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Chapter

Allergic Bronchopulmonary Aspergillosis/Mycosis: An Underdiagnosed Disease

Solange Oliveira Rodrigues Valle, Augusto Sarquis Serpa and Faradiba Sarquis Serpa

Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is an immune-allergic disease of the lung due to a hypersensitivity reaction to antigens of *Aspergillus fumigatus* after colonization into the airways. Predominantly, it affects patients with bronchial asthma and those having cystic fibrosis (CF). Despite being recognized as a distinct entity nearly 70 years ago, this disease remains underdiagnosed. This may be due to the diagnostic methods employed, lack of standardized tests, and diagnostic criteria. The mainstay treatment for ABPA is systemic steroid. Azole antifungal agents represent an alternative for the treatment of exacerbations and are preferential strategy for corticosteroids sparing. Biologic drugs are expected to play an important role in the treatment of ABPA based on their mechanism in inhibition of type 2 inflammation, regulation of eosinophils and IgE levels, and modulation of inflammatory cytokines. Therefore, other studies are necessary for a better understanding of this disease so that an early detection can be done as well as a correct management.

Keywords: allergic bronchopulmonary aspergillosis, *Aspergillus fumigatus*, asthma, cystic fibrosis, diagnostic criteria, bronchiectasis, eosinophilia

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA) was first identified in 1952 by Dr. K. F.W. Hinson who described eight cases with typical clinical characteristics, including bronchitis/asthma, eosinophilia, bronchiectasis and/or mucus plugs, and isolation of *Aspergillus fumigatus* in lung tissue [1]. In 1968, ABPA was first reported in the United States [2] and 6 years later, in Brazil by our department at Federal University of Rio de Janeiro but remains underdiagnosed to this day, both in Brazil and worldwide [3].

ABPA is a complex pulmonary disorder characterized by an exaggerated hypersensitivity reaction to *Aspergillus* generally *fumigatus* specie, resulting in airway inflammation, mucus plugging, and bronchiectasis [4]. People most at risk of developing ABPA are patients with asthma or cystic fibrosis (CF). Given the propensity of the disease to cause irreversible complications, it is essential to formulate screening protocols for ABPA in these patients. Early detection of the disease is crucial for a better prognosis.

2. Epidemiology

The prevalence of ABPA remains uncertain and is likely to differ across geographical locations. ABPA affects 2.5–15% of patients with asthma and 7–9% of patients with CF, subject to variations within the studied population [5, 6]. In a recent systematic literature review, the pooled prevalence of ABPA in adults with asthma was 11.3%, and in adults, asthmatics sensitized to *A. fumigatus* (*Af*) was 37% [7]. For children, the pooled prevalence of ABPA in subjects with asthma was 9.9% [8]. Studies conducted in our center demonstrated 19% of ABPA prevalence among asthmatics sensitized to *Af* [9] and 12,5% of ABPA prevalence in children diagnosed with CF [10]. Worldwide, more than 4 million people are affected by ABPA [6, 11].

Additionally, genetic predisposition, such as specific HLA-DR alleles, may contribute to the development of ABPA in susceptible individuals [12]. There is no particular age or gender predilection for the occurrence of ABPA, although ABPA is uncommon in patients without asthma or CF [13].

The real prevalence of ABPA is difficult to determine due to the diagnostic methods employed, lack of standardized tests, diagnostic criteria, and the populations studied.

3. Pathogenesis

The pathogenesis of ABPA is complex, involving genetic factors, host–pathogen interactions, hypersensitivity reactions, eosinophilic inflammation, and cytokine dysregulation.

Genetic factors may contribute to the susceptibility to ABPA. Human leukocyte antigen (HLA) genotyping studies have identified specific HLA-DR alleles, such as HLA-DR2 and HLA-DR5, to be associated with an increased risk of developing ABPA in asthmatic and CF patients, respectively [12]. On the other hand, HLA-DQ2 contributes to resistance [14].

Aspergillus is an airborne ubiquitous saprophytic fungus that is found in soil and grows on decaying vegetation [15]. Spores are small (2–3 mm), facilitating their deposition throughout the airways. Inhalation of *Aspergillus* spores can lead to colonization and germination in the airways of susceptible individuals, such as those with asthma or CF [16]. *Aspergillus* spores persist in lower airways and develop the ability to germinate into mycelial filaments. This results in the secretion of metabolites that drive the activation of mucosal innate immune response and exposition of *Aspergillus* to the immune system. The impaired mucociliary clearance and local immune response in these individuals facilitate the persistence of *Aspergillus* hyphae in the airways, triggering an exaggerated immune response [17].

