan T, Shah A, Muralidhar K, Sarma PU. Association of polymorphisms in the collagen region of SP-A2 with increased levels of total IgE antibodies and eosinophilia in patients with allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 2003;111(5):1001-7.
30. Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis. 2008;197(4):618-21.
31. Overton NL, Denning DW, Bowyer P, Simpson A. Genetic susceptibility to allergic bronchopulmonary aspergillosis in asthma: a genetic association study. Allergy Asthma Clin Immunol. 2016;12:47.
32. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol. 2012;129(2):280-91; quiz 292-3.
33. Aimanianda V, Bayry J, Bozza S, Kniemeyer O, Perruccio K, Elluru SR. Surface hydrophobin prevents immune recognition of airborne fungal spores. Nature. 2009;460(7259):1117-21.
34. Kita H. ILC2s and fungal allergy. Allergol Int. 2015;64(3):219-26.
35. Tomee JF, Wierenga AT, Hiemstra PS, Kauffman HK. Proteases from *Aspergillus fumigatus* induce release of proinflammatory cytokines and cell detachment in airway epithelial cell lines. J Infect Dis. 1997;176(1):300-3.
36. Borger P, Koeter GH, Timmerman JA, Vellenga E, Tomee JF, Kauffman HF. Proteases from *Aspergillus fumigatus* induce interleukin (IL)-6 and IL-8 production in airway epithelial cell lines by transcriptional mechanisms. J Infect Dis. 1999;180(4):1267-74.
37. Kauffman HF, Tomee JF, van de Riet MA, Timmerman AJ, Borger P. Protease-dependent activation of epithelial cells by fungal allergens leads to morphologic changes and cytokine production. J Allergy Clin Immunol. 2000;105(6 Pt 1):1185-93.
38. World Health Organization. International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee [internet]. Available from: https://allergen.org/search.php?allergen source=aspergillus+fumigatus&searchsource=Search. Accessed 06/02/2024.
39. Muthu V, Sehgal IS, Dhooria S, Aggarwal AN, Agarwal R. Utility of recombinant *Aspergillus fumigatus* antigens in the diagnosis of allergic bronchopulmonary aspergillosis: a systematic review and diagnostic test accuracy meta-analysis. Clin Exp Allergy. 2018;48:1107-36.
40. Arruda LK, Platts-Mills TAE, Longbottom JL, El-Dahr JM, Chapman MD. *Aspergillus fumigatus*: identification of 16, 18, and 45 kd antigens recognized by human IgG and IgE antibodies and murine monoclonal antibodies. J Allergy Clin Immunol. 1992;89:1166-76.
41. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol. 2012;129(2):280-91.
42. Knutsen AP, Slavin RG. Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis. Clin Dev Immunol. 2011;2011:843763.
43. Hohl TM, Feldmesser M. *Aspergillus fumigatus*: principles of pathogenesis and host defense. Eukaryot Cell. 2007;6(11):1953-63.
44. Roboubi A, Audousset C, Fréalle É, Brun AL, Laurent F, Vitte J, et al. Allergic bronchopulmonary aspergillosis: A multidisciplinary review. J Mycol Med. 2023;33(3):101392.
45. Agarwal R, Khan A, Aggarwal AN, Gupta D. Link between CFTR mutations and ABPA: a systematic review and meta-analysis. Mycoses. 2012 Jul;55(4):357-65.
46. Agarwal R, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A, Jindal SK. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. Chest. 2007;132(4):1183-90.
47. Muthu V, Sehgal IS, Prasad KT, Dhooria S, Aggarwal AN, Garg M, et al. Allergic bronchopulmonary aspergillosis (ABPA) sans asthma: A distinct subset of ABPA with a lesser risk of exacerbation. Med Mycol. 2020;58:260.
48. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention [internet]. 2024. Available from: https://ginasthma.org/2024-report/. Accessed 09/10/2024.
49. Agarwal R, Sehgal IS, Muthu V, Denning DW, Chakrabarti A, Soundappan K, et al. Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying and treating allergic bronchopulmonary aspergillosis/mycoses. Eur Respir J. 2024;63(4):2400061.
50. Patterson R, Greenberger PA, Radin RC, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. Ann Intern Med. 1982;96:286-91.
51. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):433-42.
52. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med. 1977;86(4):405-14.
53. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013;43(8):850-73.
54. Saxena P, Choudhary H, Muthu V, Sehgal IS, Dhooria S, Prasad KT, et al. Which Are the Optimal Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis? A Latent Class Analysis. J Allergy Clin Immunol Pract. 2021;9(1):328-335.e1.
55. Asano K, Hebisawa A, Ishiguro T, Takayanagi N, Nakamura Y, Suzuki J, et al. New clinical diagnostic criteria for allergic bronchopulmonary aspergillosis/mycosis and its validation. J Allergy Clin Immunol. 2021;147(4):1261-1268.e5.
56. Muthu V, Singh P, Choudhary H, Sehgal IS, Dhooria S, Prasad KT, et al. Diagnostic cutoffs and clinical utility of recombinant *Aspergillus fumigatus* antigens in the diagnosis of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract. 2020;8:579-87.
