Allergology International 72 (2023) 507–520

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited Review Article

Relationship between Aspergillus and asthma

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ARTICLE INFO

Article history:
Received 28 July 2023
Available online 24 August 2023

Keywords:
ABPA
Allergic bronchopulmonary mycosis
Bronchiectasis
Cystic fibrosis
Fungal asthma

ABSTRACT

Fungal sensitization is highly prevalent in severe asthma. The relationship between fungus and asthma, especially *Aspergillus fumigatus*, has been the subject of extensive research. The ubiquitous presence of *A. fumigatus*, its thermotolerant nature, the respirable size of its conidia, and its ability to produce potent allergens are pivotal in worsening asthma control. Due to the diverse clinical manifestations of fungal asthma and the lack of specific biomarkers, its diagnosis remains intricate. Diagnosing fungal asthma requires carefully assessing the patient's clinical history, immunological tests, and imaging. Depending on the severity, patients with fungal asthma require personalized treatment plans, including inhaled corticosteroids and bronchodilators, and antifungal therapy. This review provides a comprehensive overview of the association between *Aspergillus* and asthma by reviewing the relevant literature and highlighting key findings. We discuss the diagnosis of various entities included in fungal asthma. We also debate whether newer definitions, including allergic fungal airway disease, offer any additional advantages over the existing ones. Finally, we provide the current treatment options for the individual entities, including *A. fumigatus-associated asthma*, severe asthma with fungal sensitization, and allergic bronchopulmonary mycoses.

Introduction

Asthma is a chronic inflammatory disorder characterized by variable airflow limitation manifesting clinically with intermittent cough, wheezing, and chest tightness. Airway hyperresponsiveness to diverse triggers (environmental, infectious, and others) is a hallmark of asthma. Atopy, a genetic predisposition to mount an abnormal immunoglobulin E (IgE) response to various antigens or allergens, is a significant risk factor for asthma. Nearly 56% of asthma cases were attributable to atopy in the National Health and Nutrition Examination Survey from the United States.[1] Several triggers can worsen asthma control, including house dust mites, molds, pollens, animal dander, and cockroaches. Of these, molds or fungi assume importance since they are associated with life-threatening asthma exacerbations and are amenable to pharmacological treatment in severe cases.[2,3]

Fungi form a large group of eukaryotic organisms with a characteristic chitin cell wall.[4,5] Of the vast and diverse fungi (>1 million species), only a few are pathogenic or allergenic to humans. The association between asthma and mold exposure has been known for nearly a century.[6,7] More recently, mouse models using inhaled fungal allergens have improved our understanding of fungal asthma.[8–10] However, the precise mechanisms and the extent to which molds contribute to asthma remain elusive. The difficulty is partly due to the lack of specific diagnostics, symptom variability, and spore burden over time. Interestingly, the presence of fungi in the airway may not correspond to allergic sensitization or asthma severity.[11,12] Further, cross-sensitization to different antigens and co-sensitization to several allergens poses challenges in interpreting commonly available tests for fungal allergy.[13–15] Moreover, fungal asthma may range from mild or asymptomatic to severe, with extensive lung damage characterized by bronchiectasis. While some severe phenotypes like allergic bronchopulmonary mycosis have been well characterized,[16] there is considerable ambiguity and non-uniformity in describing the less severe ones.[17]

The clinically important fungi associated with asthma include *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, and *Penicillium* spp, the latter two being thermotolerant (capable of growing in the environment and at body temperature).[18] Of these, the most important fungus is *A. fumigatus*, the most common agent causing allergic bronchopulmonary mycosis. This review discusses the current knowledge on pathogenesis, the various terminologies used, diagnosis, and management of fungal asthma, specifically regarding *A. fumigatus*.

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Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2023.08.004

Nomenclature of fungal allergy syndromes

Fungal sensitization

Fungal sensitization is defined as increased IgE or skin test positivity against a fungus without organ dysfunction or damage.[19]

Fungal allergy

Fungal allergy is sensitization with clinical or laboratory evidence of organ dysfunction or damage.[19]

A.fumigatus-associated asthma (AFAA)

AFAA is an allergic sensitization to *A. fumigatus* in patients with mild-to-moderate asthma and near normal lung function.[20]

Allergic bronchopulmonary aspergillosis (ABPA) and allergic bronchopulmonary mycosis (ABPM)

Allergic bronchopulmonary mycoses are complex pulmonary disorders caused by severe allergies to fungi characterized by difficult-to-treat asthma and bronchiectasis.[15] Traditionally, allergic bronchopulmonary mycoses caused by *A. fumigatus* is labeled as ABPA, while ABPM is an ABPA-like syndrome caused by fungi other than *A. fumigatus*. The incidence of ABPM is far less common than ABPA.[21]

Currently, ABPA is diagnosed on a combination of clinical, radiological, and immunological findings (Table 1).[22–25] Patients of ABPA who otherwise meet all the criteria but without bronchiectasis are defined as serologic ABPA (ABPA-S),[26] while ABPA patients with bronchiectasis are classified as ABPA-B.[27]

Severe asthma with fungal sensitization (SAFS)

SAFS is a broad term for severe asthma associated with fungal sensitization.[2,7] The disorder is diagnosed in patients not meeting the criteria for ABPA or ABPM but have severe asthma and raised fungus-specific IgE.[28] While a serum total IgE <1000 IU/ml has been suggested to differentiate SAFS from ABPA-S, there is no clear evidence for this definition. Many clinicians tend to merge SAFS and ABPA-S (ASAFS) as the treatment of these entities is similar.[29] We define SAFS as fungal sensitization in a patient with severe asthma, irrespective of the serum total IgE.

Allergic fungal lung disease (AFLD)

AFLD is a broad term encompassing all allergic lung diseases caused by fungi, including airway (allergic aspergillosis and others) and parenchymal (hypersensitivity pneumonitis) disorders.

Allergic fungal airway disease (AFAD)

AFAD is an expression for allergic airway diseases caused or exacerbated by fungi.[17] Thus, AFAD includes fungal asthma, fungal bronchitis, AFAA, SAFS, ABPA, and ABPM. In addition, AFAD will also have fungal allergies complicating chronic obstructive pulmonary disease and other causes of bronchiectasis.

Fungal asthma

Fungal asthma includes all allergic fungal syndromes complicating asthma ranging from AFAA, SAFS, ABPA-S, and ABPA-B (Fig. 1).

Table 1
Various criteria used for diagnosing ABPA.

Rosenberg–Patterson Criteria (1977)[22]	ISHAM ABPA working group criteria (2013)[23]	Modified ISHAM ABPA working group criteria (2021)[24]	Asano *et al.* criteria (2021)[25]
Major: 1. Asthma. 2. Peripheral blood eosinophilia. 3. Immediate skin reactivity to *Aspergillus* antigen. 4. Precipitating antibodies against *Aspergillus* antigens. 5. Elevated serum immunoglobulin E. 6. History of pulmonary infiltrates (transient or fixed). 7. Central bronchiectasis. Minor: 1. *Aspergillus fumigatus* in sputum (repeated culture or microscopy). 2. History of expectorating brown plugs. 3. Late skin reactivity to *Aspergillus* antigen.	Predisposing conditions: 1. Asthma or CF. Obligatory: 1. Positive type 1 Aspergillus skin test or elevated IgE against *A. fumigatus.* 2. Total IgE >1000 IU/mL (If all other criteria are satisfied, a total IgE <1000 IU/mL is acceptable). And ≥2 of the following: 1. Precipitating antibodies or IgG against *A.fumigatus.* 2. Radiographic opacities consistent with ABPA. 3. Peripheral blood eosinophilia >500 cells/μL in treatment-naïve patients (maybe historical).	Presence of all the following: 1. Asthma. 2. *A.fumigatus*-specific IgE >0.35 kUA/L. 3. Serum total IgE >500 IU/mL. And at least 2 of the following: 1. *A.fumigatus* specific IgG >27 mgA/L.[†] 2. Bronchiectasis on CT chest. 3. Peripheral blood eosinophilia >500 cells/μL.	1. Current or previous history of asthma. 2. Peripheral blood eosinophilia (≥500 cells/μL). 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 CT. 9. Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history. 10. High attenuation mucus on CT chest. Definite ABPA/ABPM: presence of ≥6 features Probable ABPA: patients fulfilling 5 of the 10 components

[†] Cut-offs vary with ethnicity.

