



The impact of fungal allergic sensitization on asthma

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Purpose of review

Fungal sensitization may contribute to the development of asthma as well as asthma severity. The purpose of this review is to summarize existing knowledge about the pathophysiology, diagnosis, and management of fungal sensitization in asthma and highlight unmet needs and target areas for future investigation.

Recent findings

Fungal sensitization may occur by a normal or aberrant immune response. Allergic sensitization to fungi is mediated by the adaptive immune response driven by T_H2 cells and the innate immune response driven by the innate lymphoid cells group 2. Diagnosis of fungal sensitization can be made by either skin prick testing or measurement of fungal-specific serum IgE. Fungal sensitization in asthma has been associated with worse disease severity, including reduced lung function, increased risk of hospitalizations, and life-threatening asthma. A spectrum of disease related to fungal sensitization has been described in asthma including allergic bronchopulmonary mycosis and severe asthma with fungal sensitization (SAFS). The role of antifungals and targeted biologic therapy in asthma with fungal sensitization need further investigation.

Summary

There is increasing awareness of the contribution of fungal sensitization to asthma severity. However, there are no therapies with proven efficacy. Randomized clinical trials are needed to further investigate the role of biologics.

Keywords

allergic bronchopulmonary mycosis, fungal asthma, severe asthma with fungal sensitization, T_H2 cells, triazoles

INTRODUCTION

Asthma is a chronic airway inflammatory disease characterized by bronchial hyperresponsiveness and reversible airflow obstruction. It is a heterogeneous disease with variable clinical presentations, underlying mechanisms, and outcomes. Patients with severe asthma represent a small subgroup of patients but have greater healthcare utilization than those with less severe disease [1]. Severe asthma is defined as ‘asthma which requires treatment with high-dose inhaled corticosteroids and a second controller (and/or systemic corticosteroids) to prevent it from being “uncontrolled,” or which remains “uncontrolled” despite this therapy’ [2].

Fungal exposure is one factor which may influence the development of asthma as well as contribute to its severity and poor control. Fungi are ubiquitous eukaryotic organisms, and fungi have been identified in the sputum mycobiome of asthmatics [3^{••}] exposure to fungi occurs through inhalation of spores or yeast cells. However, fungal sensitization and disease caused by fungi are not

common. Allergic bronchopulmonary aspergillosis (ABPA) is the most well characterized form of fungal asthma resulting from hypersensitivity to *Aspergillus fumigatus* [4]. Clinical presentation is variable but can include uncontrolled asthma, recurrent pulmonary infiltrates, and bronchiectasis. Laboratory criteria for the diagnosis of ABPA include serum IgE more than 1000 ng/ml, elevated fungal-specific IgE or IgG, and eosinophilia [5]. Similar disease presentation can occur with sensitization to fungi other than *Aspergillus* and is referred to as allergic

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KEY POINTS

- Fungal sensitization within the airways may occur by a normal or aberrant immune response. The normal immune response to clear fungi is mediated by T_H1 and T_H17 cells. Aberrant allergic response to fungi is driven by T2 inflammation mediated by T_H2 cells and innate lymphoid cells.
- Fungal sensitization may be a unique asthma phenotype associated with more severe symptoms and life-threatening disease.
- There are limited effective treatments for severe asthma with fungal sensitization (SAFS). Studies demonstrate mixed response to triazole antifungals and more studies are needed on the efficacy of targeted biologics in SAFS.

bronchopulmonary mycosis (ABPM) [6]. Fungal sensitization, on the other hand, is an immune-mediated response to a fungus without evidence of inflammation or tissue damage [6].

The term severe asthma with fungal sensitization (SAFS) was proposed by Denning *et al.* [7] and reflects a specific asthma phenotype characterized by severe asthma, evidence of fungal sensitization, and exclusion of ABPA [5]. However, patients with asthma and fungal sensitization may not all fit the definition of severe asthma. Therefore, the term allergic fungal airway disease or airway mycosis have also been proposed to describe fungal lung disease [8,9]. This review aims to summarize the existing evidence and new insights about the pathophysiology, diagnosis, and management of fungal sensitization in asthma and highlight target areas for future investigation.