ABPA is characterized by a combination of type I (immediate) and type III (immune complex-mediated) hypersensitivity reactions [16]. In type I hypersensitivity, *Aspergillus* antigens bind to immunoglobulin E (IgE) on the surface of mast cells and basophils, leading to the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins, causing bronchoconstriction, increased vascular permeability, and mucus production [18]. In type III hypersensitivity, immune complexes composed of *Aspergillus* antigens and immunoglobulins (IgG) deposit in the

lung tissue, activating complement and attracting inflammatory cells, leading to tissue damage and eosinophilic inflammation [19].

Eosinophils play a central role in the pathogenesis of ABPA, contributing to airway inflammation, mucus production, and bronchial hyperresponsiveness [16].

There is a strong type-2 (T2) inflammation in ABPA combining a massive infiltration of airways by eosinophils and a high level of polyclonal IgE. Cytokines, such as interleukin IL-4, IL-5, and IL-13, produced by Th2 cells, stimulate eosinophil recruitment, activation, and survival [20]. Additionally, IL-4 and IL-13 promote the production of IgE by B cells and induce goblet cell hyperplasia, increasing mucus secretion. Airway inflammation leads to production of dense eosinophil mucus containing Charcot–Leyden crystals that obstructs airways. Mutation in CF transmembrane conductance regulator (CFTR) may play a role in ABPA even in the absence of CF, although this is still not clear [21].

4. Clinical manifestation

The clinical presentation of ABPA is heterogeneous, ranging from mild to severe respiratory symptoms. The primary clinical manifestations of ABPA are respiratory symptoms, which are often similar to those of asthma or CF, making the differentiation between these conditions difficult [22]. Common respiratory symptoms of ABPA include paroxysmal episodes of coughing, wheezing, dyspnea, and chest tightness [23]. Patients with ABPA may also experience recurrent episodes of pulmonary exacerbations, characterized by worsening respiratory symptoms and increased sputum production [4].

A characteristic feature of ABPA is the expectoration of brownish-black mucus plugs, which contain fungal hyphae and eosinophilic material [23]. These mucus plugs can lead to airway obstruction and impaired mucociliary clearance, contributing to the development of bronchiectasis and recurrent infections [22].

Systemic symptoms, such as fever, malaise and weight loss, may occur in ABPA, particularly during exacerbations [23]. These symptoms are thought to be related to the release of inflammatory mediators and the immune response to *Aspergillus* antigens [4].

Evolution is marked by the occurrence of ABPA exacerbations characterized by the onset, or an increase in, the clinical manifestations of ABPA often associated with radiological abnormalities and elevation of eosinophils and total IgE.

5. Diagnostic criteria

ABPA occurs mainly in patients diagnosed with asthma or CF. The diagnosis is based on a combination of clinical manifestations, radiological, and immunological features [24]. A thorough examination of the existing literature highlights the importance of early recognition and appropriate management of ABPA to prevent disease progression and associated complications. Over the years, the diagnostic criteria and approaches for ABPA have evolved significantly (**Table 1**).

The first diagnostic criteria described for ABPA were primarily based on clinical features, blood eosinophilia, and radiological findings [1]. In the 1970s, after the description of the IgE antibody isotype, serology came to occupy a central role in diagnosing ABPA. Rosenberg and Patterson proposed two groups of criteria to improve diagnostics. These criteria (seven primary, three secondary) have since been the most used in the diagnosis of ABPA [25].

| ABPA Criteria	
Rosenberg–Patterson (1977) [25]	Primary criteria 　1. Asthma 　2. Peripheral blood eosinophilia 　3. Immediate skin reactivity to *Aspergillus* antigen 　4. Precipitating antibodies to *Aspergillus* antigen 　5.5 5. Elevated serum IgE concentration 　6. History of pulmonary infiltrates (transient or fixed) 　7. Central bronchiectasis Secondary criteria •　*Aspergillus fumigatus* in sputum •　History of expectoration of brown plugs •　Late skin reactivity to *Aspergillus* antigen (Arthus reaction) ABPA "likely": primary criteria 1 to 6 are present. ABPA "certain": all primary criteria are present.
Modified ISHAM criteria (2013) [26]	Predisposing condition •　Asthma or cystic fibrosis Obrigatory criteria •　Total IgE level > 500 kIU/l •　Serum IgE against *Aspergillus fumigatus* > 0,35 kUA/l or positive skin test Other criteria •　Blood eosinophilia >500 cels/µL * •　Precipitins or increased IgG antibody to *Aspergillus* •　CT scan showing bronchiectasis •　Mucus impactation on CT scan Obrigatory criteria: both must be presented Other criteria: at least two must be presented, *without systemic corticosteroid
Modified ISHAM criteria (2021) [27]	Predisposing condition •　Asthma Obrigatory criteria •　Total IgE level > 500 kIU/l •　Serum IgE level against *Aspergillus fumigatus* > 0,35 kUA/l or positive skin test Other criteria •　Blood eosinophilia >500 cels/µL •　Precipitins or increased IgG antibody to *Aspergillus* > 27 mg$_A$/l •　CT scan showing bronchiectasis •　Mucus impactation on CT scan Obrigatory criteria: both must be present Other criteria: at least 2 must be present
Asano Criteria (2021) [28]	For Allergic Bronchopulmonary Mycosis 　1. Asthma 　2. Blood eosinophilia >500/µL 　3. Total IgE level > 417 kIU/l 　4. Positive immediate skin test or specific IgE >0,35 kUA/l for filamentous fungi 　5. Growth of filamentous fungi in culture of sputum or bronchial lavage fluid 　6. Presence of fungal hyphae in mucus plugs 　7. Central bronchiectasis on CT scan 　8. Presence of plugs on CT scan/bronchoscopy, or history of mucus plug expectoration 　9. High attenuation mucus on CT scan Diagnosis ABPM: At least six criteria must be present