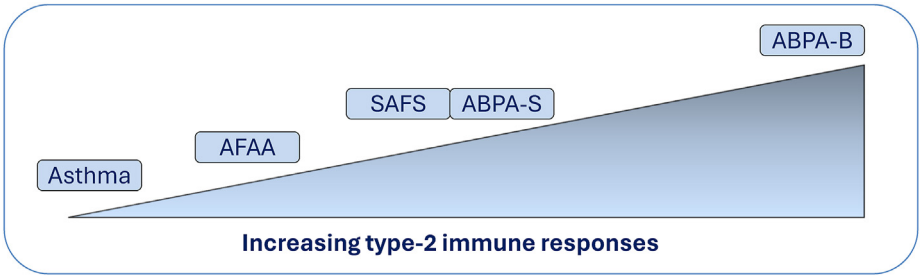

Fig. 1. Current classification of fungal asthma caused by *Aspergillus fumigatus*.

Is there a need to change the fungal asthma terminology?

AFAD is proposed as a more liberal term to characterize the association between fungi and asthma.[30] While AFAD is being recommended as a more inclusive entity, AFAD is probably too broad a term, with several limitations. AFAD includes patients with asthma or any airway disease (COPD, bronchitis, and bronchiectasis) and evidence of fungal sensitization. Further, cross-sensitization, co-sensitization, and fungi colonizing the airways complicate the diagnosis of AFAD. Lumping diseases into broad groups is generally done when there is inadequate data and characterization of individual disease entities is awaited. In the research on fungal asthma, there are well-described entities such as ABPA and others (Fig. 1). Interestingly, in one study where the authors performed a cluster analysis in patients with AFAD, there was a clear separation between SAFS and ABPA. In the era of personalized asthma therapy, splitting the disease into its endotypes is a norm.[31] Thus, lumping all disease entities of fungal asthma into AFAD would not be the way forward.

Moreover, the treatment would finally be based on pathophysiological mechanisms and lung damage (such as bronchiectasis, fixed airflow obstruction, mucus plugging, lung collapse, and others). For instance, it would not be appropriate to treat fungal sensitization in patients with uncontrolled asthma with antifungals where only asthma medications would suffice. Similarly, we do not treat ABPA-S with glucocorticoids or antifungal agents.[32] Finally, treatment for ABPA-B is not required in all patients with fungal asthma.[33] Thus, despite its apparent lumping of disease, the treatment of AFAD finally requires splitting them into categories (mild, moderate, or severe).[30] The classification of AFAD is likely to be different from the current classification, but would be required. We suggest improving current classification definitions rather than having a new terminology to avoid further confusion. Patients who do not qualify for SAFS or ABPM and still manifest symptoms should be categorized further as AFAD to assess whether therapy for fungal colonization or fungal sensitization improves clinically meaningful outcomes.

Pathogenesis of fungal asthma

The thermotolerant nature and a respirable spore size (2–5 μm diameter) are essential attributes of pathogenic fungi. *A. fumigatus* is the prototype thermotolerant fungi and undergoes dynamic changes in the airway. Inhaled *A. fumigatus* spores shed their outer proteinaceous rodlet layer and expose β glucans.[34] The fungi are recognized through their pathogen-associated molecular patterns (PAMPs; β glucans, chitin, galactomannan, and galactosaminogalactan) by the pattern recognition receptors (PRRs; toll-like receptors [TLRs], protease-activated receptors [PAR], surfactant proteins, mannose receptors, and others) and promote Th2 upregulation by two mechanisms (Fig. 2).[35] First, the fungal antigens are endocytosed by the DCs, which migrate to the lymph nodes and serve as antigen-presenting cells (APCs) to Th2 cells. Secondly, the fungi may damage or stimulate the respiratory epithelial cells directly, resulting in the secretion of 'alarmins' (IL-33, IL-25, thymic stromal lymphopoietin [TSLP]) and activating the Th2 response.[36] Fungal proteases also cleave the full-length IL-33 (a typical alarmin) to its more active form, leading to the production of type 2 cytokines via the type 2 innate lymphoid cells (ILC2).[37–39]

The major downstream regulators of the activated pathways (Th2, ILC2, and direct damage to the epithelial cells by the fungus) include IL-4, IL-5, and IL-13 (Fig. 2, green shaded region). IL-5, a crucial mediator of eosinophilic inflammation, acts on eosinophils (and basophils), promoting their recruitment, growth, and maturation. Eosinophils contribute to several manifestations of fungal asthma. Charcot-Leyden crystals are formed due to the polymerization of eosinophil galectin-10 and contribute to airflow limitation.[40] The viscosity of mucus secretions is currently attributed to eosinophil extracellular DNA traps (EETs) released from eosinophil cell death (EETosis, analogous to NETosis).[41,42] IL-4, secreted by the Th2 cells act on B-cells and promote the class switching from IgG to IgE, another hallmark of allergic inflammation.[43] IL-13 mediates AHR, goblet cell stimulation, and mucus production.

Apart from the Th2 stimulation, DCs may also activate Th17 T-cells, producing IL-17. IL-17-mediated responses are essential for protection against infection. However, their exact role in fungal asthma is unclear.[44–47] IL-17 may have diverse functions,[48,49] with some studies showing that IL-R1 signaling (through type 1 and type 17 responses) can contribute to the severity of fungal asthma.[47] However, another study demonstrated that Th17 responses through the TLR-6 pathway downregulated allergic inflammation in fungal asthma.[44] More recently, a novel C-type lectin receptor (MelLec), which recognizes the fungal melanin component of fungal cells, has been shown to promote allergic inflammation (mediated through Th17 cells) to *A. fumigatus*.[50] Further, the Th17 response aimed to protect against mucocutaneous *Candida albicans* cross-react with *A. fumigatus* in the airway and can lead to allergic inflammation in susceptible individuals.[51] Thus, dysbiosis in the intestinal tract and colonization with *C. albicans* may promote allergic lung inflammation due to cross-reactive Th17 cells and gut-resident mononuclear macrophages (an example of the fungal gut–lung axis).[52] Antigen-specific T regulatory cells in respiratory mucosa also play an important role in tolerance, and antigen-specific escape from the control of Treg may result in allergy.[53] An imbalance between the Th2 inflammation and Treg activities might determine the development of fungi-related airway disease.

