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Review

Pulmonary aspergillosis in patients with asthma

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Abstract

Asthma is a complex respiratory condition characterized by airway inflammation and hyper-responsiveness, and poses a significant global health burden, affecting millions worldwide. Its origins lie in interactions between genetic, environmental, and host factors. While typically manageable, asthma can lead to severe exacerbations and complications if left untreated. The association between asthma and fungal infections, particularly with *Aspergillus* species, has garnered attention due to its impact on disease severity and management. We aim to provide a comprehensive overview of this association focusing on its various clinical presentations, risk factors, diagnostic approaches, and treatment strategies. Allergic bronchopulmonary aspergillosis (ABPA) emerges as a prevalent form of aspergillosis in asthmatic individuals, presenting challenges in both diagnosis and management. We discuss the evolving diagnostic criteria for ABPA, emphasizing the importance of clinical suspicion, radiological findings, serological tests, and pulmonary function tests. Moreover, we address the therapeutic interventions, review the roles of systemic glucocorticoids, antifungal agents, and emerging novel therapeutic agents. Early detection and intervention in fungal infections in asthma patients, particularly ABPA, are essential to mitigate exacerbations, improve symptom control, and prevent severe complications. This review underscores the necessity for heightened awareness and proactive management of fungal infections in the context of asthma, aiming to enhance patient care and quality of life.

Key words: asthma; fungal infections; *Aspergillus*; aspergillosis; allergic bronchopulmonary aspergillosis.

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Introduction

Asthma is a heterogeneous condition characterized by airway hyper-responsiveness and chronic airway inflammation. It is marked by reversible bronchoconstriction, which can become persistent if not properly treated. Common respiratory symptoms include wheezing, shortness of breath, and cough; which can vary in intensity and fluctuate over time. [1,2]. Symptoms are triggered by many different factors such as respiratory infections, exercise, allergens, pollutants, change in weather conditions, and comorbidities. It is a multifactorial disorder. Usually, symptoms may respond well to medication and sometimes remain absent for weeks or months; but in non-negligible number of cases the condition may be life-threatening, especially in low- and middle-income countries [1,3].

Asthma is a serious global health problem for all age groups, affecting 1% to 29% of the population in different countries [4]. Asthma affects approximately 300 million people globally, with over 27 million individuals affected in the United States alone. It is one of the leading chronic diseases among children [5,6]. Asthma is widely recognized as a condition that often starts in childhood, though it can develop at any age. Its etiology is linked to a combination of genetic factors, host factors, and environmental influences [6]. With this in mind, asthma should be considered in patients that have history of respiratory symptoms in childhood, allergic rhinitis or eczema, or a family history of asthma; and is present with aforementioned respiratory symptoms [7].

Our understanding of the precise pathophysiological mechanisms underlying the onset of asthma remains incomplete and largely unexplored in its entirety. Development of new diagnostic tools, better understanding of pathophysiological mechanisms, defining asthma phenotypes, and developing new management strategies remain a challenge. Asthma is now regarded as an umbrella term for conditions with similar clinical manifestations but distinct underlying pathophysiological mechanisms. It may not be a single disease, but rather a group of heterogeneous phenotypes with varying prognoses [7].

Severe asthma represents a small subgroup of patients with diagnosed asthma (up to 5% of all cases) [1,2]. The European Respiratory Society (ERS)/American Thoracic Society (ATS) defines severe asthma as "asthma which requires treatment with high dose of inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids), but remains "uncontrolled" despite this therapy" [1,8]. These patients experience persistent symptoms and frequent exacerbations that may result in hospitalizations. Poor lung function persists despite optimal standard therapy, significantly impacting their quality of life. Additional treatments, such as biologic therapy, should be considered for such patients [1]. It is important to distinguish between severe asthma and uncontrolled asthma. The most common problems that need to be addressed before making a diagnosis of severe asthma are incorrect inhaler technique, poor adherence, over-use of short-acting beta-agonists (SABA), comorbidities, persistent environmental exposures, and psychosocial factors [9]. Patients with severe asthma or frequent exacerbations are at a higher risk of developing fungal infections due to the frequent use of oral corticosteroids or high doses of inhaled corticosteroids.