Table 1.
Diagnostic criteria for ABPA.

However, these criteria lacked sensitivity and specificity, leading to underdiagnosis or misdiagnosis. In 2013, the ABPA Working Group of the International Society for Human and Animal Mycology (ABPA-ISHAM) proposed new diagnostic criteria to provide standardized guidelines for ABPA diagnosis [26]. New evidence then came to light about the "sensibility and specificity" of the ISHAM criteria. This evidence emerged through a study that used a latent class analysis to explore the performance of various existing and novel diagnostic criteria [27]. It has been demonstrated that IgE-specific tests are more responsive than skin tests to identify sensitization to *Aspergillus* and that the sensitivity and specificity of these criteria increased using a threshold for total IgE at 500 kIU/l [27]. In addition, a *cut-off* for specific IgG to *Aspergillus* was proposed. This evidence led the ISHAM to modify the diagnostic criteria. These modifications offered improved diagnostic performance and were published in 2021 [27]. The criteria proposed by ISHAM were validated but revealed that the sensitivity was poor for cases with non-*Aspergillus* Allergic Bronchopulmonary Mycosis (ABPM). Asano et al. proposed and validated new diagnostic criteria that showed improved sensitivity and specificity compared to Rosenberg-Paterson and ISHAM's previous criteria, even in atypical cases without asthma or non-*Aspergillus* ABPM (**Table 1**) [27].

The diagnostic of ABPA often follows an algorithm that integrates multiple pieces of clinical, immunological, and radiological information. The starting point is a clinical assessment, looking for key symptoms and risk factors, especially asthma or CF and then elevated specific IgE to *Af*. Total serum IgE levels are also evaluated, which typically exceed 500 IU/mL, while peripheral eosinophils >500 cels/μL and specific IgG-*Af* > 27 mg$_A$/l provide further evidence of a patient's immunological response to the fungus [27]. Chest high-resolution computed tomography (HRCT) is another essential component of the algorithm because it provides a classification of ABPA based on the features observed (**Figure 1**).

While recent updates to diagnostic criteria have led to some advances, ABPA remains a challenging condition to diagnose in clinical practice. It is important to note that the diagnostic algorithm may vary slightly based on specific guidelines and updates in diagnostic technology, for example, the determination of specific IgE levels indicative of ABPA is subject to debate. Patterson et al. in 1983 had already described that the levels of specific IgE and IgG for *Af* were twice as high in patients with ABPA as compared to patients with Af-sensitive asthma [29]. Employing a cutoff of 0.35 kUA/L for *Af*-IgE could potentially result in overdiagnosis of ABPA [30]. Furthermore, the cutoff to IgG-Af proposed in ISHMA criteria was determined in Asian population using the ImmunoCAP® method and is much lower than values reported by other European studies in ABPA patients [31].