57. Tanimoto H, Fukutomi Y, Yasueda H, Takeuchi Y, Saito A, Watai K, et al. Molecular-based allergy diagnosis of allergic bronchopulmonary aspergillosis in *Aspergillus fumigatus*-sensitized Japanese patients. Clin Exp Allergy. 2015;45:1790-800.
58. Caminati M, Feleszko W, Michel M, Annesi-Maesano I, Vitte J, EAACI Task Force Diagnosis, Management of ABPA. *Aspergillus fumigatus* and personalized medicine: Toward a clinically reliable algorithm. Allergy. 2022;77(11):3476-7.
59. Oliveira E, Giavina-Bianchi P, Fonseca LAM, França AT, Kalil J. Allergic bronchopulmonary aspergillosis' diagnosis remains a challenge. Respir Med. 2007;101(11):2352-7.
60. Agarwal R, Dua D, Choudhary H, Aggarwal AN, Sehgal IS, Dhooria S, et al. Role of *Aspergillus fumigatus*-specific IgG in diagnosis and monitoring treatment response in allergic bronchopulmonary aspergillosis. Mycoses. 2017;60:33-9.

61. Shinfuku K, Suzuki J, Takeda K, Kawashima M, Morio Y, Sasaki Y, et al. Validity of Platelia Aspergillus IgG and Aspergillus precipitin test to distinguish pulmonary aspergillosis from colonization. Microbiol Spectr. 2023;11: e0343522.
62. Hamada Y, Fukutomi Y, Nakatani E, Saito A, Watai K, Kamide Y, et al. Optimal *Aspergillus fumigatus* and Asp f 1 serum IgG cut-offs for the diagnosis of allergic bronchopulmonary aspergillosis. Allergol Int. 2021;70:74-80.
63. Kopp W, Fotter R, Steiner H, Beaufort F, Stammberger H. Aspergillosis of the paranasal sinuses. Radiology. 1985;156(3):715-6.
64. Dillon WP, Som PM, Fullerton GD. Hypointense MR signal in chronically inspissated sinonasal secretions. Radiology. 1990;174(1):73-8.
65. Agarwal R, Khan A, Garg M, Aggarwal AN, Gupta D. Chest radiographic and computed tomographic manifestations in allergic bronchopulmonary aspergillosis. World J Radiol. 2012;4(4):141-50.
66. Agarwal R, Khan A, Gupta D, Aggarwal AN, Saxena AK, Chakrabarti A. An alternate method of classifying allergic bronchopulmonary aspergillosis based on high-attenuation mucus. PLoS One. 2010;5(12):e15346.
67. Valle SOR, Serpa AS, Serpa FS. Allergic Bronchopulmonary Aspergillosis/Mycosis: An Underdiagnosed Disease [Internet]. Infectious Diseases. IntechOpen; 2023. Available from: http://dx.doi.org/10.5772/intechopen.112166.
68. Giavina-Bianchi P, Kalil J. Diagnosis of Allergic Bronchopulmonary Aspergillosis Exacerbations. J Allergy Clin Immunol Pract. 2017 Nov-Dec;5(6):1599-600.
69. Greenberger PA. Clinical Aspects of Allergic bronchopulmonary aspergillosis. Frontiers in Bioscience. 2003;8:119-27.
70. Patterson K, Strek ME. Allergic Bronchopulmonary Aspergillosis. Proc Am Thorac Soc. 2010;7:237-44.
71. Vlahakis NE, Aksamit TR. Diagnosis and Treatment of Allergic Bronchopulmonary Aspergillosis. Mayo Clin Proc. 2001;76:930-8.
72. Valle SOR, França AT. Aspergilose broncopulmonar alérgica: panorama atual. Revista do Hospital Universitário Pedro Ernesto. 2008;7:62-71.
73. Abreu DB, Silva D, Plácido JL. Aspergilose broncopulmonar alérgica. Rev Port Imunoalergologia. 2022;30(2):85-100.
74. Boaventura R, Sibila O, Agusti A, Chalmers JD. Treatable traits in bronchiectasis. Eur Respir J. 2018;52(3):1801269.
75. Agarwal R, Muthu V, Sehgal IS, Dhooria S, Prasad KT, Aggarwal AN. Allergic Bronchopulmonary Aspergillosis. Clin Chest Med. 2022;43(1):99-125.
76. Cohen-Cymberknoh M, Blau H, Shoseyov D, Mei-Zahav M, Efrati O, Armoni S, et al. Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis. J Cyst Fibros. 2009;8(4):253-7.
77. Singh Sehgal I, Agarwal R. Pulse methylprednisolone in allergic bronchopulmonary aspergillosis exacerbations. Eur Respir Rev. 2014;23(131):149-52.
78. Agarwal R, Muthu V, Sehgal IS, Dhooria S, Prasad KT, Garg M, et al. A randomised trial of prednisolone versus prednisolone and itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. Eur Respir J. 2021;59(4):2101787.