Asthma and infection with *Aspergillus*

The human respiratory tract is exposed to many ubiquitous fungi or fungal enzymes daily. The fungi can colonize the respiratory tract directly, or indirectly through the cell wall; and cause problems by acting as aeroallergens or as a pathogen causing infection [10]. Severity of fungal infections ranges from asymptomatic mild infections to potentially life-threatening systemic infections. According to literature, more than 150 million people are affected by serious fungal diseases that can be fatal [11]. The main fungal pathogens responsible for the serious fungal diseases are *Aspergillus*, *Candida*, *Cryptococcus* species, *Pneumocystis jirovecii*, and *Histoplasma capsulatum* [11,12]. Early recognition and management of serious fungal infections, ensuring patient compliance with long-term treatment, avoiding drug-drug interactions, education, and treating comorbidities are paramount in ensuring better patient outcomes [13].

Aspergillus fumigatus accounts for 90% of human infections [14]. It is a trimorphic filamentous fungus with vegetative mycelium, multifactorial virulence (helpful for surviving in the host and evading the immune system), thermotolerance, resistance to azoles, and toxins and allergens [15,16]. Major clinical conditions associated with *Aspergillus* and asthma include allergic bronchopulmonary aspergillosis (ABPA), chronic pulmonary aspergillosis (CPA), allergic fungal rhinosinusitis (AFRS), and severe asthma with fungal sensitization (SAFS) [17]. Approximately 3 million people suffer from CPA. This progressive lung disease is associated with a poor prognosis and a high 5-year mortality rate [16,18].

ABPA is the most severe form of this fungal infection with prevalence among patients with asthma being 1 to 3.5%. A higher frequency of *Aspergillus* and fungal sensitization is associated with more severe asthma [19]. A recent meta-analysis revealed that 25% of asthmatic adults in tertiary care settings are sensitized to *A. fumigatus*. Among these sensitized individuals, approximately 37% are at risk of developing ABPA [20]. Notably, studies from India reported the highest prevalence of ABPA, highlighting potential regional variations in its occurrence.

Identifying *A. fumigatus* sensitization is a crucial step in diagnosing allergic fungal infections. While asymptomatic sensitized patients or those lacking the diagnostic criteria for allergic fungal infections may not require immediate treatment, careful evaluation is essential. This is because more than one-third of sensitized individuals face a significant risk of progressing to ABPA [20].

These findings underscore the importance of evaluating asthmatic patients for *A. fumigatus* sensitization. Ideally, all asthmatic patients should be assessed for ABPA, as the condition can manifest even in individuals with mild asthma. However, in resource-limited settings, prioritization is necessary. Focus should be on patients with severe asthma or those with poorly controlled symptoms, as they are at a higher risk and may benefit most from targeted evaluation and intervention.

Risk factors and pathogenesis

Environmental exposure is not the only risk factor for fungal infection. Socio-economic factors, geo-ecological characteristics, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) infection, chronic obstructive pulmonary disease (COPD), and asthma can also play an important role in the development of fungal infection [10]. Caution must be exercised with individuals who are immunocompromised due to hematological conditions; prolonged neutropenia; transplantation; long-term or high-dose corticosteroid therapy; or underlying lung conditions such as tuberculosis or nontuberculous mycobacterial infections (NTM), cystic fibrosis, or lung cancer. These underlying conditions can lead to

structural changes in the lungs, increasing susceptibility to fungal infections. [10,21]. Additionally, immunosuppressive treatments such as corticosteroids, commonly used in asthma management, can predispose patients to fungal infections or exacerbate their severity.

Genetics, microbiome, and environmental factors influence the development and severity of asthma [15]. The immune system is shaped during early childhood development and plays a crucial role in determining the endotype of allergic asthma [22,23]. High levels of indoor or outdoor fungal exposure can serve as a secondary trigger in individuals who are genetically predisposed to allergic asthma, potentially worsening existing asthma symptoms.