ALLERGIC IMMUNE RESPONSE TO FUNGI

Allergen exposure plays an important role in triggering and exacerbating asthma symptoms. Fungi secrete and contain biologically active substances including proteases, β -glucans, and other proteins which may act as fungal allergens. Fungi can perpetuate asthma through one of two possible mechanisms – from an aberrant allergic response within the airways to inhaled fungal antigens or, alternatively, from appropriate immune response to fungal pathogens within the airways [9]. Epithelial tight junctions and mucous secreted by goblet cells in the airway epithelium provide a physical barrier to fungi. T_H1 and T_H17 cell responses are necessary for the clearance of fungal organisms and the development of protective immunity against fungi [10]. T_H1 and T_H17 cells release cytokines, including TNF-

α , IFN- γ , and IL-17A and IL-17B, which stimulate phagocyte activity as well as the production of opsonizing antifungal antibodies by B cells [11]. In a prospective cohort study of children of allergen-sensitized parents, children with higher levels of fungal exposure had higher asthma prevalence and significantly higher serum levels of IL-17A than patients with low fungal exposure [12]. In a second group of children with asthma in the same study, fungal exposure was associated with increased asthma symptoms [13]. Thus, IL-17 may play a role in the relationship between fungal exposure and asthma severity.

Allergic asthma is characterized by sensitization to allergen and is associated with an allergen-induced type 2 immune response (Fig. 1). Dendritic cells in the airway lumen can sample allergen, or allergens may be introduced to submucosal dendritic cells by entering via disrupted epithelium. Activated dendritic cells then migrate to regional lymph nodes where they stimulate differentiation of naïve T cells into T_H2 cells. T_H2 cells secrete cytokines IL-4, IL-5, and IL-13 [14]. T_H2 cells also stimulate IgE isotype switching in B cells. IgE can then enter the bloodstream [15] and subsequently bind to high-affinity receptor (Fc ϵ RI) on mast cells, triggering these cells to release proinflammatory mediators and increase synthesis of cytokines upon re-exposure to the allergen. This, in turn, leads to bronchoconstriction, increased vascular permeability, and increased mucous production in the airway.

Innate lymphoid cells (ILCs) also play an important role in the response to fungi. IL-33 is normally stored in the nucleus of airway epithelial cells. Exposure to fungal allergens leads to the release of IL-33 from epithelial cells and the production of thymic stromal lymphopoietin (TSLP) and IL-25. IL-33, IL-25, and TSLP then activate ILC group 2 cells to produce large quantities of the T2 cytokines IL-5 and IL-13 [16]. IL-13 promotes differentiation and proliferation of T_H2 cells, and IL-5 stimulates the maturation of eosinophils. In an experimental model, following exposure to the fungal allergen *Alternaria alternata*, mice developed peribronchiolar infiltration of inflammatory cells and airway eosinophilia along with rapid increase in levels of IL-33 followed by increased IL-5, and IL-13 in bronchoalveolar lavage fluid. These findings suggest that IL-33 mediates the subsequent type 2 cytokine response [17] and support the important role of ILCs in the allergic response to fungi. In 82 children with severe asthma, 38 of whom had SAFS, IL-33 levels in bronchoalveolar lavage fluid and tissue were significantly higher in those with compared with those without fungal sensitization [12]. Similarly, in adults with severe asthma, serum IL-33 levels were

