Epidemiology of the relationship between allergic bronchopulmonary aspergillosis and asthma

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Purpose of review
Allergic bronchopulmonary aspergillosis (ABPA) can complicate the natural history of asthmatic patients, especially the more severe ones, worsening disease control and increasing the need for therapies, steroids in particular, and medical care. The aim of the present review is to summarize the latest epidemiological data related to the relationship between asthma and ABPA and to offer a summary of the most recent strategies that could potentially facilitate in the identification of ABPA in asthmatic patients.

Recent findings
In the last years, great efforts have been made by researchers worldwide to provide reliable epidemiological data on fungal sensitization and ABPA, especially in severe asthma patients both in adult and pediatric population. Data differ depending on the geographical area and population studied, but pooled data show a concerning 11% of severe asthma patients having ABPA and one out of four asthmatic patients being sensitized to fungi, *Aspergillus fumigatus* in particular.

Summary
Reliable epidemiological data and advances in the diagnostic procedures can facilitate the detection of ABPA among asthmatic patients, improving the management of a still under-recognized and challenging condition.

Keywords
allergic bronchopulmonary aspergillosis, asthma, epidemiology, molecular

INTRODUCTION

Bronchial asthma represents the most common noncommunicable airways diseases with an inflammatory background worldwide [1]. Allergic bronchopulmonary aspergillosis (ABPA) is a complex dis-immune pulmonary disorder caused by an impaired response to *Aspergillus fumigatus* airways exposure [2▪].

Allergic bronchopulmonary aspergillosis (ABPA) is traditionally included among asthma comorbidities, especially in the case of severe asthma phenotypes. In fact, in addition to cystic fibrosis, asthma represents the most relevant predisposing condition to ABPA, which substantially contributes to asthma burden [3].

Nevertheless, the prevalence of ABPA in asthma patients remains unclear. Many reasons may account for that, including the variable presence of *A. fumigatus* in different areas according to the specific environmental features, a challenging recognition due to asthma–ABPA overlapping clinical expression, and not uniform and universally recognized diagnostic criteria [4▪▪].

However, early recognition and appropriate treatment for ABPA can reduce its impact on asthma burden and prevent the progression of specific ABPA-related traits including bronchiectasis, bronchial remodeling and fibrosis. Robust epidemiological data could support physicians in identifying at risk patients in different environmental settings.

The present review aims to summarize the recent pathobiological and epidemiological data related to the relationship between ABPA and asthma, and to provide an overview of the newest

[a]Asthma Center and Allergy Unit, Center for Hyper-eosinophilic dysimmune conditions, Integrated University Hospital of Verona, [b]Department of Medicine, University of Verona, Verona, Italy, [c]University Hospital of Reims, Laboratory of Immunology and [d]INSERM UMR-S 1250 P3CELL, University of Reims, Reims, France

Correspondence to Marco Caminati, Asthma Center and Allergy Unit, Integrated University Hospital of Verona, Verona, piazzale A Scuro 37126 Verona, Italy. Tel: +39 3289582878;
e-mail: marco.caminati@univr.it

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KEY POINTS

- Allergic bronchopulmonary aspergillosis (ABPA) is an impaired immune response to Aspergillus airway colonization.
- ABPA can frequently complicate the clinical picture of asthma patients, especially the more severe ones.
- The new advances related to the epithelial barrier dysfunction concept supports under a pathobiological perspective the connection between the two conditions.
- Data report that 25% of severe asthmatic patients are sensitized to fungi and 10% have ABPA, with differences depending on the geographical area analyzed, but the diagnosis is still challenging and delayed.
- Advances in diagnostic tools, including molecular diagnosis and updates in diagnostic criteria are helping physicians worldwide in the recognition of ABPA.

strategies potentially facilitating the detection of ABPA in asthma patients.

ASTHMA AND ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS: COMORBIDITIES OR COEXISTING DISEASES?