Polymorphism in the receptors and mediators involved in pulmonary fungal immunity probably underlies allergic fungal lung diseases, including SAFS and ABPA.[54–56] For instance, even fungal colonization is genetically determined. The genetic variant rs35699176 causes impaired expression of the transcriptional factor ZNF77 in bronchial epithelium, causing defective bronchial

epithelial cell integrity and culminating in conidial adhesion, germination, and growth.[57] In another study, single nucleotide polymorphisms (SNPs) involving TLR3, dectin-1, IL-10, mannose-binding lectin (MBL2), CCL2, CCL17, and other genes associated with aspergillosis were identified more frequently in SAFS than atopic asthma.[58] Polymorphisms in CF transmembrane conductance regulator (CFTR) gene,[56,59] mannose-binding lectin,[60] and a few HLA restrictions (HLA-DRB1*15, B1*16; HLA DR5 [HLA DRB18-*11 and HLA DRB181*12]) have been reported as a risk factor for ABPA.[61,62] Similarly, SNPs in IL-13, IL-4 receptor alpha (IL4RA) have been associated with ABPA.[63,64]

Mechanisms by which fungi worsen asthma

Fungi can worsen asthma by three different mechanisms. The first pathway is related to non-thermotolerant fungi, where the fungi do not colonize the airway. Here, the inhalation of spores or hyphal products act as allergens in already sensitized patients, the classic example being thunderstorm asthma and Alternaria-related asthma.[65,66] The second mechanism is associated with thermotolerant fungi like *A. fumigatus* and *Penicillium* spp. that colonize the airways and release fungal proteases during hyphal growth, with worsening of asthma.[67] With increasing type-2 immune responses, the patient may develop SAFS and ABPA (Fig. 1). In the third scenario, infection of nails and skin by dermatophytes like *Trichophyton tonsurans* causes fungal sensitization, which can cause worsening asthma control due to cross-reactive T-cells.[68,69] However, there is limited evidence for this mechanism.

Prevalence of sensitization to *A.fumigatus*

Fungal sensitization has been associated with worse lung function, increased oral glucocorticoid use, and hospitalization than non-fungal sensitized patients.[70–74] Typically, 20–30% of patients show sensitization to fungal allergens in severe asthma, most commonly *A. fumigatus*.[70–74] In a recent systematic review, the prevalence of Aspergillus sensitization (AS) in asthma (73 studies, 23,003 asthmatics) ranged from 1.6 to 73%, with a pooled prevalence of 25.1% (95% confidence intervals [CI], 20.5–30.0).[75] The prevalence of ABPA in asthma (47 studies, 9822 asthmatics) varied from 0.80 to 70%, with a pooled prevalence of 11.3% (95% CI, 8.7–14.2). Unfortunately, the systematic review identified only four population-based studies (Finland [n = 2],[76,77] United States [n = 1],[78] India [n = 1][79]) that have reported the prevalence of AS in asthma. The prevalence of AS reported from Finland ranged between 5.3 and 11.3%, while the prevalence from India and the US was 16.4 and 16.9%, respectively. Only one study from India reported the community prevalence of ABPA (5.7%). All the remaining studies in the systematic review were from a tertiary care setting. Notably, the prevalence of ABPA in AS (36 studies, 2954 asthmatics) ranged from 1.9 to 90%, with the pooled prevalence being 37.0% (95% CI, 27.9–46.6).

Thus, screening all asthmatics for AS in tertiary care is vital, given the high prevalence (25%). Also, the prevalence of underlying ABPA in AS is very high (37%), and the diagnosis of AS should trigger the performance of other investigations to exclude ABPA (Fig. 3).

Diagnosis of fungal allergy syndromes

Skin tests

An immediate type of cutaneous sensitivity after a skin prick or intradermal injection of antigen indicates the presence of fungus specific IgE. Unfortunately, skin testing has several limitations. The quality of the skin test is operator dependent. Further, there is a batch-to-batch variability of the antigen used for performing the test and a theoretical risk of anaphylaxis.[80] Moreover, skin tests are inferior to *A. fumigatus*-specific IgE for diagnosing AS.[24,81]

Fungus-specific IgE

Elevated *A. fumigatus*-specific IgE (>0.35 kUA/L) is the most sensitive test for diagnosing AS. The most widely used method for performing fungal-specific IgE is the fluorescent enzyme immunoassay using the Phadia platform. In two different studies, the sensitivity of *A. fumigatus*-IgE for diagnosing ABPA ranged from 98.2 to 100%. However, the specificity of *A. fumigatus*-specific IgE is about 70%. Thus, raised *A. fumigatus*-IgE should be followed by other tests to exclude ABPA. In fungal allergy syndromes, we first perform *A. fumigatus*-IgE. If *A. fumigatus*-IgE is normal, we seek sensitization to other fungi, including *Alternaria* and *Cladosporium* (Fig. 3).

Serum total IgE

Serum total IgE is a valuable investigation in diagnosing *A. fumigatus* allergy syndromes as a normal value excludes ABPA or ABPM as the cause of the patient's current symptoms. Various cut-offs for total IgE have been used in the literature (417 IU/mL, 500 IU/mL, 1000 IU/mL). We currently use a cut-off of 500 IU/mL as it provides optimal performance in diagnosing ABPA.[24] Serum total IgE is also used to differentiate SAFS from ABPA. However, we define SAFS as fungal sensitization in severe asthma, irrespective of the serum total IgE.

Fungus-specific IgG

Detection of IgG against *A. fumigatus* was the earliest serological test used for diagnosing ABPA.[82] IgG can be detected using enzyme immunoassays or immuno-precipitation methods. Recently, we found that one additional positive result could be detected for every six (95% CI, 5–7) tests performed with immunoassay compared to immunoprecipitation.[83] Notably, the cut-offs for *A. fumigatus*-IgG vary with ethnicity. *A. fumigatus*-IgG is an important investigation in fungal allergy syndromes, as it helps differentiate between fungal sensitization and allergic bronchopulmonary mycoses, with elevated levels found only in the latter.[84]

Recombinant fungal antigens

The commonly used antigens for the diagnosis of fungal allergy syndromes are crude proteins that exhibit broad cross-reactivity with several unrelated fungal allergens.[13,85] To circumvent the problem of cross-reactivity, IgE can be measured against purified natural or recombinant allergens to diagnose true sensitization.[14] Currently, we can measure the levels of IgE and IgG antibodies against recombinant *A. fumigatus* antigens (rAsp f1, f2, f3, f4, and f6) using a commercially available platform (Phadia, Thermofisher Scientific, Uppsala, Sweden). The rAsp antigens f1, f2, and f4 are specific to *A. fumigatus*. Previously, it was suggested that rAsp f1 and f3 are markers of AS, while f4 and f6 are indicators of ABPA.[86] However, we and others have shown that the most useful antigens are rAsp f1, f2, and f4.[87,88] The IgE against rAsp f1 yielded the best combination of sensitivity (89%) and specificity (100%). Importantly, the sensitivity and specificity of IgE against either rAsp f1 (cut-off, 4.5 kUA/L) or f2 (cut-off, 1.3 kUA/L) for diagnosing ABPA were 100% and 81%, respectively.[88] Where both Asp f1 and f2 fail to yield a diagnosis, a combination of Asp f1, f2, and f4 is helpful.[88] It is