Recently, the application of molecular allergology has been proposed. These tests evaluate IgE-directed against alergens components of *Af* (r*Asp*) to improve diagnosis taking into account that *Af*-specific IgE cannot distinguish sensitization from allergy to *Af* [32]. It is well established that specific proteins of *Af* could play a significant role in ABPA, and these can be detected through this approach. The presence of either r*Asp* f1 or r*Asp* f3 demonstrated high sensitivity and r*Asp* f4 or r*Asp* f6 showed high specificity in diagnosing ABPA in patients with asthma and CF [33]. Based on the proposal of a diagnostic algorithm that includes r*Asp* to improve the accuracy of diagnosis [32], the EAACI ABPA Task Force proposed changes to the algorithm and reinforced the need to adequate recommendations for countries with limited resources (**Figure 2**)[30].
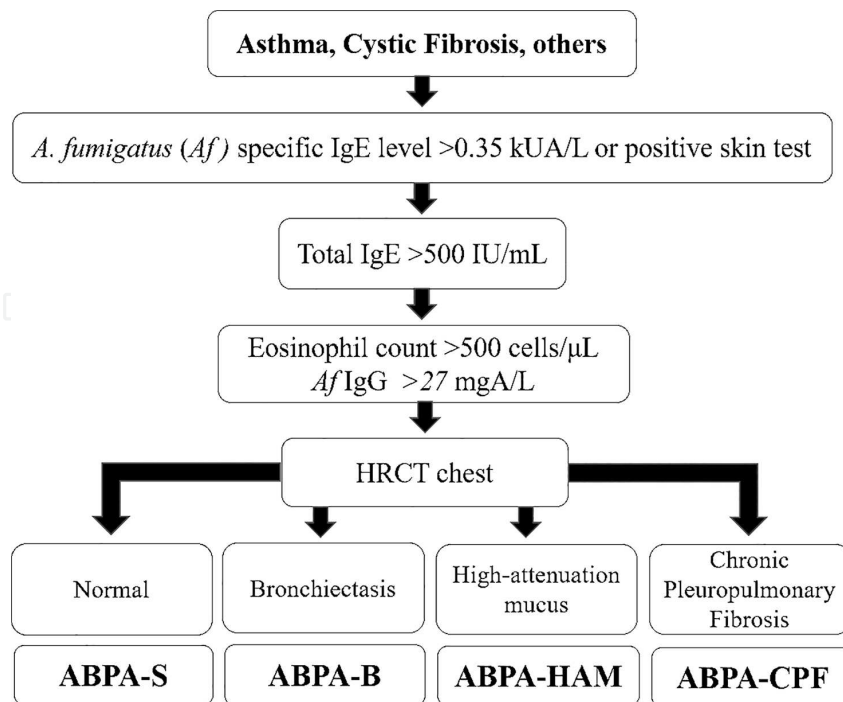
Figure 1.
Algorithm to diagnosis and radiographic classification of ABPA. Af: Aspergillus *fumigatus; HCTR: Highresolution computed tomography; ABPA-S: Serologic ABPA; ABPA-B: ABPA with bronchiectasis; ABPA-HAM: ABPA with high-attenuation mucus; ABPA-CPF: ABPA with chronic pleuropulmonary fibrosis.*
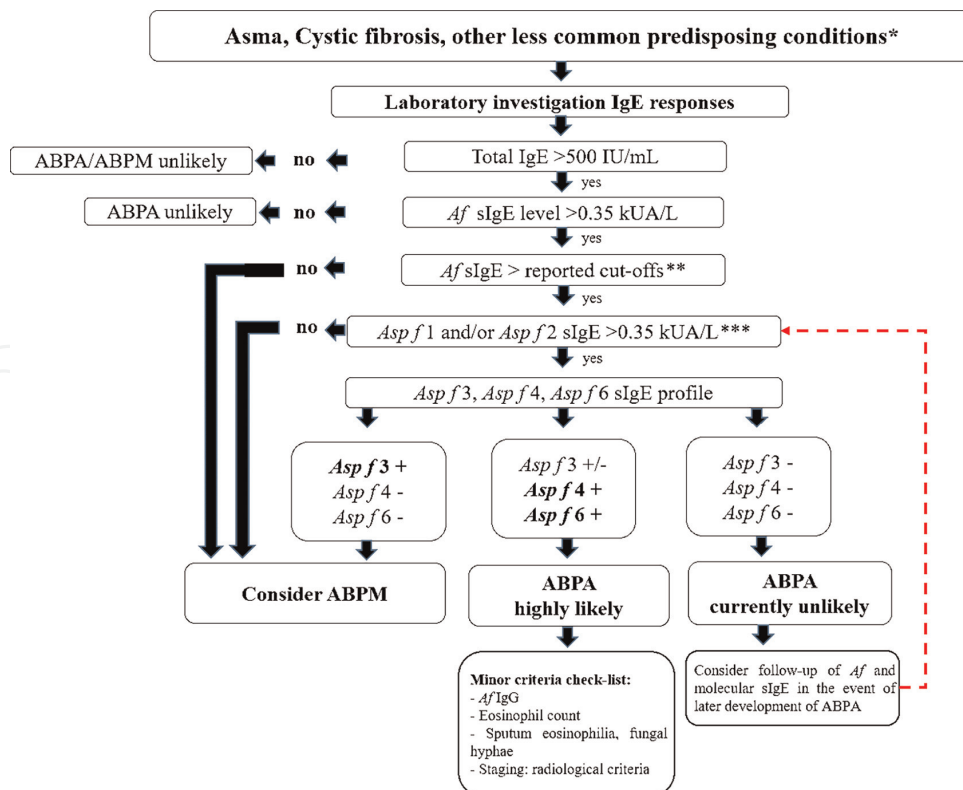
Figure 2.
Laboratorial investigation of recombinant Aspergillus *antigen-based algorithm for diagnosing ABPA. *chronic obstructive pulmonary disease, altered bronchopulmonary structure; **consider the establishment of locally validated cut-offs; ***consider the ratio of sIgE to molecular allergens vs. Af sIgE.*