ABPA is traditionally included among asthma comorbidities, especially in the case of severe asthma phenotype. Recent insights related to the pathobiology of both the conditions have provided a new perspective to look at the intimate connection between ABPA and asthma.

A. fumigatus is a widespread component of the environmental exposome, so that the exposure of bronchial system of any individuals to its spores represents a common situation [2▪]. Although healthy can effectively clear the environmental determinants, including *A. fumigatus* spores, from their lungs without any complication, atopic and asthmatic are characterized by specific airway susceptibility leading to an impaired immune response against exposome components, whether truly dangerous or not for human health [2▪]. The mechanisms underlying such impaired response are complex and not yet fully understood. Of note, the lack or the loss of bronchial epithelium integrity, both in terms of anatomical structures and immunological functions, has been identified by an increasing amount of evidence as a key determinant of that kind of susceptibility [5]. Similarly, the central role of epithelial bronchial barrier has been recently demonstrated in asthma pathobiology across different asthma phenotypes and severity grades [6].

Genetic polymorphisms in proteins related to barrier homeostasis, such as surfactant protein A2, CFTR, or mannose-binding lectin, have been found in ABPA patients [7]. That genetic background might contribute to generate a physical and functional predisposing condition to aberrant immune responses to fungi. Furthermore, it has been described that *A. fumigatus* can directly damage bronchial epithelial cells with its proteases, and/or interact with surface pathogen recognition receptors. In both cases, epithelial cytokines release, including TSLP, IL-25, IL-33, and ILC2 stimulation mediates a type 2 immune response in concert with DC-mediated Th2 lymphocyte activation [8]. Within the type 2 cascade, the plasma cell recruitment leads to a disproportionate production of total and specific IgE, as well as of IgG antibodies, driving a type I and a type III/IV hypersensitivity reaction, respectively. In addition, exaggerated eosinophils recruitment occurs, sustaining and amplifying the underlying type 2 inflammation [9] (Fig. 1).

In bronchial asthma, severe asthma particularly, various environmental factors, including allergens, pathogens, pollutants, smoke, are able to exert and amplify a direct epithelial damage and to mediate an epithelial-driven immune cascade by interacting with the innate immunity receptors on the airways surface [10]. Both the mechanisms can trigger different immune responses across the wide spectrum of known asthma inflammation drivers, including: ILC2 and Th2 lymphocytes, activating a eosinophilic/allergic response; ILC1 and IFNγ–TNFα-mediated cascade; ILC3 and IL-17–IL-22 pattern [5]. When ABPA coexists, asthma pathobiology is predominantly characterized by type 2 cytokine production and allergic/eosinophilic inflammation [11].

When comparing severe asthma and ABPA, some differences in terms of underlying immunological background, including the IgG-driven type III/IV hypersensitivity, and of clinical features, including recurrent radiological opacities, which are not typically part of asthma pathobiology and clinical profile, respectively, can be identified. However, ABPA has been defined as a specific severe asthma endotype [12], encompassing various sub-endotypes where a prevalent allergic, eosinophilic, or fungal immune response dominates the clinical picture [11] (Fig. 1). It is not so surprising in the light of the central role the epithelial barrier dysfunction exerts as a shared pathobiological primum moves in both asthma and ABPA. It accounts for the immunological and clinical similarities characterizing the