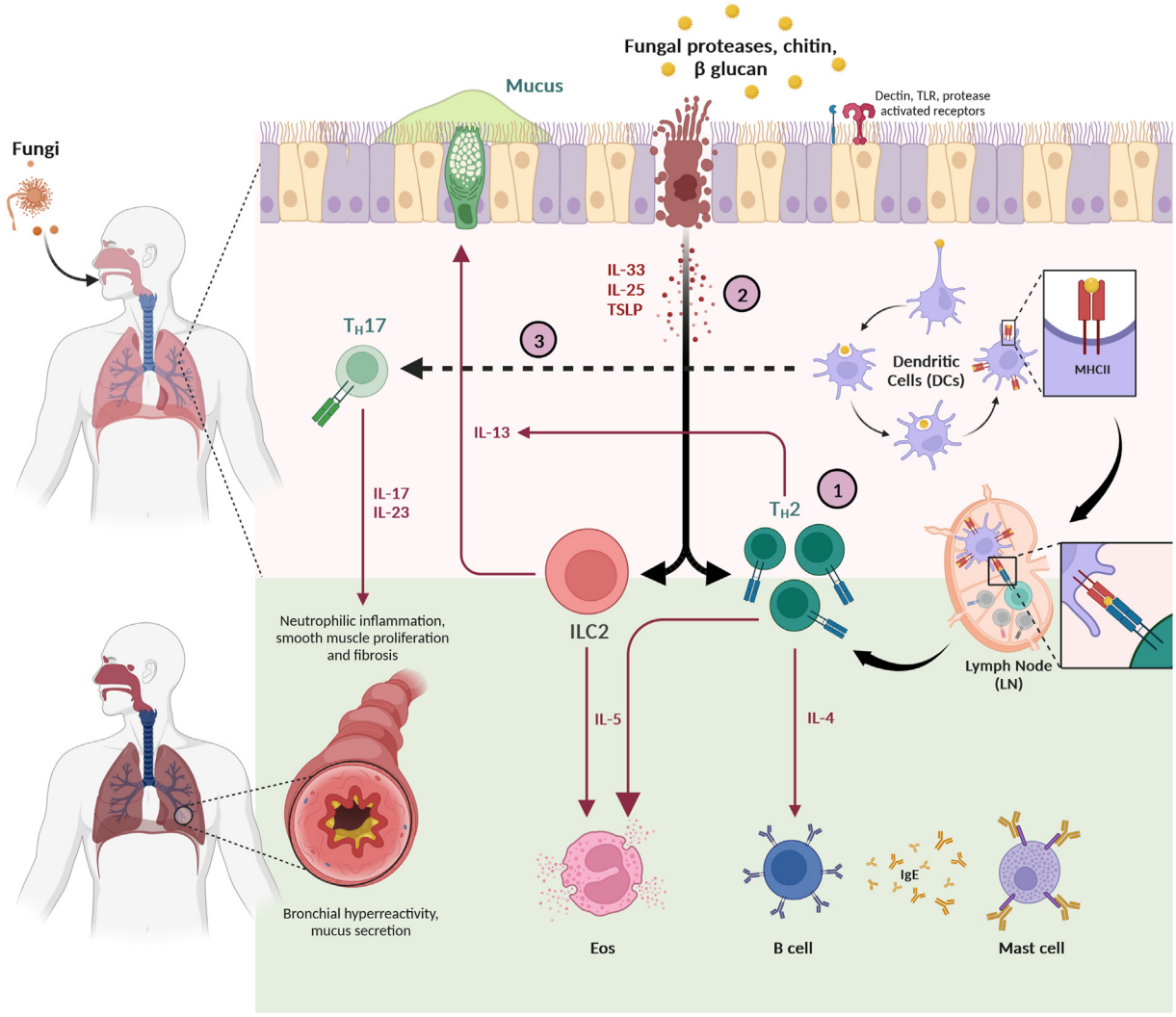

Fig. 2. Overview of the inflammatory pathways triggered by fungi in allergic asthma. The initial immune mechanisms after exposure to fungal allergens are demonstrated in the pink-shaded region, while the downstream mediators and the effects of allergic inflammation are depicted in the green-shaded area. Following exposure to fungi or their components, three main pathways can be activated in susceptible individuals. PAMPs from fungi (usually proteases) are recognized by PRR (such as dectin-1, toll-like receptors [TLRs]) in the lung epithelial cell surface. The dendritic cells (DC) recognize the fungal allergen and migrate to the lymph node leading to allergen-specific T helper 2 T-cells (Th2 cells). The fungal proteases can damage the respiratory epithelium and result in the release of alarmins (interleukin-33 [IL-33], IL-25, and thymic stromal lymphopoietin [TSLP]), which in turn stimulate Th2 and the type −2 innate lymphoid cells (ILC-2). The DCs may also promote the Th17 pathway and the resultant production of IL-17. The effects of the major downstream pathways (depicted in the green-shaded region) are mediated by IL-4, IL-5, and IL-13. IL-4 mediates the class switching and production of IgE antibodies, which then home to the mast cell and are released on exposure to the allergen. IL-5 is a key mediator for eosinophil recruitment, maturation, and survival and is central to eosinophilic inflammation. IL-13 from ILC2 and Th2 cells promotes mucus hypersecretion.

likely that recombinant antigens may replace crude antigens in the diagnosis of Aspergillus-related allergy syndromes (Fig. 4).

Total eosinophil count

Most fungal allergy syndromes are driven by eosinophilic inflammation. While the sensitivity and specificity of peripheral blood eosinophil count is poor,[89] it is an important investigation in diagnosing fungal asthma. The total eosinophil count is a marker of recurrent exacerbations in ABPA,[90] likely predicts a better response with a combination of prednisolone and itraconazole,[91] and is a biomarker for the use of biological agents targeting IL-5, IL-5 receptor, and IL-4 receptor.[92] The currently used cut-off for absolute eosinophil count is 500 cells per microliter.

Sputum cultures

Sputum cultures have little role in diagnosing ABPA for several reasons. The sensitivity of conventional sputum fungal cultures ranges from 10 to 27%,[91,93,94] and can increase to as much as 62% if undiluted high volume (about 1 mL) sputum is used for culture.[94] Unfortunately, there is often a dissociation between colonizing and sensitizing fungi.[12] On several occasions, the colonizing fungi is often not the sensitizing fungi. Moreover, *A. fumigatus* can be isolated from sputum in asthmatics without ABPA and in healthy individuals.[73,95] Nevertheless, repeated isolation of a fungus from the respiratory tract suggests a sensitizing agent.[25] Sputum cultures are also helpful for drug sensitivity testing, which may detect antifungal resistance and assist in choosing the right drug.[96]

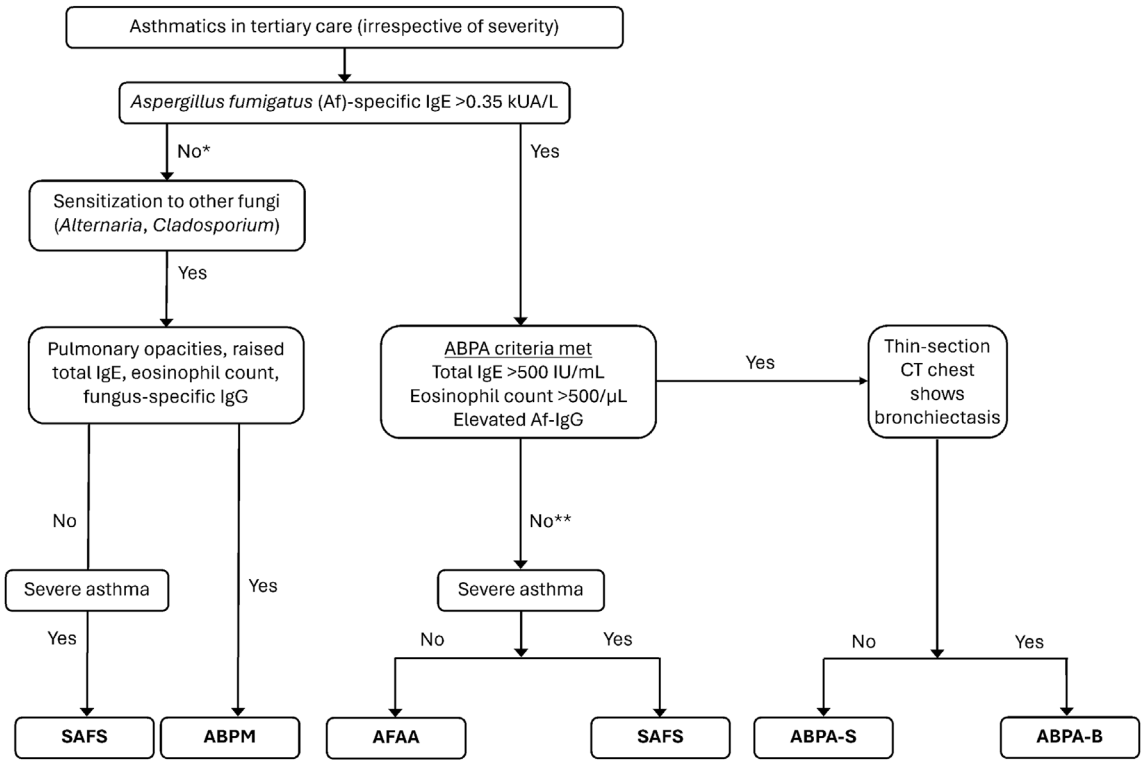

Fig. 3. Algorithm for the diagnosis of *Aspergillus fumigatus*-related lung allergy syndromes [*Check for Aspergillus sensitization q 2-5y, **Repeat total IgE q 2–5 y and evaluate for ABPA if total IgE >500 IU/mL].