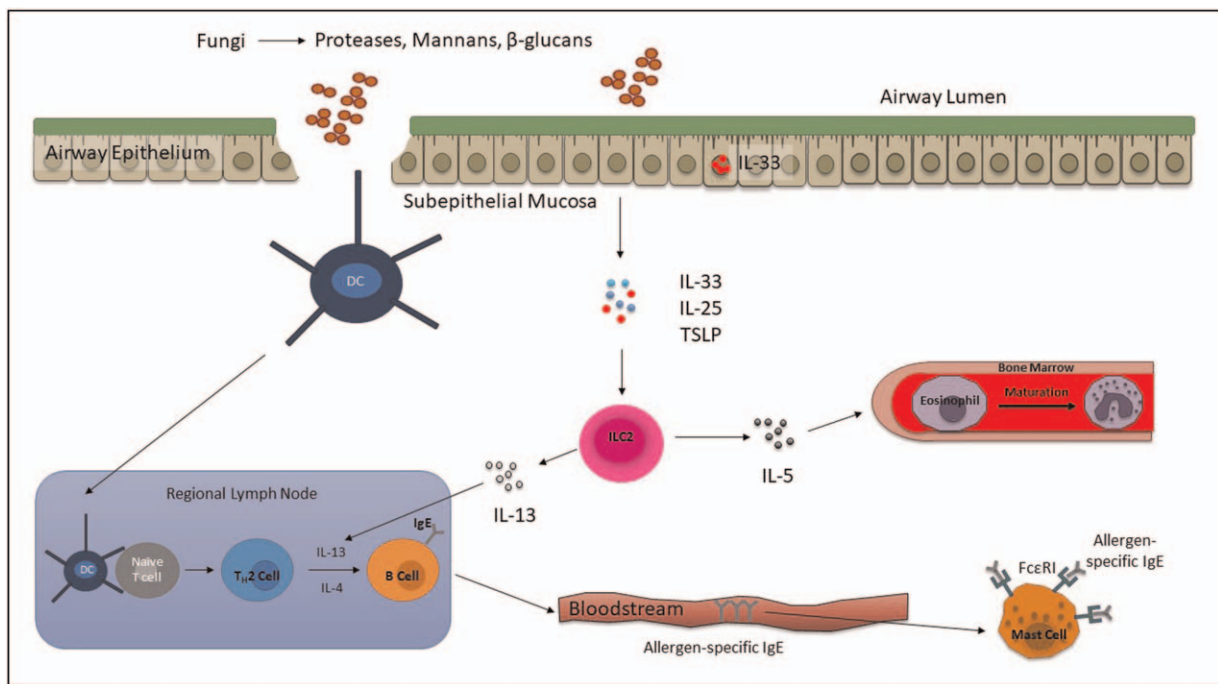


FIGURE 1. Epithelial tight junctions and mucus secreted by goblet cells provide a physical barrier against fungal invasion. However, fungal allergens can enter the airway through disrupted epithelium or via dendritic cells in the submucosa. The activated dendritic cells then migrate to regional lymph nodes where they stimulate naïve T cells to differentiate into T_H2 cells. These T_H2 cells produce the T2 cytokines IL-4 and IL-13 which help to stimulate B cells to produce IgE [13]. IgE released into the circulation binds to the high-affinity receptor (FcεRI) on mast cells which sensitizes them to respond when there is reexposure to the allergen [14]. IL-33, which is normally stored in the nucleus of airway epithelial cells, is released on exposure to fungal allergens. IL-33 release then stimulates production of IL-25 and thymic stromal lymphopoietin. IL-33, IL-25, and thymic stromal lymphopoietin activate group 2 innate lymphoid cells to produce T2 cytokines IL-5 and IL-13 [15]. IL-5 promotes the maturation of eosinophils.

significantly higher in patients with fungal sensitization compared with those without fungal sensitization [18]. Taken together, these studies provide further support of the important role of IL-33 in asthma with fungal sensitization.

DIAGNOSIS OF FUNGAL SENSITIZATION

Diagnosis of fungal sensitization can either be made by skin prick test (SPT) or by measurement of fungal-specific serum IgE. However, testing is limited by lack of standardized, high-quality fungal extracts and presence of taxonomically related cross-reactivity among fungi [19]. SPTs are performed by introducing a small amount of allergen extract through the skin and assessing for a wheal and flare response. Testing for specific serum IgE is generally based on the binding IgE to fungal proteins followed by detection using labeled anti-IgE. The immunoassay capture (ImmunoCap, Thermo Fisher Scientific, Waltham, MA, USA) system is one commonly used platform.