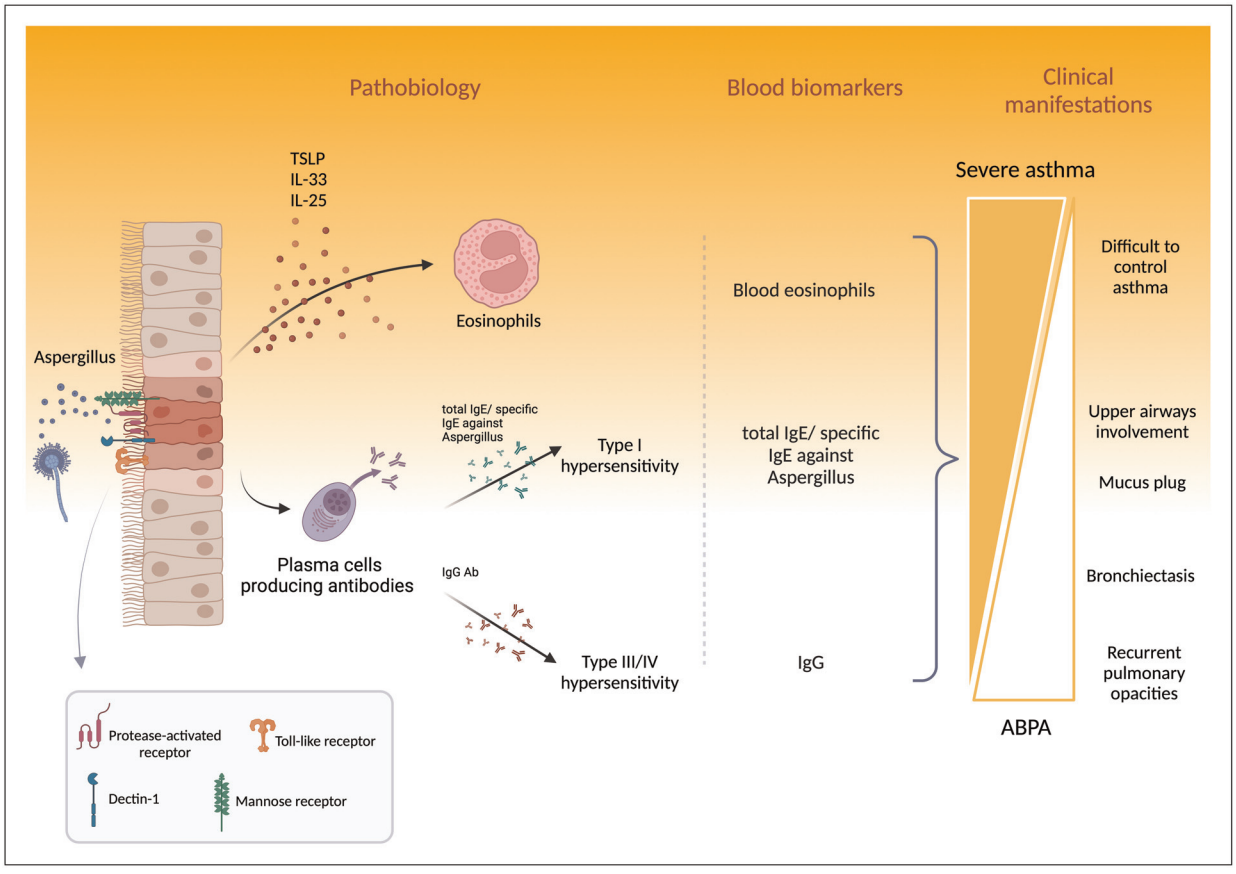

FIGURE 1. Overview of severe asthma– allergic bronchopulmonary aspergillosis spectrum in terms of pathobiology, biomarkers and clinical expression.

patients suffering from such conditions, making sometimes challenging the identification of ABPA in severe asthma patients.

EPIDEMIOLOGICAL OVERVIEW OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS AND ASTHMA: STATE OF THE ART

The prevalence of *A. fumigatus* sensitization in asthmatic patients and of ABPA among those *A. fumigatus*-sensitized asthmatic patients was recently re-evaluated. Worldwide, the pooled prevalence of *A. fumigatus* sensitization in patients with severe asthma was found at 25%, [4▪▪]. Population-based *A. fumigatus* sensitization figures for overall asthmatic patients have not yet been determined for most countries; however, available studies from the United States, Finland and India show variability between 5 and 17% [13]. The pooled prevalence of ABPA was 11.3% among severe asthmatic patients, but a deeply concerning figure of 37% of ABPA prevalence among *A. fumigatus*-sensitized asthmatic patients was also reported [4▪▪].