Computed tomography (CT) of the chest

CT thorax is a valuable investigation as it detects organ damage (bronchiectasis) due to allergic bronchopulmonary mycoses (Fig. 5). Other findings commonly on CT chest are centrilobular nodules, tree-in-bud opacities, and mucus impaction. The pathognomonic radiological sign for the diagnosis of ABPA is high-attenuation mucus, which is mucus visually denser than paraspinal skeletal muscle (>70 HU). The presence of high-attenuation mucus confirms ABPA as a cause of the underlying bronchiectasis.[97]

Algorithmic approach to diagnosing fungal allergy syndromes

We recommend screening all asthmatic patients visiting tertiary care (or special asthma clinics) for AS using *A. fumigatus*-specific IgE. In those with raised *A. fumigatus*-IgE (>0.35 kUA/L), we perform

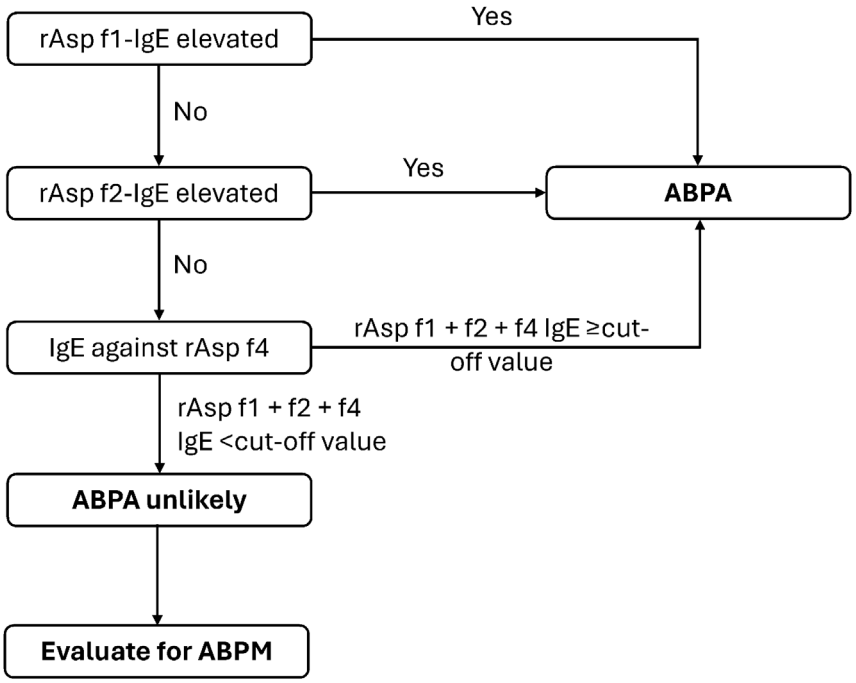

Fig. 4. Algorithm for diagnosing allergic bronchopulmonary aspergillosis using molecular-based allergy diagnostics.

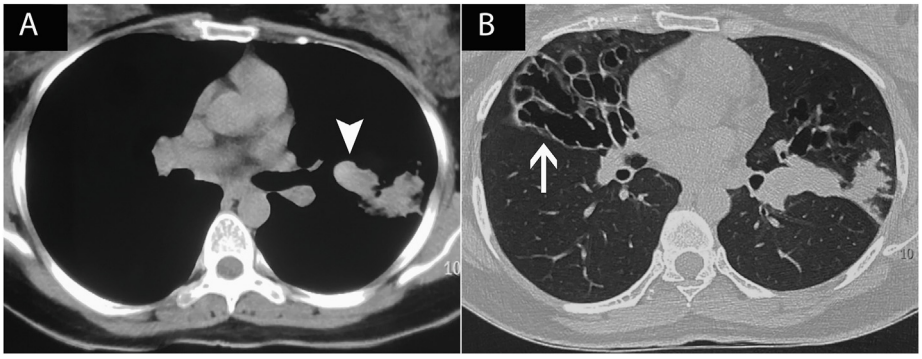

Fig. 5. Computed tomography of the thorax of a patient with allergic bronchopulmonary aspergillosis shows mucus impaction in subsegmental airways (panel **A**, mediastinal windows). There is the presence of high-attenuation (arrowhead) mucus. Corresponding lung windows (panel **B**) show the presence of bronchiectasis (arrow) besides the mucus-filled bronchi.

serum total IgE. If the serum total IgE is > 500 IU/mL, other investigations should be done, including *A. fumigatus*-specific IgG, total eosinophil count, and computed tomography (CT) of the chest. Patients with AS, controlled asthma, and not meeting the criteria for ABPA are classified as AFAA, while those with AS, severe asthma, and not meeting the criteria for ABPA are labeled SAFS. We do not use serum total IgE cut-offs (500 or 1000 IU/mL) for differentiating SAFS from ABPA-S. ABPA is diagnosed by the modified ISHAM ABPA working group criteria or its modifications thereof (Table 1).[22–25,98] We perform screening for sensitization to other fungi (*Alternaria*, *Cladosporium*) only in those without AS (Fig.3).

Treatment of fungal asthma

Environmental control by reducing dampness and employing air filtration systems improves indoor air quality by minimizing fungal spore counts.[19] Additionally, educating patients on allergen avoidance and recognizing early signs of worsening is crucial for effectively managing fungal asthma. The treatment of fungal asthma depends on the severity of the disease (AFAA, SAFS, ABPA-S, or ABPA-B). The goal of therapy is to prevent asthma exacerbations in AFAA and SAFS, while the treatment goal in ABPA is preventing both asthma and ABPA exacerbations and worsening of bronchiectasis.

Treatment of AFAA

In patients with AFAA, the underlying asthma is non-severe. The aim is to achieve asthma control using a stepwise approach with the least possible inhaled medications.[99] We initiate treatment with low-dose inhaled corticosteroids (ICS) and formoterol using a single inhaler for both maintenance and relief (Fig. 6).[100] We do not treat AFAA with antifungal azoles.

Treatment of SAFS

In SAFS, uncontrolled asthma is attributed to chronic exposure to fungi and proteins that cause persistent activation of the Th2 pathway. Thus, subjects with SAFS should benefit from reducing airway fungal burden and suppression of Th2 inflammation.[92,101] However, only a few clinical trials have investigated the role of oral antifungal agents and biological agents in treating SAFS (Table 2).