Immunocompetent individuals possess highly effective antifungal defense mechanisms, such as antimicrobial peptides, mucociliary clearance, and macrophage phagocytosis; which prevent fungi from causing infections [22,24]. Respiratory epithelial cells act as the primary blockade with the mucociliary escalator. Antimicrobial peptides may hinder fungal entry and prevent them from reaching the lung tissue. Numerous receptors on the surface of the respiratory epithelia recognize fungal antigens and trigger epithelial cells to release cytokines to activate innate leukocytes that counter fungi. Dendritic cells promote fungal-specific T cell response and when activated produce inflammatory cytokines which induce allergic inflammation and asthmatic responses [24,25]. *Aspergillus* conidia are small enough to penetrate the deep broncho-alveolar spaces in the lower airways. Fungal conidia can interact with the airway epithelial barrier, triggering inflammatory signals in response [22]. Both cellular and humoral immunity play an important role. Cellular immunity involves neutrophils, macrophages, and dendritic cells; and the humoral immune system involves the complement system, antimicrobial peptides, acute phase proteins, and circulating antibodies [26]. Recognition by the complement system and activation of the cascade seems to interfere with fungal dissemination [16,26]. This defense mechanism in patients with asthma and *Aspergillus* infection is usually based on TH2 cells and characterized by inflammatory cell (predominately eosinophil) recruitment, elevated serum IgE, inflammation, mucus hypersecretion, and airway remodeling [22]. Asthmatics with fungal infection have similar characteristics to those that are not sensitized to fungi except for longer duration of symptoms and higher levels of IgE in the serum [22].

A recent study found that isolation of *A. fumigatus* from sputum is associated with elevated airborne levels of the fungus in homes of patients with asthma. Fairs *et al*. suggested that the home environment should be considered as a potential source of *Aspergillus* exposure and may predispose people with asthma to airway colonization and subsequent infection with asthma exacerbation [27]. The mucus can become extremely thick and difficult to clear during asthma exacerbations, particularly in patients with bronchiectasis, providing an ideal environment for the colonization and proliferation of pathogens. Bronchiectasis is commonly seen as a comorbidity in asthma patients. Aspergilloma can develop in areas of lung damage associated with bronchiectasis, and fungal bronchitis may eventually lead to the formation of bronchiectasis [28]. Chang *et al*. found that systemic corticosteroids could increase the risk of aspergillosis among hospitalized coronavirus disease 2019 (COVID-19) patients. They suggested that physicians should be particularly cautious about the potential risks of development of aspergillosis [29].

Clinical presentation

Asthmatic patients with aspergillosis may exhibit a range of symptoms, none of which are specific to this condition. Additionally, an asymptomatic period could persist for several years. The characteristic symptoms of pulmonary aspergillosis however are low-grade chronic fever, cough and expectoration of brown mucus and plugs, wheezing, and chest pain [30]. These symptoms are also commonly observed in patients with tuberculosis or inflamed bronchiectasis, necessitating further diagnostic evaluation. Cough in these patients is often attributed to other causes, such as smoking, rather than infection. However, according to various studies, cough remains the most prevalent symptom, reported in 92–95% of cases [16,18]. Fever and hemoptysis are typically the second and third most common symptoms, respectively. The severity of hemoptysis can vary, ranging from mild to life-threatening [30]. Additionally, gradual weight loss over an extended period may manifest prominently in untreated cases. Wheezing commonly accompanies asthma exacerbations induced by infections like aspergillosis. Malaise, fatigue, night sweats, and chest pain may also be indicative of this fungal infection [16,30].

The challenging aspect of diagnosing *Aspergillus* infection is the persistence of concurrent lung diseases and comorbidities, thereby concealing and intertwining symptoms. Conditions such as emphysema, asthma, lung cancer, and prior cavitary tuberculosis can obscure the presentation of aspergillosis [31,32]. Consequently, clinicians must remain vigilant and consider *Aspergillus* infection among patients exhibiting

prolonged symptoms. Thus, there is a need for the development of new diagnostic methods, and improvement of existing diagnostic strategies, tailored to this patient population.