Recent data show variable prevalence of ABPA in asthmatic patients depending on geographical area with studies from Australia, UK, India, Italy, and Africa displaying results between 3.2 and 24.3% [14–16] (Table 1). Various factors contribute to *A. fumigatus* sensitization and the prevalence of allergic bronchopulmonary aspergillosis (ABPA) in asthma patients. Environmental conditions play a significant role in the fungi lifecycle, and *A. fumigatus* thrives in hot-moist climates. This partly explains the higher prevalence of ABPA in asthma patients in some countries including India when compared with the rest of the world (16.8 vs. 7.9%) [17]. However, host susceptibility is crucial, as not all asthma patients exposed to similar conditions develop ABPA. In India, a higher prevalence of ABPA is noted in rural areas, whereas in the United Kingdom, asthma patients living in urban areas face a higher risk of developing the disease [17,18]. Of note, there is variability depending on the population analyzed: in India, for example, the investigation at referral centers reported higher prevalence of ABPA in asthmatic patients than studies based on community patients (16.8 vs. 5.7%, respectively) [18].

Table 1. Recent data on allergic bronchopulmonary aspergillosis and fungal sensitization prevalence in asthmatic patients in different geographical areas

Country	Worldwide [21▪▪]	Worldwide [4▪▪]	UK/USA [4▪▪]	India [18]	India [17]	Worldwide excluding India, UK and USA [4▪▪]	Italy [14]	UK [15]	Australia [16]	Africa [20]
Year	2023	2023	2023	2023	2023	2023	2021	2021	2020	2019
Population analyzed	Asthmatic patients, children	Asthmatic patients, adults	Asthmatic patients, adults	Asthmatic patients, community	Asthmatic patients, tertiary care	Asthmatic patients, adults	Asthmatic patients, adults	Asthmatic patients, adults	Asthmatic patients, adults	Asthmatic patients
ABPA prevalence (%)	9.9	11.3	12.6	5.7	16.8	5.8	24	6.8	5	1.6–21.2
Fungal sensitization prevalence (%)	16.1	25.1	–	16.4	–	–	40	23.9	30	23

ABP, allergic bronchopulmonary aspergillosis.

ABPA is generally considered an adulthood disease, particularly when excluding cystic-fibrosis-related cases. Regional differences emerge globally, with Japanese and European ABPA patients typically being older than their Indian and Chinese counterparts (51–72 and 60 ± 11 vs. 35 ± 13 and 42 ± 18, respectively) [17]. Interestingly, older ABPA patients in India appear to have a less severe phenotype, exhibiting lower bronchiectasis and a minor tendency toward ABPA exacerbations [19]. Evaluating fungal asthma epidemiology, in Africa, it has been shown a pooled fungal sensitization of 23%, with ABPA prevalence estimated at 1.6–21.2%, which is consistent with observations in other countries [20].

The burden of ABPA in children should not be overlooked, as recent meta-analysis data indicate a high prevalence, especially in India, of *A. fumigatus* sensitization and ABPA in asthmatic patients under 18 years of age (16 and 10%, respectively) and of ABPA among *A. fumigatus*-sensitized individuals (21%) [21▪▪]. Regarding sex prevalence, both male and female individuals appear to be equally affected, with a slight female predisposition noted in specific geographical areas [22].

These findings highlight the need for systematic screening of asthmatic patients for *A. fumigatus* sensitization, aiming at early diagnosis, prior to irreversible lung damage and loss of function [13].

POTENTIAL LIMITATIONS TO ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS EPIDEMIOLOGICAL ESTIMATION

Challenges in allergic bronchopulmonary aspergillosis diagnosis

The diagnosis of ABPA is a challenging one, both at the initial stage and during relapses, because of variable clinical, immunological and radiological presentations, multiple diagnostic criteria, and variable access to state-of-the art methods for diagnosis and treatment. Despite these drawbacks, practitioners from all involved specialties need to focus on the identification of ABPA at its early stages, that is, when the mere *A. fumigatus* sensitization or fungal allergy starts crossing the line towards the severe disease stage represented by ABPA [13,23].