Role of antifungal agents

Three randomized control trials (RCTs; fluconazole [n = 1], itraconazole [n = 1], voriconazole [n = 1]) and three observational studies (itraconazole [n = 2], voriconazole [n = 1]) have evaluated the role of oral antifungal azoles in SAFS.[69,102–106] Ward *et al.* included 11 patients with *Trichophyton*-sensitized SAFS.[69] The use of fluconazole for five months led to a decrease in mean oral prednisolone dose and improvement in asthma control in all patients. Notably, there was a relapse of asthma symptoms in 6 of the 11 patients after stopping fluconazole. However, the small sample size limited meaningful conclusions.[69] Denning *et al.* randomized 58 subjects with SAFS (sensitization to any fungi) to receive either

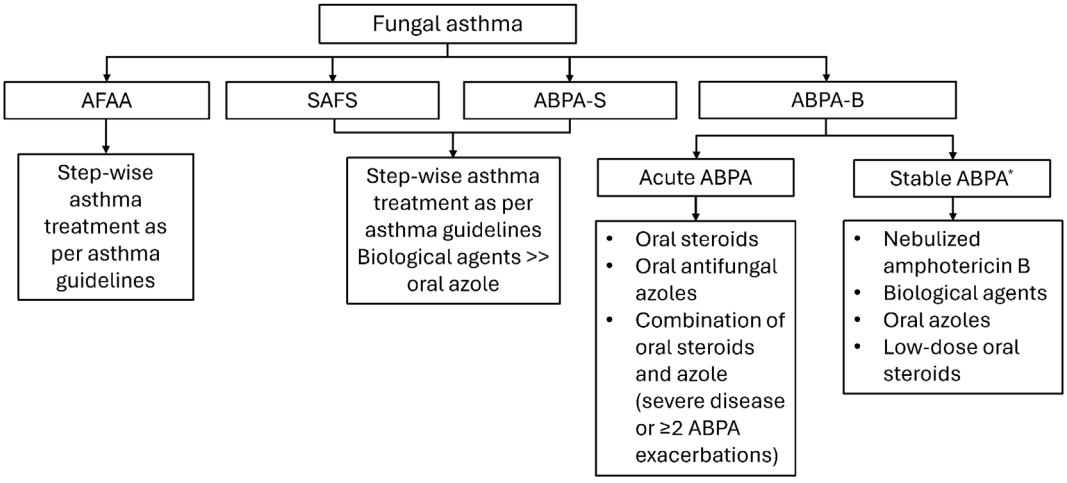

Fig. 6. Treatment options for various entities included in fungal asthma (* with frequent exacerbations).

Table 2
Studies describing the treatment of severe asthma with fungal sensitization (SAFS), fungal asthma, or allergic bronchopulmonary aspergillosis (ABPA).

Author/year	Number of patients	Inclusion criteria	Sensitizing fungi	Study design	Intervention	Control arm	Primary outcome	Key secondary outcomes
SAFS								
Ward GW *et al.* (1999)[69]	11 (all patients had rhinosinusitis)	Severe asthma and positive skin prick test	*Trichophyton*	RCT (Phase 1: fluconazole or placebo for 5 months; Phase 2: fluconazole for all patients)	Fluconazole for 5 months	Plb	Reduction in mean oral prednisolone dose, improvement in asthma control	Relapse of asthma symptoms in 6/11 patients after stopping fluconazole and worsening of peak expiratory flow.
Denning DW *et al.* (2009)[102]	58 with SAFS. 41 completed 32 weeks of therapy	Severe asthma (poorly controlled), BTS level 4 or 5; serum TIGE <1000 IU/mL; and either a positive skin test or raised specific IgE to any fungus	*A.fumigatus, Cladosporium, Alternaria, Penicillium, Candida, Trichophyton, and Botrytis*	RCT	Oral Itr for 32 weeks	Plb	Mean change in AQLQ (Itr, +0.85 vs. Plb, −0.01)	(1) no difference in asthma exacerbations. (2) improvement in rhinitis score in Itr arm. (3) significant higher fall in serum TIGE in Itr arm (4) similar change in FEV1 (5) Reduced plasma cortisol levels in Itr arm
Pasqualotto AC *et al.* (2009)[103]	33 (22 SAFS, 11 ABPA)	Severe asthma (poorly controlled), BTS level 4 or 5; serum TIGE <1000 IU/mL; and either a positive skin test or raised fungus-specific IgE	*A.fumigatus*	Retrospective	Oral Itr for 6–12 months	-	Change in lung function (FEV1): FEV1 increased by 190 mL after treatment	Serum TIGE fell by 24.5%; eosinophils fell by 26.7%. Oral glucocorticoid discontinued in 4/10 patients. Dosage of oral steroids reduced by 60%. Reduction in number of oral glucocorticoid courses by 65%. No reduction in ICS or number of asthma hospitalizations.
Chishimba L *et al.* (2012)[104]	25 (5 SAFS, 20 ABPA)	Severe asthma (poorly controlled), BTS level 4 or 5; Serum TIGE <1000 kU/L; and either a positive skin test or raised fungus-specific IgE	-	Retrospective	Oral voriconazole (300–600 mg/day)	-	Clinical improvement in 4/5 patients with SAFS at 6 months. 1/5 remained stable	Improved quality of life (however data for SAFS not given separately)
Agbetile J *et al.* (2014)[105]	65 (59 received treatment)	Asthma, *A.fumigatus*-IgE >0.35 IU/L or a skin prick test response >2 mm larger than control, and at least 2 severe exacerbations (requiring a minimum of 3 days of high-dose oral glucocorticoids for asthma symptoms) in the previous 12 months	-	RCT	Oral voriconazole for 3 months (n = 32)	Plb (n = 27)	No difference in severe exacerbations (voriconazole vs. placebo; 1.16 vs. 1.41). Improvement in AQLQ at 3 months: no difference in AQLQ between two arms (mean difference, 0.2)	No difference in other quality of life measures (ACQ-6, VAS for asthma control, and nasal polyp questionnaire). No difference in FEV1, sputum eosinophil counts, reduction in serum TIGE
Lin CY *et al.* (2020)[106]	73	Severe asthma (GINA step 5). SAFS: severe asthma and positive fungus-specific IgE	*P.chrysogenum, A.fumigatus, C. herbarum, A.alternata*	Retrospective	4 groups: Group I (n = 16), severe asthma; Group II (n = 16), SAFS; Group III (n = 31), fungal isolates in respiratory secretions; Group IV (n = 10), SAFS and fungal isolates in respiratory secretions. Overall, 25 patients (groups II-IV) received oral Itr 100 mg	Observation	Only patients in Group III demonstrated improvement in FEV1 and ACT after treatment with Itr. Reduction in asthma exacerbation in Group III with Itr. Number of exacerbations reduced in the observation arm in Group III.	Not clearly defined.

(*continued on next page*)

Table 2 (*continued*)