Chest radiographic imaging plays a vital role in the diagnosis and management of ABPA and may exhibit features, ranging from normal to manifestations of pulmonary fibrosis (**Table 2**) [34]. This spectrum of presentations reflects the potential progression of the disease and the variability of the individual's response to *Aspergillus*. Several studies have investigated these radiographic features [34–36]. HRCT was demonstrated to be the gold standard for detecting bronchiectasis distribution and in identifying subtle radiographic changes, such as tree-in-bud opacities, which may indicate small airway involvement in ABPA [36, 37].

In the acute stage of ABPA, transient pulmonary infiltrates may be observed, typically manifesting as patchy opacities or consolidation [26, 34–36]. These infiltrates may resolve spontaneously or with treatment.

As ABPA progresses, more prominent, persistent changes can be detected in HRCT. These include central bronchiectasis, predominantly in the upper lobes [35]. High-attenuation mucus (HAM) within bronchi, often associated with bronchial dilations resembling a "finger-in-glove" sign, is another critical feature [26]. HAM is said to be present when the density of mucus is visibly greater than that of the paraspinal muscle, and that it may be related to the presence of calcium salts and metal ions (manganese or iron) [38] or desiccated mucus [39]. Chronic stage indicators also encompass bronchial wall thickening and parenchymal scarring, reflective of long-standing inflammation and damage [34–36]. Centrilobular nodules with a "tree-in-bud" pattern, indicative of small airway inflammation, often associated with chronic inflammation, are commonly identified in ABPA [37]. The end stage of the disease is fibrotic and can be identified by the presence of fibrosis and architectural distortion, predominantly involving upper lobes. Pulmonary fibrosis can manifest as traction bronchiectasis, honeycombing, and volume loss on HRCT [34, 37].

Chest radiography findings	
Transitory	• Peripheral infiltrate • Air-fluid levels • Consolidations • Toothpaste image • Train line image • Lobe or segmental collapse
Permanent	• Bronchiectasis • Parallel line image • Ring shadow • Pulmonary fibrosis
High-resolution chest tomography findings	
Bronchi	• Bronchiectasis • Mucus plug with high attenuation • Dilated bronchi • Occluded bronchi • Bronchial thickening
Parenchyma	• Cavitation • Bullous emphysema • Pleural involvement • Pneumothorax • Pleural fibrosis

Table 2.
Radiographics features described in ABPA.
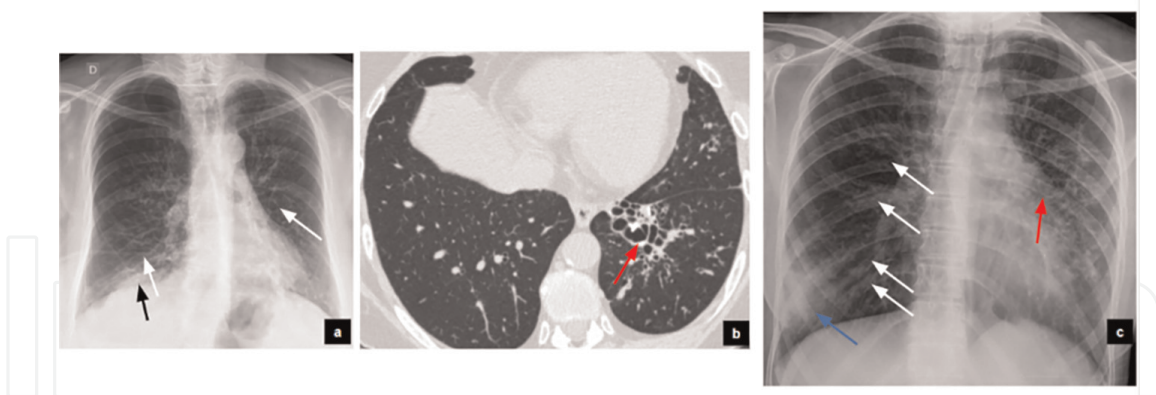
Figure 3.
(a) A 64-year-old female. Radiograph with consolidation in the right lower lobe (black arrow), in addition to some bilateral bronchiectasis with parietal thickening (white arrows). (b) Chest CT of the same patient demonstrates multiple central bronchiectasis in the left lower lobe with thickening and interspersed hyperdense content, a finding highly specific for ABPA (allergic bronchopulmonary aspergillosis). (c) a 16-year-old female. Radiograph shows consolidations in the peripheral region of the left lung (red arrow) and in the right lower lobe (blue arrow), in addition to bronchiectasis with thickened walls, the tram-track sign (white arrows).