Difficult recognition of allergic bronchopulmonary aspergillosis in severe asthma patients

Several factors may contribute to make the recognition of ABPA in patients with severe asthma challenging. Firstly, both conditions express a similar clinical profile commonly characterizing severe

forms of eosinophilic asthma so that ABPA might not be suspected. In terms of symptoms, dyspnea, wheezing, mucus production, and coughing may be referred to both ABPA and severe eosinophilic/allergic asthma, as well as a compromised lung function. Additionally, both conditions show a positive response to corticosteroid therapy, making it difficult for clinicians to consistently rely on symptoms or functional assessment alone to suspect ABPA. Even when ABPA is hypothesized, a superficial diagnostic evaluation, such as initially employing skin testing, can lead to misdiagnosing the condition [13]. In fact, even in the absence of positive skin prick for aspergillus, ABPA cannot be excluded; on the opposite, the detection of positive skin prick test for aspergillus is not enough to confirm the diagnosis.

Furthermore, the boundaries between asthma with fungal sensitization, serologic ABPA, and overt ABPA might not be clearly defined, especially when different threshold values are proposed based on ethnicity or geographic location [17]. Asthma and ABPA also share common biomarkers, including increased blood eosinophils, total IgE, and exhaled nitric oxide (FeNO), reflecting the similar immunological background described above. However, appropriate cutoffs and combinations of biomarkers may be helpful in distinguishing between asthma and ABPA. Despite these potential challenges, multiple sets of criteria have been proposed over the years to aid the diagnostic process.

On a practical ground, every patient suffering from allergic/eosinophilic asthma should be considered at risk of developing ABPA. It means that the diagnostic work up of type 2 asthma should always consider ABPA diagnostic criteria, even more, but not limited to that case, in the presence of bronchiectasis, mucus plugs, recurrent pulmonary opacities (Fig. 1). Also, ABPA might act as a determinant contributing to a more difficult-to-control disease in asthma patients, as well as a trigger of the loss of asthma control over time; in those situations, ABPA diagnosis should always be explored.

OVERCOMING THE ISSUE: NEW TOOLS FOR ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS EARLY RECOGNITION

Early recognition of ABPA is not only facilitated by new diagnostic tools but also by clinical re-evaluation of conventional ones, and combination of both approaches. The ABPA Task Force of the European Academy of Allergy and Clinical Immunology (EAACI) has published a diagnostic algorithm for ABPA, based on clinical, imaging, and laboratory data, including assessment of available *A. fumigatus* molecular allergens in a two-step process: confirmation of genuine *A. fumigatus* sensitization using the marker allergens Asp f 1 and Asp f 2, followed by evaluation of the risk of ABPA using the disease-associated allergens Asp f 3, Asp f 4 and Asp f 6 [24▪▪]. Pushing forward the use of *A. fumigatus* molecular allergens, cutting-edge methodology was reported as a proof of concept, with Asp f 4 in basophil activation tests showing promising diagnostic value for ABPA [25].

Reevaluation of *A. fumigatus*-specific IgG versus IgE screening was reported in a systematic review and meta-analysis that confirmed better diagnostic specificity of *A. fumigatus*-specific IgE (89 versus 73%, $P < 0.001$) [26]. Interestingly, this study also demonstrated better diagnostic sensitivity with *A. fumigatus*-specific IgG (93 versus 83%, $P < 0.001$). These findings are in keeping with the natural history of isotype switch from IgG to IgE and with translational studies showing elevated allergen-specific IgG responses in allergic patients prior to the development of allergen-specific IgE responses [27]. Progress in the available tools for in-vitro *A. fumigatus* IgE and IgG assessment, including point-of care devices that can be employed by clinicians, is also reported, and is expected to contribute to early identification of ABPA patients [28–31].

Although the pathophysiological relationship between *A. fumigatus* colonization and sensitization remains unclear, a convincing study showed the diagnostic value of fungal hyphae visualized in sputum for ABPA identification [32▪]. This method may, however, not be widely applicable, as it requires specialized laboratory technicians and methods for microscopic examination of sputum samples.