Diagnosis of aspergillosis

Individuals with asthma face an increased susceptibility to fungal infections, particularly aspergillosis. In contrast to other chronic lung conditions such as COPD, tuberculosis, and sarcoidosis; allergic forms of aspergillosis predominate in asthma patients, while invasive aspergillosis and chronic pulmonary aspergillosis occur less frequently.

Asthma is characterized by heightened airway responsiveness to various triggers, including environmental and infectious factors; and identifying these triggers is crucial for the treatment strategies. Given that *Aspergillus* and other fungi can exacerbate asthma symptoms and even pose life-threatening risks, prompt diagnosis and intervention are paramount for effective management.

The most common form of pulmonary aspergillosis in patients with asthma is ABPA, with estimated prevalence between 0.25% to 11% in all patients with asthma. However, the reported prevalence of ABPA in this population has varied widely and may be greater than 20% among those with poorly controlled asthma [33].

Although asthma is a cardinal feature of ABPA, its severity varies greatly. The majority of patients experience long-standing, and often difficult-to-control, asthma; while others may experience mild symptoms or even remain relatively asymptomatic.

ABPA is typically suspected based on clinical manifestations. Diagnosis is confirmed through radiological and serological examinations. Most patients exhibit clinical asthma, often presenting with intermittent wheezing, expectoration of sputum containing brown plugs, pleuritic chest pain, and fever.

There are several diagnostic criteria based on which we can establish a diagnosis of ABPA. Rosenberg *et al*. proposed the first diagnostic criteria for ABPA in 1977 [34]. The International Society for Human and Animal Mycology (ISHAM) also provided diagnostic criteria with a few updates [35,36]. Asano *et al*. provided new diagnostic criteria for ABPA in patients without cystic fibrosis in 2021, that showed improved sensitivity and specificity compared to the previous criteria, even in atypical cases without asthma or non-*Aspergillus* allergic bronchopulmonary mycosis (ABPM) [35]. These criteria are summarized in Table 1. Patients that meet 6 or more of these criteria are diagnosed with ABPA; those that meet 5 criteria are diagnosed with probable ABPA [35].

The ISHAM criteria for diagnosis of ABPA have been revised recently [36]. The essential components of the diagnostic criteria have been recognized, and three additional criteria, of which two must be present in order to establish the diagnosis, have been added. Predisposing conditions, including asthma, and other important considerations have also been identified [36]. The revised ISHAM criteria are summarized in Table 2.

Radiological examination

The chest radiographs may appear normal initially; however, during acute exacerbations, transient pulmonary infiltrates typically manifest in the upper lobe, and are centrally located. Mucoid impaction of airways may lead to transient opacifications, presenting as band-like opacities from the hilum with rounded distal margins, resembling a "gloved finger" appearance. Radiological signs such as the "ring sign" and "tram lines" indicate thickened and inflamed bronchi and may be observed in chest radiography. Progressively, central bronchiectasis and pulmonary fibrosis may develop. High-resolution computer tomography (HRCT) is valuable for defining bronchiectasis and demonstrating these changes more sensitively [37]. The finding of central bronchiectasis has been reported to have a sensitivity of 91.9% and a specificity of 80.9% [38].

High-attenuation mucus (HAM), characterized by mucus denser than paraspinal muscles on non-contrast thoracic computed tomography (CT), is a

Table 1. Clinical diagnostic criteria for allergic bronchopulmonary mycosis (ABPM) in patients without cystic fibrosis [34].

1.	Current or previous history of asthma or asthmatic symptoms.
2.	Peripheral blood eosinophilia (≥ 500 cells/mm^3).
3.	Elevated total serum IgE levels (≥ 417 IU/mL).
4.	Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi.*
5.	Presence of precipitins or specific IgG for filamentous fungi.*
6.	Filamentous fungal growth in sputum cultures or bronchial lavage fluid.*
7.	Presence of fungal hyphae in bronchial mucus plugs.
8.	Central bronchiectasis on computed tomography (CT).
9.	Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history.
10.	High attenuation mucus in the bronchi on CT.