The nuanced insights that HRCT offers into the extent and characteristics of ABPA make it a key tool in the image-based classification of this disease [26, 35].

Using HRCT, ABPA can be classified into four types or phenotypes. Patients showing no abnormalities on chest scan are classified as having serologic ABPA (ABPA-S) [26, 40]. In contrast, those with evidence of central bronchiectasis are labeled as having ABPA Central Bronchiectasis (ABPA-CB) [26, 40]. The presence of HAM leads to the categorization of the disease as ABPA-High Attenuation Mucus (ABPA-HAM) [36, 40]. Lastly, if at least two radiological features suggestive of fibrosis (fibrocavitary lesions, pulmonary fibrosis, and pleural thickening) are observed in the absence of mucoid impaction (or HAM), the disease is classified as ABPA-Chronic Pleuropulmonary Fibrosis (ABPA-CPF) (**Figures 1**, **3**, and **4**) [36, 40].

Timely recognition and appropriate monitoring of radiographic changes are essential for optimizing patient care and outcomes in ABPA.

6. Staging of ABPA

Staging of ABPA is an important aspect of its diagnosis, management, and understanding of the disease's progression. These stages were initially proposed by
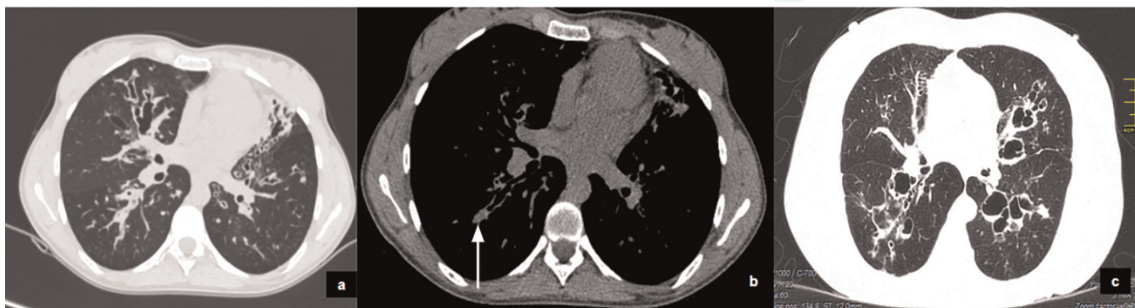
Figure 4.
CT imaging of patients diagnosed with ABPA: (a) multiple bilateral bronchiectasis with parietal thickening and mucoid impactation; (b) mucoid impactation in mediastinal window of the same patient (white arrow); (c) central bronchiectasis in a corticosteroid-dependent patient who has experienced multiple exacerbations.

Stage	Clinical, radiographic, and laboratorial features
0 - Asymptomatic	• No previous diagnosis of ABPA • Controlled asthma • Fulfilling the diagnostic criteria of ABPA
1 - Acute	• No previous diagnosis of ABPA • Uncontrolled asthma/symptoms consistent with ABPA • Satisfying the diagnostic criteria of ABPA
1a - With mucoid impaction	• Mucoid impaction observed on thoracic imaging
1b - Without mucoid impaction	• Absence of mucoid impaction on thoracic imaging
2 - Remission	• Clinical and/or radiological improvement and • Decline in serum total IgE by $\geq$25% of baseline at 8 weeks
3 - Exacerbation	• Clinical and/or radiological worsening and • Increase in serum total IgE by at least 50% from the new baseline established during response/remission
4 - Remission	• Sustained clinical and radiological improvement and • Serum total IgE levels persisting at or below baseline (or increase by <50%) for $\geq$6 months off treatment
5a - Treatment-dependent ABPA	• Two or more exacerbations within 6 months of stopping therapy OR • Clinical and/or radiological worsening, along with increase in serum total IgE levels, on tapering oral steroids/azoles
5b – Steroid dependent asthma	• Systemic corticosteroids required for control of asthma while the ABPA activity is controlled (as indicated by serum total IgE and thoracic imaging)
6 - Advanced ABPA	• Extensive bronchiectasis due to ABPA on chest imaging AND • Complications (cor pulmonale and/or chronic Type II respiratory failure

Adapted from Agarwal et al. [24]. Ref. [40].