Author/year	Number of patients	Inclusion criteria	Sensitizing fungi	Study design	Intervention	Control arm	Primary outcome	Key secondary outcomes
					twice daily for 3 months.			
Wardlaw A *et al.* (2020)[107]	576 subjects; fungal sensitized asthma (n = 191)	Fungus-specific IgE >0.35 kU/L	*C.albicans, A.fumigatus, Malassezia* spp, *P.chrysogenum*	Post hoc analysis of RCT	Mepolizumab 75 mg intravenously or 100 mg subcutaneously (SC) for 32 weeks	Plb	Mepolizumab did not reduce the annual rates of clinically significant exacerbations in fungal sensitized asthma. No difference in the change in FEV1. Trend towards improvement in SGRQ and ACQ scores with mepolizumab	Not defined clearly.
Wark P *et al.* (2020)[29]	218 (62, fungal sensitized; 156, not sensitized)	Severe asthma, *A.fumigatus-specific* IgE >0.35 kU/L or positive skin test and serum TIGE <1000 IU/L	-	Retrospective	Omalizumab	-	Mean change in ACQ-5 at 24 months: −2.1. Mean change in incident rate ratio of exacerbations at 24 months: 0.35.	-
Dhariwal J *et al.* (2021)[108]	184 (31, SAFS; 23/31 had sensitization to Aspergillus or penicillium species and 8/31 to candida)	Severe asthma and positive specific IgE to any fungal allergen (>0.35 kU/L) in the absence of ABPA	*A.fumigatus, A.niger, A.flavus, P.chrysogenum, C.albicans, C.herbarum,* and *Alternaria*	Retrospective	Mepolizumab or Benralizumab for 48 weeks	-	Reduction in asthma exacerbation rates in SAFS. No difference in the time-to-first exacerbation. There was an improvement in ACQ-6, significant reduction in oral steroid dose.	-
Akinseye C *et al.* (2023)[109]	17	Moderate-severe asthma (FEV1, 35−79% predicted, FeNO ≥25 ppb, ACQ-5 score ≥1.5, and blood eosinophils ≥300 cells/μL at screening); fungal-specific IgE >0.35 KU/L	*A.fumigatus or P.chrysogenum*	RCT	GSK3772847 (anti IL-33 monoclonal antibody): 10 mg intravenously at weeks 0, 4, 8 (n = 8)	Plb (n = 9)	No differences observed in blood eosinophils or FeNO between treatment arms	-
Kritikos V *et al.* (2023)[110]	61	Severe asthma and fungal sensitization (n = 34) or physician diagnosis of ABPA (n = 25)	-	Retrospective	Mepolizumab for 12 months	-	Improvements in ACQ-5 and lung function, and reduction in median dose of oral glucocorticoids.	Not defined clearly
ABPA								
Stevens DA *et al.* (2000)[111]	55 (10 ABPA-s)	Glucocorticoid-dependent ABPA	-	RCT	Itr 200 mg BD (n = 28) for 16 weeks	Plb (n = 27)	50% reduction in steroid dose and 25% reduction in serum TIGE and clinical or radiological improvement seen in 46% (13/28) itraconazole arm and 19% (5/27) control arm.	Response rate higher in ABPA without bronchiectasis than those with bronchiectasis (43% vs. 20%). Itr resulted in higher responses in those without bronchiectasis than placebo (60% vs. 31%)
Wark PA *et al.* (2003)[112]	29 (patient number of ABPA-s and ABPA-B not given separately)	Stable ABPA	-	RCT	Itr 200 mg BD (n = 15)	Plb (n = 14)	Itr decreased the sputum eosinophils, decreased sputum ECP, and decreased serum total IgE.	There were fewer exacerbations with Itr than plb
Agarwal R *et al.* (2011)[113]	21 (all ABPA-s)	Stable ABPA with uncontrolled asthma	-	Retrospective	1600 μg inhaled budesonide and formoterol 24 μg	-	Subjective improvement in symptoms with ICS, but the asthma remained uncontrolled. All subjects had asthma control after treatment with oral prednisolone	Not clearly defined
Voskamp AL *et al.* (2015)[114]	13 (all ABPA-B)	Chronic ABPA	-	Cross-over observational study	Omalizumab 375 mg subcutaneously every two weeks (n = 13)	Plb	Fewer asthma exacerbations during active treatment (2 exacerbations) than placebo (12 exacerbations)	Reduction in FeNO and night awakening during treatment phase than Plb.

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Table 2 (*continued*)

Author/year	Number of patients	Inclusion criteria	Sensitizing fungi	Study design	Intervention	Control arm	Primary outcome	Key secondary outcomes
					for four months or a Plb, followed by a three-month washout period and cross-over			
Agarwal R *et al.* (2016)[115]	92 (26 ABPA-S)	Acute ABPA	-	RCT	High-dose prednisolone	Medium dose prednisolone	ABPA exacerbations at 1 and 2 years were similar.	Response rate and fall in serum TIGE were higher with high dose prednisolone. Time to first exacerbation after stopping treatment was not different between the two groups
Ram B *et al.* (2016)[116]	21 (all ABPA-B)	Stable ABPA		RCT	ABDC (10 mg [2 mL]) twice a day for 3 times/week and nebulized budesonide 1 mg twice a day, 3 times/ week for 4 months (n = 12)	Nebulized budesonide 1 mg twice a day, 3 times/ week for four months (n = 9)	Trend towards a longer time to first ABPA exacerbation in the ABDC arm.	ABDC resulted in fewer ABPA exacerbations at 1-year 1/12 vs. 6/9
Agarwal R *et al.* (2018)[117]	131 (9 ABPA-S)	Acute ABPA	-	RCT	Prednisolone (n = 63) for 4 months	Itr 400 mg/day (n = 68) for 4 months	Composite response at six weeks significantly higher with prednisolone (100%) than with Itr (88%).	No difference in ABPA exacerbation rates at 1 and 2 years after randomization
Agarwal R *et al.* (2018)[118]	50 (all ABPA-B)	Acute ABPA		RCT	Prednisolone (n = 25) for 4 months	Oral voriconazole 400 mg/day (n = 25) for 4 months	Composite response rate similar in both arms at six weeks and three months. No difference in ABPA exacerbation rates at 1 and 2 years after randomization.	Time-to-first ABPA exacerbation was similar. No difference in asthma exacerbations between the two groups.
Godet C *et al.* (2022)[119]	139 (ABPA-B or infiltrates on CT)	Stable ABPA		RCT	Nebulized LAMB (25 mg) once a week for six months (n = 65)	Nebulized isotonic saline (n = 74) once a week for six months	Similar rate of ABPA exacerbation	Time-to-first exacerbation longer in the LAMB arm
Agarwal R *et al.* (2022)[91]	191 (5 ABPA-S)	Acute ABPA		RCT	Prednisolone–Itr combination (n = 97)	Prednisolone (n = 94)	Trend towards fewer ABPA exacerbation in combination (20.6%) vs. prednisolone monotherapy (33%) 1 year after randomization.	No difference in treatment response at 6 weeks, time-to-first exacerbation, or adverse events. No difference in asthma exacerbations after 2 years.

ABDC, amphotericin B deoxycholate; ABPA-B, ABPA with bronchiectasis; ABPA-s, serologic ABPA; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BTS, British thoracic society; FeNO, fraction of exhaled nitric oxide; FEV1, forced expiratory volume in first second; ICS, inhaled corticosteroids; Itr, itraconazole; LAMB, liposomal amphotericin B; Plb, placebo; ppb, parts per billion; RCT, randomized control trial; SGRQ, Saint George's Respiratory Questionnaire; TIGE, serum total immunoglobulin E.

oral itraconazole for 32 weeks or a placebo.[102] There was a statistically significant improvement in the quality of life score (primary outcome), with the mean difference in the asthma quality of life questionnaire (AQLQ) score being 0.86. However, the proportion of subjects achieving a delta AQLQ score ≥0.5 was similar in both arms. Further, there was no difference in the asthma exacerbation rate or change in FEV1 in the two arms. Finally, only 41 subjects completed 32 weeks of itraconazole therapy.[102] Another study by Agbetile *et al.* randomized 65 patients with SAFS to receive voriconazole or placebo for three months.[105] The authors found no difference in reduction in severe asthma exacerbations or the AQLQ score between the two study arms.[105] One small retrospective study demonstrated the benefit of oral itraconazole only in patients with severe asthma and the presence of fungus in respiratory secretion and not in patients with SAFS.[106]

Role of biological agents in SAFS

Most studies describing the role of biological agents in SAFS are retrospective (n = 4).[29,107,108,110] Akinseye *et al.* did not observe any difference in blood eosinophil levels, or fractional exhaled nitric oxide in patients with SAFS treated with anti-IL-33 monoclonal antibody.[109] However, this RCT comprising 17 subjects was terminated prematurely due to low recruitment.[109] Wardlaw *et al.* found a non-significant trend toward improvement in St. George's Respiratory Questionnaire (SGRQ) and asthma control questionnaire (ACQ) in a subgroup of patients with SAFS in the mepolizumab arm (post hoc analysis of the MENSA study describing the use of mepolizumab in severe eosinophilic asthma).[107] There was no difference in the annualized asthma exacerbation rates or improvement in FEV1.[107] In a retrospective study, mepolizumab or benralizumab treatment for 48 weeks reduced asthma exacerbation rates, improved ACQ-6, and led to a reduction in median dose of oral glucocorticoids in patients with SAFS.[108] Notably, using mepolizumab or benralizumab caused similar improvement in patients without SAFS.[108] Similar observations were reported by Kritikos *et al.* in a recent study of 12-month therapy with mepolizumab in severe asthmatics with or without fungal sensitization.[110] Wark *et al.* included 218 patients with severe asthma, of whom 62 had SAFS.[29] The authors described a significant improvement in asthma control, exacerbation reduction, and median dose of oral glucocorticoid after 24 months of treatment with omalizumab. However, like mepolizumab, the magnitude of the effect was similar irrespective of fungal sensitization.[29] Thus, current evidence suggests that patients with SAFS should be treated like severe asthma.