Patients that meet 6 or more of these criteria are diagnosed with ABPM. * Filamentous fungi in criteria 4 to 6 should be identical.

Table 2. Revised International Society for Human and Animal Mycology (ISHAM) ABPA working group consensus criteria for diagnosing allergic bronchopulmonary aspergillosis (ABPA).

Predisposing conditions (asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis) or a compatible clinico-radiographical presentation.
Essential components
Aspergillus fumigatus-specific IgE ≥ 0.35 kUA·L^{-1}
Serum total IgE ≥ 500 IU·mL^{-1}
Other components (at least two)
Positive IgG against *A. fumigatus*
Blood eosinophil count ≥ 500 cells·μL^{-1}
Chest computed tomography consistent with ABPA (bronchiectasis, mucus plugging, high-attenuation mucus) or chest radiograph findings consistent with ABPA
Important considerations
Expectoration of mucus plugs, finger-in-glove, and fleeting opacities on chest radiograph
Positive type 1 skin test is acceptable when *Aspergillus*-IgE is unavailable.
Serum total IgE < 500 IU·mL−1 may be acceptable if all other criteria are fulfilled.
A. fumigatus-specific IgG can be detected using lateral flow assays or enzyme immunoassays. In the absence of population-specific cut-offs, manufacturer recommendations may be used.
High-attenuation mucus is pathognomonic of ABPA and confirms ABPA diagnosis, even if all other criteria are not fulfilled.
Elevated IgE against rAsp f1, f2, and f4 supports the diagnosis of ABPA and could be used as another component for diagnosing ABPA.

pathognomonic feature of ABPA [39]. It has a sensitivity of 35% and a specificity of 100% [40]. Moreover, HAM has been known to predict the immunological severity of ABPA most accurately [39]. In a study by Agarwal *et al*., the presence of HAM and central bronchiectasis were found to be predictors of ABPA recurrence [39].

Skin test

Immediate cutaneous sensitivity following a skin prick or intradermal injection of antigen signifies the presence of fungus-specific IgE. Although skin testing for *Aspergillus* is a major criterion, it lacks specificity for ABPA and can yield positive results in 1–2% of the general population, and 14–38% of individuals with asthma. [40,41]. Additionally, approximately 10% of ABPA patients may test negative for skin reactivity. The administration of systemic corticosteroids, commonly used in ABPA treatment, as well as treatment of poorly controlled asthma and severe asthma, can also lead to false-negative tests. Nevertheless, despite these limitations, skin testing could be regarded as the initial preferred diagnostic test for suspected ABPA, especially in resource-limited settings [36].

Total serum IgE, and IgG and IgE specific to A. fumigatus

Total serum IgE levels, as well as IgG and IgE specific to *A. fumigatus* are valuable tests for the diagnosis aspergillosis. When these values are normal, ABPA can be excluded. Positive results of the aforementioned skin tests should be confirmed by measuring total serum IgE, and IgE specific to *Aspergillus* [37].

Different thresholds for total IgE have been reported in the literature (e.g., 417 IU/mL, 500 IU/mL, 1000 IU/mL).[36] The latest revised ISHAM ABPA guidelines define a cut-off value of 500 IU/mL, instead of 1000 IU/mL, as it offers higher sensitivity (98% vs. 91%) [36]. Serum total IgE levels are also employed to distinguish between SAFS and ABPA. However, SAFS is defined as fungal sensitization in severe asthma, regardless of serum total IgE levels [42]. Increased levels of IgG and IgE specific to *A. fumigatus* are indicative in confirming or ruling out the diagnosis. This major criterion is observed in almost all individuals diagnosed with ABPA [43].

Although bronchoscopy is not essential for ABPA diagnosis; if performed, bronchoalveolar lavage (BAL) may exhibit elevated eosinophil levels and IgE concentration, with occasional detection of *Aspergillus* on fungal stain or culture [44].