79. Chishimba L, Niven RM, Cooley J, Denning DW. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. J Asthma. 2012;49(4):423-33.
80. Agarwal R, Sehgal IS, Dhooria S, Muthu V. Allergic bronchopulmonary aspergillosis. Chest. 2020;157(2),403-16.
81. Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. Expert Rev Respir Med. 2016;10(12):1317-34.
82. Tomomatsu K, Yasuba H, Ishiguro T, Imokawa S, Hara J, Soeda S, et al. Real-world efficacy of anti-IL-5 treatment in patients with allergic bronchopulmonary aspergillosis. Sci Rep. 2023;13(1):5468.
83. Ramonell RP, Lee FE, Swenson C, Kuruvilla M. Dupilumab treatment for allergic bronchopulmonary aspergillosis: A case series. J Allergy Clin Immunol Pract. 2020;8(2):742-3.
84. Jin M, Douglass JA, Elborn JS, Agarwal R, Calhoun WJ, Lazarewicz S, et al. Omalizumab in Allergic Bronchopulmonary Aspergillosis: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2023;11(3):896-905.
85. Ogta H, Sha K, Kotetsu Y, Enokizu-Ogawa A, Katahira K, Ishimatsu A, et al. Tezepelumab treatment for allergic bronchopulmonary aspergillosis. Respirol Case Rep. 2023;11(5):e01147.
86. Nishimura T, Okano T, Naito M, Tsuji C, Iwanaka S, Sakakura Y. Complete withdrawal of glucocorticoids after dupilumab therapy in allergic bronchopulmonary aspergillosis: A case report. World J Clin Cases. 2021;9(23):6922-8.
87. Mikura S, Saraya T, Yoshida Y, Oda M, Ishida M, Honda K, et al. Successful Treatment of Mepolizumab- and Prednisolone-resistant Allergic Bronchopulmonary Aspergillosis with Dupilumab. Intern Med. 2021;60(17):2839-42.
88. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021;384:1800-9.
89. Grupo Brasileiro de Estudos de Fibrose Cística - CGEFC. Registro Brasileiro de Fibrose Cística ano 2020 [internet]. Available from: http://portalgbefc.org.br/. Accessed 08/03/2023.
90. Ong T, Ramsey BW. Cystic Fibrosis: A Review. JAMA. 2023;329(21):1859-71.
91. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181S:S4-S15.e1. Erratum in: J Pediatr. 2017;184:243.
92. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis—state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis. 2003;37 Suppl 3:S225-64. Erratum in: Clin Infect Dis. 2004 Jan 1;38(1):158.
93. Athanazio RA, Silva Filho LVRF, Vergara AA, Ribeiro AF, Riedi CA, Procianoy EDFA, et al. Brazilian guidelines for the diagnosis and treatment of cystic fibrosis. J Bras Pneumol. 2017;43(3):219-45.
94. Bercusson A, Jarvis G, Shah A. CF Fungal Disease in the Age of CFTR Modulators. Mycopathologia. 2021;186(5):655-64. doi: 10.1007/s11046-021-00541-5.
95. Gothe F, Schmautz A, Häusler K, Tran NB, Kappler M, Griese M. Treating Allergic Bronchopulmonary Aspergillosis with Short-Term Prednisone and Itraconazole in Cystic Fibrosis. J Allergy Clin Immunol Pract. 2020;8(8):2608-14.e3.
96. Chowdhary A, Agarwal K, Kathuria S, Gaur SN, Randhawa HS, Meis JF. Allergic bronchopulmonary mycosis due to fungi other than Aspergillus: A global overview. In Critical Reviews in Microbiology. 2014;40(1):30-48.
97. Rick EM, Woolnough K, Pashley CH, Wardlaw AJ. (2016). Allergic fungal airway disease. In Journal of Investigational Allergology and Clinical Immunology. 2016;26(6):344-54.
98. Wardlaw AJ, Rick EM, Ozyigit LP, Scadding A, Gaillard EA, Pashley CH. New perspectives in the diagnosis and management of allergic fungal airway disease. In Journal of Asthma and Allergy. 2021;14:557-73.
99. Nasu S, Satoh S, Shimizu K, Matsuno O, Morishita H, Yaguchi T, et al. Spontaneous regression of allergic bronchopulmonary mycosis due to curvularia lunata. Internal Medicine. 2018;57(2):243-6.
100. Fukutomi Y, Tanimoto H, Yasueda H, Taniguchi M. Serological diagnosis of allergic bronchopulmonary mycosis: Progress and challenges. In Allergology International. 2016;65(1):30-6.

101. Michel M, Gomez C, Sereme Y, Gouitaa M, Chartier C, Blanchard P, et al. Evaluation of Cellular Responses for the Diagnosis of Allergic Bronchopulmonary Mycosis: A Preliminary Study in Cystic Fibrosis PatientsFront Immunol. 2020;10:3149.

102. Moss RB. Diagnosing allergic bronchopulmonary aspergillosis/mycosis: Return to lost horizons. Journal of Allergy and Clinical Immunology. 2021;147(4):1212-4.

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