We treat all SAFS patients with a combination of moderate-to-high dose ICS and inhaled long-acting β-2 agonist (formoterol) using a single inhaler therapy approach (Fig. 6).[120] We also use inhaled long-acting antimuscarinic agents followed by leukotriene inhibitors if the asthma control is still sub-optimal.[99] Despite optimal asthma therapy, some patients have poor asthma control requiring prolonged or multiple courses of systemic glucocorticoids. In patients with SAFS, we prefer to use a biological agent rather than antifungal azoles, although azoles are a reasonable alternative.[2,102,103,107,108,121] A crucial treatment goal in SAFS is the discontinuation of systemic glucocorticoids and reduction in the dose of ICS.

Treatment of acute ABPA

ABPA results from an exuberant inflammatory response to *Aspergillus* in the airways, and the treatment involves either reducing the fungal burden or decreasing the inflammatory response, or both.[16] Three RCTs have evaluated oral antifungal azoles, and one RCT compared two doses of systemic glucocorticoids in ABPA.[91,111,112,115,117,118] We compared oral itraconazole with oral prednisolone in treatment-naïve ABPA patients in an RCT.[117] While prednisolone had a higher response rate at six weeks than itraconazole, the exacerbation frequency at 1 and 2 years after randomization was similar in the two groups.[117] We found similar results in another small study comparing oral voriconazole with prednisolone.[118] In another study, our group compared medium-dose prednisolone with high-dose and found no difference in ABPA exacerbation rates 1 and 2 years after randomization.[115] Thus, systemic glucocorticoids and oral antifungal azoles have similar long-term efficacy, although systemic glucocorticoids have better short-term effectiveness. A recent study comparing a combination of itraconazole and prednisolone with prednisolone monotherapy found a non-significant trend toward a lower ABPA relapse with combination therapy one year after randomization.[91] Most subjects in the studies mentioned above had severe bronchiectasis.[91]

We initially treat ABPA-B patients with systemic glucocorticoids or oral antifungal azoles (itraconazole or voriconazole), with the latter preferred in those with at-risk for complications due to glucocorticoids (obesity, osteopenia, and others). A combination of itraconazole and glucocorticoids can be used in patients with severe ABPA (≥10 segments with bronchiectasis on CT thorax, peripheral blood eosinophil count ≥1000 cells/μL or those with steroid dependent ABPA). We also use combination therapy in those with ≥2 ABPA relapses. In previous studies, high-dose ICS alone did not improve outcomes in patients with ABPA.[113,122] We use ICS mainly for asthma control in patients with ABPA. Most studies on ABPA therapy have included patients with ABPA-B, with little data on ABPA-S. At our center, we treat patients with ABPA-S like SAFS, as mentioned above.[16,32]

Treatment of stable ABPA

Treatment during stable disease aims to prevent future exacerbations with minimal treatment and treatment-related adverse events. Four RCTs (itraconazole [n = 2] and nebulized amphotericin B [n = 2]) have investigated the role of antifungal agents during stable ABPA.[111,116,119,112] Stevens *et al.* included 55 patients with steroid-dependent ABPA and randomized patients to receive either oral itraconazole or placebo for 28 weeks.[111] There was a 50% reduction in the glucocorticoid dose, and a higher proportion of subjects had a clinico-radiological response in the itraconazole arm.[91] Subsequently, Wark *et al.* demonstrated a decline in the sputum eosinophils with itraconazole, with fewer exacerbations in the itraconazole arm than in the placebo.[112] Both studies had a small sample size and did not report long-term outcomes.[111,112] Two recent studies have evaluated the role of nebulized amphotericin B as maintenance during stable disease in preventing future ABPA exacerbations.[116,119] In a pilot study, the use of nebulized amphotericin B deoxycholate reduced the ABPA exacerbations at one year.[116] In the larger NEBULAMB study, while the primary outcome was not significant, the time to first exacerbation was significantly longer with nebulized liposomal amphotericin B than in the control group.[119]

Biological agents for stable ABPA

The role of biological agents in treating ABPA is discussed in detail elsewhere.[16,123,124] Most evidence on ABPA is from case series or retrospective studies.[125] Five monoclonal antibodies targeting the Th2 pathway have been tried in ABPA. Omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-IL-4Rα), and tezepelumab (anti-thymic stromal lymphopoietin) have been tried in ABPA.[16,92] Most experience is with

omalizumab. A recent meta-analysis of 49 studies of omalizumab in ABPA found a reduction in annualized exacerbations and oral glucocorticoid use and an improvement in lung function with omalizumab.[125,114] In a post hoc analysis of three RCTs, dupilumab reduced annualized severe exacerbation rates by 81% ($p = 0.01$) and improved pre-bronchodilator FEV1 by 0.26 L ($p = 0.09$) and 0.33 L ($p = 0.07$) at week 24 and 52 in patients with moderate-to-severe asthma and ABPA-S.[126] Notably, omalizumab and dupilumab reduced asthma exacerbation rate and not ABPA exacerbation rate. Thus, based on current evidence, biological agents should only be used as salvage therapy.

In those with stable ABPA, our first-line approach is to use only anti-asthma therapy. However, in those with frequent exacerbations (≥2 in the last 12 months), we use itraconazole, nebulized amphotericin B, biological agents, or low-dose glucocorticoids (Fig. 6).

Future directions

Despite seven decades of research, the pathogenesis of fungal asthma and ABPA remains elusive. Investigating the role of specific immune pathways and genetic predisposition to Aspergillus-induced asthma can provide valuable insights into disease pathogenesis. Understanding the intricate immunological interactions between *Aspergillus* and the host immune system is critical for developing targeted therapies. Identifying new biomarkers for Aspergillus-induced asthma could facilitate early diagnosis and treatment monitoring. Randomized trials in accurately phenotyped patients could lead to more effective and personalized treatment strategies. Future studies should prospectively evaluate the role of biological agents as first-line therapy, comparing them with systemic glucocorticoids or oral antifungal azoles. Developing novel inhaled antifungal agents with improved efficacy and safety will likely improve outcomes in Aspergillus-induced asthma. There is also a need to explore novel drug targets and delivery approaches. Finally, the impact of various environmental interventions, such as air filtration and mold reduction strategies, on fungal asthma outcomes will inform evidence-based preventive measures.

Conclusions

There is a complex relationship between Aspergillus and asthma. Diagnostic challenges are inherent in Aspergillus-related asthma due to the diverse clinical manifestations and the lack of specific biomarkers. Distinguishing between various entities of fungal asthma requires careful evaluation of the patient's clinical history, serological tests, and imaging studies. Recombinant *A. fumigatus* antigens allow for a more specific and sensitive diagnostic approach than traditional methods for early and accurate identification of Aspergillus-related asthma. Preventive measures are essential in reducing *Aspergillus* exposure and subsequent asthma exacerbations. The management of fungal asthma involves judicious use of inhaled corticosteroids, bronchodilators, and antifungal therapy. Biological agents are likely to emerge as an important treatment option for fungal asthma. Due to the lack of evidence, biologics are currently reserved for cases of fungal asthma that do not respond well to standard treatments.

Conflict of interest

The authors have no conflict of interest to declare.

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