In a retrospective study of 74 patients with asthma, testing against *Alternaria* was performed,

including bronchoprovocation, SPTs, and measurement of serum-specific IgE, to determine the predictive values of SPTs and IgE for bronchoprovocation. SPTs had an area under the receiver operative curve of 0.957, indicating a very high diagnostic accuracy for bronchial reactivity to *Alternaria*. Specific serum IgE had lower diagnostic accuracy, but accuracy improved with increasing anti-*Alternaria* IgE values [20]. This study suggests that skin testing with *Alternaria* identifies patients with asthma and fungal sensitivity. Mari *et al.* [21] investigated fungal sensitization (to *Alternaria*, *Aspergillus*, *Candida*, *Cladosporium*, *Penicillium*, *Saccharomyces*, and *Trichophyton*; DHS, Antony, France) in patients with allergic rhinitis or asthma and found that 19% had a positive SPT to at least one fungal allergen. Reaction to *Alternaria* and *Candida* were most common. In patients sensitized to only one fungus using specific IgE, fewer sensitized patients were detected than with SPT [21]. In a study of patients with severe asthma, 66% were sensitized to one or more fungi by SPT and/or specific serum IgE. However, there was poor concordance between SPT and specific serum

IgE tests, with only 77% of patients having concordant results [22]. Differences in fungal extracts between SPT and serum tests may contribute to the lack of concordance. Because SPT has a high negative predictive value while the ImmunoCap is more sensitive, it has been suggested that both should be used to ensure appropriate diagnosis of fungal sensitization [8,22].

RELATIONSHIP BETWEEN FUNGAL SENSITIZATION AND ASTHMA SEVERITY

The exact prevalence of fungal sensitization in patients with asthma is unknown. In a study of Japanese adults with severe asthma, 29% showed sensitization to at least one fungal allergen by serum-specific IgE [18]. However, in the aforementioned study comparing SPT and serum IgE, fungal sensitization was found in 66% in patients with severe asthma [22]. In a substudy of patients with severe eosinophilic asthma, 32% of the enrolled 576 patients demonstrated sensitivity to fungal allergens (9% to fungal allergens alone and 23% to both fungal and perennial/seasonal allergens) [23²⁴]. In patients with asthma referred to subspecialty clinics, 17% had fungal sensitization in one study [24], whereas 76% had sensitization to at least one fungus in another [25]. Differences in patient populations, testing methods, and geographic locations likely contribute to the large differences seen in the prevalence of fungal sensitization in patients with asthma.

There is evidence that the prevalence of fungal sensitization increases with asthma severity. Two large studies based on the European Community Respiratory Health Survey found that fungal sensitization, particularly to *Alternaria*, in patients with asthma increased with asthma severity [26,27]. For example, sensitization to either *Alternaria* or *Cladosporium* was 22.1% in patients with severe asthma compared with 10.8% in patients with mild asthma, resulting in an odds ratio (OR) of 2.34 [95% confidence interval (CI) of 1.56–3.52] [27].

Fungal sensitization has also been associated with specific markers of disease severity, including lung function, hospitalizations, and life-threatening asthma. In a study examining the relationship between IgE-sensitization to *A. fumigatus*, culture, and clinical features of asthma, *Aspergillus* sensitization was associated with worse lung function and higher rate of detection of *Aspergillus* in the sputum [28]. Similarly, lung function was found to be lower in patients sensitized to thermotolerant filamentous fungi compared with patients not sensitized to any fungi (73% predicted versus 82% predicted) in another study of patients with asthma [25].

Fungal sensitization was present in 76% of patients requiring multiple hospitalizations for asthma but only 16% of patients with mild asthma requiring no hospitalizations [29]. Out of 11 children and young adults with asthma who suffered from respiratory arrest, 10 had positive SPTs to *Alternaria* (91%) as compared with 31% of patients with asthma with no history of respiratory arrest, resulting in an adjusted OR of 189.5 (95% CI 6.5–5535.8) for the risk of respiratory arrest with *Alternaria* sensitization [30]. Higher prevalence of fungal sensitization but not sensitization to nonfungal allergens has also been found in patients with asthma admitted to the ICU compared with patients with asthma treated in the emergency department or hospitalized for asthma and those never admitted to the hospital [31]. Similarly, Medrek *et al.* [24] found that patients with asthma and fungal sensitization were more likely to require ICU admission and mechanical ventilation than patients with sensitization to nonfungal allergens or patients without sensitization. Taken together, these studies suggest that there is a potential causal relationship between fungal sensitization and severe and life-threatening asthma.