The role of clinician's experience in identifying early-stage ABPA was highlighted in a prospective study conducted in an Indian tertiary care, showcasing mild versus moderate or severe ABPA presentations [33]. Laboratory criteria, including *A. fumigatus*-specific IgE, total IgE, circulating eosinophil numbers, should be considered as a marker for potential ABPA even in the absence of radiological findings in order to avoid missing the diagnosis. ABPA as a function of the patient's age was reported to be milder in terms of both clinical and laboratory findings, drawing the clinicians' attention to the possible mis-diagnosis and under-diagnosis of ABPA in patients older than 60 years [19].

The diagnosis of ABPA is based on the analysis of multiple variables, with no 100% specific biomarker identified so far. Combined scores have been proposed since the description of the disease, and the recent development of mathematical models based on machine learning, artificial intelligence and other computer-assisted diagnostic aids are

expected to contribute to early diagnosis of ABPA. As a proof of concept, clinical and radiological features of ABPA were used for building a model, which showed promising results for ABPA diagnosis [34].

PRACTICAL RELEVANCE OF ACCURATE EPIDEMIOLOGICAL DATA

When occurring in severe asthma patients, ABPA substantially contributes to more difficult to control disease, leading to an increasing need for pharmacological therapy including higher doses or inhaled steroids, oral steroids and/or antifungal treatments, which exposes the patient to a relevant risk of drug-related comorbidities [35]. In one word, ABPA heavily impacts on the overall asthma burden.

In addition, specific ABPA-related traits, including bronchiectasis, bronchial remodeling, fibrosis, may rapidly occur or irreversibly evolve in the case a proper treatment is delayed because of ABPA misrecognition [15].

Nowadays, physicians have the chance to prevent or effectively manage that scenario, thanks to new targeted treatments, which provides an innovative option addressing some pathobiological drivers of ABPA, including eosinophils and total IgE [36]. Although developed for severe asthma, an increasing amount of evidence supports the use of monoclonal antibodies targeting IgE (omalizumab) or IL-5 cascade (mepolizumab and benralizumab) in ABPA as steroid-sparing agents able to minimize ABPA impact on severe asthma and its own progression [37].

Under that perspective, early recognition of ABPA in severe asthma patients becomes even more mandatory.

Robust epidemiological data may provide information about the *weight* of ABPA or the profile of ABPA patients in a specific population. In the light of ABPA clinical spectrum, very similar to severe eosinophilic asthma, and the complex diagnostic confirmation, as reviewed above, epidemiological evidence might help clinicians in developing an appropriate awareness as well as in identifying at-risk patients according to the peculiarities of each environmental setting, in order to provide them the best standard of care for their condition at its very initial stages.

CONCLUSION

The recent insights on pathobiological mechanisms underlying asthma and ABPA have provided a new way to look at their intimate connection. Under that perspective, every clinician taking care of asthma patients, especially the most severe ones, should be aware of asthma–ABPA interactions, which may hamper the achievement of asthma control or reciprocally amplify the burden of both the conditions. That awareness, and, on a clinical ground, tailoring the diagnostic work-up accordingly, is even more relevant in the personalized era we are living, when more chances are provided to clinicians to interfere with the disease trajectory in affected patients.

In order to overcome the challenging diagnosis of ABPA in asthma patients, new diagnostic tools and updated diagnostic criteria are nowadays available, as described above. However, a further substantial help is provided by epidemiological data, supporting the clinician in the early identification of ABPA. Under that perspective, more robust epidemiological evidence is needed and should be prioritized as part of the precision medicine approach.

The recent advances in basic knowledge, the updated diagnostic tools and criteria, and the further chances provided by the targeted treatment options, as well as the existing and hopefully increasing epidemiological information suggest to look at ABPA as a fully treatable trait in severe asthma patients, a perspective stimulating to provide them the best standard of care for that condition at its very initial stages.

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