Eosinophillia

Elevated serum eosinophil count is commonly encountered in ABPA, and is considered a minor criterion. However, eosinophilia is neither sensitive nor specific for diagnosing ABPA. The levels may significantly decrease in patients receiving steroids, which can lower clinical suspicion when used for other purposes. This reduction is often utilized to monitor response to therapy [42]. Additionally, eosinophilia can occur in various conditions, including several that lead to pulmonary infiltrates and respiratory symptoms, thereby complicating the diagnosis of ABPA.

Sputum cultures positive for Aspergillus

Aspergillus is ubiquitous and may be present in respiratory cultures in the absence of active disease. Conversely, cultures for *A. fumigatus* may be negative in patients with ABPA, especially those treated with

corticosteroids.

The effectiveness of traditional sputum fungal cultures varies between 10% to 27%. However, utilizing undiluted high-volume sputum (approximately 1 mL) for culture can enhance sensitivity up to 62% [43,45,46].

Pulmonary function tests

While pulmonary function tests may not be diagnostic of ABPA, they frequently demonstrate reversible obstructive lung disease, which may progress to irreversible stages later. Restrictive lung disease with reduced diffusion capacity might be evident during acute exacerbations or advanced stages. Monitoring disease progression over time can be facilitated by pulmonary function tests.

Treatment

The treatment plan for ABPA in patients with asthma encompass several objectives, including managing symptoms associated with asthma, preventing or addressing pulmonary exacerbations specific to ABPA, alleviating pulmonary inflammation, and mitigating the advancement towards severe fibrotic or cavitary lung diseases.

At present, systemic glucocorticoids stand as the foremost effective medications for ABPA [47]. However, the ideal dosing regimen for prednisolone remains uncertain due to a dearth of clinical trials [47]. Typically, the conventional treatment approach involves initiating prednisolone at a dose of 0.5 mg/kg per day for a fortnight, followed by 0.5 mg/kg every alternate day. Subsequently, the dosage is gradually reduced and ultimately halted within 3 months.

Adding oral itraconazole or voriconazole alongside steroids in individuals with recurrent or chronic ABPA could be beneficial and may potentially lead to a faster reduction in corticosteroid dosage [45]. Itraconazole and voriconazole work by reducing the fungal load, which helps control the antigenic stimulus, and thus decrease the inflammatory response [48,49].

Omalizumab, a humanized monoclonal antibody targeting IgE, has been proposed for the treatment of ABPA, particularly in patients with asthma [50]. A recently published meta-analysis that included 473 patients with treatment-refractory ABPA found that omalizumab significantly reduced the annualized exacerbation rate compared with pretreatment, as well as reduced oral corticosteroid (OCS) use and improved forced expiratory volume during the first second of forced breath (FEV1) and asthma control [51].

Treatment monitoring involves regular assessments of the clinical response to glucocorticoid therapy, with serum total IgE concentration measurements scheduled every 1–2 months. The desired outcomes include resolution of the radiographic opacities and a minimum 35% decrease in serum total IgE levels [52].

Future perspectives

Advancing personalized therapies in this setting requires a more profound understanding of host-fungal immune interactions and identifying biomarkers for early diagnosis and monitoring. Randomized trials in well-defined patient groups can establish personalized treatment strategies, including evaluating biologics as first-line options. Developing safer and more effective inhaled antifungals, and exploring innovative drug delivery systems, are key priorities. Environmental interventions like air filtration and mold control may also offer preventive benefits.

Conclusions

Pulmonary aspergillosis can have several forms, and in patients with asthma, the most common is ABPA. Clinicians should routinely assess patients with frequent asthma exacerbations, particularly those on long-term corticosteroid therapy, and poor symptom control for signs of ABPA. Proactive screening through radiological assessments, and skin and serology testing can help identify at-risk patients early, enabling timely intervention with corticosteroids, antifungals, or biologics. Clinicians can significantly improve the quality of life and clinical outcomes for these patients by integrating awareness of fungal infections into routine asthma management, and ultimately reduce the burden of this debilitating condition.

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Conflict of interests

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