Table 3.
Staging of ABPA.

Rosenberg et al. and have been widely used [25]. The staging has been revisited and revised by Agarwal et al., who proposed a more detailed, six-stage system, which also subdivides some stages based on radiological findings (**Table 3**) [26, 40].

7. Differential diagnosis

The differential diagnosis of ABPA includes several pulmonary disorders that share clinical and radiological features with ABPA, such as asthma with *Af* sensitization, idiopathic chronic eosinophilic pneumonia, tuberculosis, nontuberculous mycobacterial infections, eosinophilic granulomatosis with polyangiitis (GEPA) [4]. Distinguishing ABPA from these conditions requires a thorough clinical assessment, including the identification of predisposing factors, and appropriate tests to confirm or exclude these conditions.

8. Treatment

ABPA is recognized as a treatable trait in patients with bronchiectasis and the expected benefits of treatment are the prevention of lung damage, improved outcome

and quality of life [41]. To achieve these goals, the management of ABPA varies depending on the stage of the disease and involves a combination use of systemic corticosteroid, antifungal therapy, immunobiological agents, and airway clearance techniques tailored to individual patient needs (**Table 4**).

Drugs		Indication
Oral corticosteroids*	• Prednisolone (or equivalent), 0.5 mg/kg over a period of 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, then reduce 5 mg every 2 week. Total duration of 3–5 months OR • Prednisolone (or equivalent), 0.75 mg/kg/day for 6 weeks, then reduce 5 mg every 6 weeks. Total duration: 6–12 months	• Acute stage • Exacerbation stage
Intravenous corticosteroid	• Methylprednisolone, 15 mg/day (note exceeding 1 g) intravenous for 3 consecutive days	• To minimize the side effects of daily corticosteroid therapy • Refractory ABPA exacerbations
Antifungal	Oral antifungal therapy:† • Itraconazol 200 mg twice a day for 16 weeks OR • Voriconazole 200 mg twice a day, for at least 24 weeks Nebulized antifungal therapy: • Amphotericin B§	• Acute stage • Exacerbation stage
Immunobiological#	• Omalizumab 150 mg: approved for ages ≥6 years, SC injection. Dose and frequency depend on the patient's weight and the serum IgE level at the start of treatment. Highest permitted serum total IgE is 1500 IU/mL OR • Mepolizumab 40 mg or 100 mg: approved for ages ≥6 years. For children 6–11 years, 40 mg SC injection every 4 weeks. For ≥12 years, 100 mg SC injection every 4 weeks OR • Benralizumab 30 mg: approved for ages ≥12 years, SC injection every 4 weeks for three doses then every 8 weeks OR • Dupilumab 200 mg or 300 mg: approved for ages ≥6 years, SC injections every 2 weeks. For children 6–11 years, dose and frequency depend on weight. For ages ≥12 years 300 mg for asthma corticosteroid-dependent severe asthma or concomitant moderate/severe atopic dermatitis OR • Tezepelumab 210 mg: approved for ages ≥12 years, SC injection every 4 weeks	• Refractory ABPA • Uncontrolled asthma • Adverse effects or • Contraindications to corticosteroids and azoles

First-line treatment. For treating the first exacerbation, corticosteroids could be used alone and combined with azoles for subsequent exacerbation.
†*Itraconazol could be used alone in those with contraindications to corticosteroids. The associated use with prednisolone may reduce the chance of exacerbations.*
#*Randomized Clinical Trials evaluating immunobiologicals are necessary to clarify the role of these agents in treatment of ABPA.*
§*Nebulized amphotericin B may be considered when prolonged use of systemic corticosteroids and/or azoles are necessary.*

Table 4.
Drugs used in the management of ABPA.

8.1 Corticosteroids

Oral corticosteroids are the first-line treatment for ABPA [42]. However, the ideal dosage and duration of treatment remain undefined, and there are several treatment regimens, each featuring varying dosages and durations of use [40]. The most common regimen begins with a daily administration of 0.5 mg/kg of prednisolone over a period of 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, then taper by 5 mg every 2 weeks to complete a total steroid duration of 3–5 months [23].

Although disease remission can be achieved in most cases treated with medium- to high-dose systemic corticosteroids, relapse occurs in a substantial proportion of patients (13.5–45%) and can become corticosteroid-dependent [42, 43].

Intravenous pulse dose of corticosteroids can be used as a substitute for oral administration. Methylprednisolone, 15 mg/day (note exceeding 1 g), has been used in children to minimize the side effects of daily corticosteroid therapy [44] and in cases of refractory ABPA exacerbations [45].

8.2 Antifungal therapy

Antifungal agents decrease the fungal burden in the airways, antigenic stimulus, inflammatory response, and can contribute to reducing exposure to systemic corticosteroids. The use of azole agents alone or in combination with corticosteroid is an option in the treatment of ABPA [46]. Azoles, such as itraconazole, is generally prescribed at a dose of 200 mg twice daily for 16 weeks [40]. The combined use of itraconazole and prednisolone resulted in a greater reduction in the one-year exacerbation rate when compared to the use of these drugs individually [46].

However, drug interactions, hepatotoxicity, and variable bioavailability may limit the use [4]. Other azoles, such as voriconazole and posaconazole, have also been effective in treating ABPA, especially in cases of itraconazole intolerance or resistance [47].

The efficacy of nebulized amphotericin B in the management of ABPA exacerbations seems to be limited. However, they may be considered when other alternative options have been exhausted [24].

8.3 Immunobiological drugs

Posttreatment recurrences of ABPA are commonly seen, whether using oral corticosteroids, antifungal therapy or a combination of both, and prolonged treatment can result in adverse effects. Therefore, the necessity for new, safe, and effective treatment strategies is clear. Given the pathogenesis of ABPA, biologics designed to target type 2 inflammation, initially developed for severe asthma management, are expected to potentially serve as effective treatment alternatives for ABPA [48]. Although limited by the scarcity of randomized controlled trials, recent case reports and case series have demonstrated the benefits of target type 2 inflammation in the treatment of ABPA [48–51].

The anti-IgE monoclonal antibody, omalizumab, has shown potential in reducing corticosteroid use, improving lung function, and preventing relapses [50]. Omalizumabe is administered subcutaneously every 2–4 weeks, with the dosage determined based on the patient's weight and baseline serum total IgE levels [50]. However, the doses used might be suboptimal due to the high levels of IgE observed in ABPA.

The two groups of biologics target IL-5/eosinophil pathway: monoclonal antibodies that target IL-5, like mepolizumab and reslizumab, and those against the IL-5 receptor-alpha chain (IL-5Rα), such as benralizumab, have demonstrated efficacy in managing resistant eosinophilic pulmonary disorders, including ABPA. These anti-IL-5/IL-5Rα mAbs have been successful in reducing exacerbation frequency, dosage of oral corticosteroids, and enhancing pulmonary function in patients with asthma-complicated ABPA, even those unresponsive to omalizumab [48].

Dupilumab, anti-IL-4Rα monoclonal antibody, have been shown therapeutic effects on the symptoms and pulmonary function [49, 52]. Some patients with ABPA refractory to treatment with omalizumab or mepolizumab responded to dupilumab treatment [49, 53].

Tezepelumab a human IgG2 monoclonal antibody that binds specifically to thymic stromal lymphopoietin (TSLP) was demonstrated to improve the control of severe asthma by normalizing broad inflammatory pathways [54]. A recently published case report on a patient using mepolizumab, showed benefits in control of symptoms and reduction of the mucus plugs and pulmonary opacities [51].

Airway clearance techniques, such as chest physiotherapy and positive expiratory pressure devices, may be beneficial in patients with ABPA, particularly those with coexisting CF [4]. These techniques can help remove mucus plugs, improve lung function, and reduce the risk of recurrent infections.

The treatment of ABPA in CF is not very different from that of ABPA in asthma. As patients with CF often have coexisting malabsorption, treatment is more complex as oral medications, especially itraconazole capsules may be poorly absorbed [4].

8.4 Monitoring of treatment

The response to treatment should be monitored with clinical parameters, chest radiograph, and measurements of the serum total IgE concentration every 8 weeks. There should be a resolution of radiographic opacities and a 25% minimum reduction in serum total IgE levels and it is necessary to establish the "new" baseline level [4]. Clinical and/or radiological worsening along with 50% increase in IgE levels suggests an exacerbation [4].

9. Conclusion

ABPA is an immune-allergic disease of airways occurring in genetically predisposed patients as asthma and CF. The exact prevalence is not yet well known, and range is quite extensive as there is no single clinical, radiological, or serological parameter to make the diagnosis, leading to the use of various diagnostic criteria. Due to the absence of a consensus, ABPA may be easily underdiagnosed. Therapeutic management is based on few controlled studies conducted in asthma and extrapolated to ABPA. The first line of treatment of exacerbations remains on use of oral corticosteroids. Azole antifungal agents represent an alternative for the treatment of exacerbations and are preferential strategy for corticosteroids sparing. Asthma biologics may be a potential pharmacological management in the future. Therefore, more studies are needed regarding the diagnostic and therapeutic criteria for a better management of these patients.

Conflict of interest

The authors declare that they have no conflict of interest regarding this work.

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