TREATMENT OF ASTHMA WITH FUNGAL SENSITIZATION

Triazole antifungals have been successfully used in the treatment of ABPA [32], but two randomized, placebo-controlled trials using triazoles in SAFS have yielded mixed results [33,34]. The Fungal Asthma Sensitization Trial evaluated the efficacy of itraconazole in SAFS [33]. Patients with asthma who were sensitized to at least one of seven fungi were randomized to receive either itraconazole 200 mg twice daily or placebo for 32 weeks. Patients treated with itraconazole showed significant improvement in Asthma Quality of Life Questionnaire (AQLQ) scores compared with the placebo group. Secondary endpoints showed improved peak flow and decreased serum IgE in the treatment arm. However, this was a small study of 58 patients, and only 41 completed the 32 weeks of therapy. The EVITA3 study investigated the effect of 3 months of treatment with voriconazole in patients with asthma [34]. Patients with asthma and specific IgE to *Aspergillus*, and at least two severe asthma exacerbations in the prior 12 months were randomized to receive voriconazole 200 mg twice daily. The primary outcomes were change in AQLQ score after treatment and the number of severe exacerbations over 12 months. Both groups showed a decrease in the number of exacerbations and an improvement in AQLQ during treatment, and there were no differences between the

two groups. Based on the available evidence, the European Respiratory Society/American Thoracic Society severe asthma guidelines have a conditional recommendation against the routine use of antifungal agents for the treatment of asthma without ABPA irrespective of sensitization to fungi [2]. Given the lack of strong evidence of benefit and potential toxicities of treatment, further data are needed to clarify the role of azoles in treatment of SAFS.

A number of biologic agents targeting the molecular pathways of type 2 asthma are currently approved for the treatment of uncontrolled, moderate-to-severe asthma. However, studies specifically focusing on patients with asthma and fungal sensitization are limited. Omalizumab is a recombinant humanized mAb against IgE. It binds to free IgE and blocks the interaction between IgE and FcεRI receptors on mast cells, basophils, and dendritic cells [35]. Because asthma with fungal sensitization may be mediated via allergen-specific IgE, omalizumab has potential benefit in patients with SAFS and has been studied in two small, retrospective studies. One study, the results of which are only available in abstract form, reports that 76 out of 168 patients with severe asthma treated with omalizumab for 16 weeks had concomitant fungal sensitization and experienced improvement in quality-of-life as measured by the AQLQ, though this improvement was less profound than in patients without fungal sensitization [36]. In the Australian Xolair Registry, patients with asthma and ABPA or SAFS were combined and compared with patients without fungal sensitization. After 24 months of treatment with omalizumab, both groups had improvements in asthma control and number of exacerbations as well as reduction in the use of oral corticosteroids with no significant differences across groups [37^{***}]. However, this study was limited by a significant loss (32% of patients) to follow-up and the inability to distinguish effects in patients with ABPA versus SAFS.

Mepolizumab is a humanized mAb against IL-5 and is an approved treatment for patients with severe eosinophilic asthma. The MENSA study was a randomized controlled trial comparing intravenous or subcutaneous mepolizumab to placebo in patients with severe eosinophilic asthma which demonstrated that treatment with mepolizumab reduced exacerbations. A post-hoc analysis was performed to investigate the effect of fungal and/or seasonal allergen sensitization on the efficacy of mepolizumab. There was a decrease in exacerbations in all groups, though this was not statistically significant in patients with fungal only sensitization [23^{***}]. When specific sensitization was examined, there was significant improvement in exacerbations

with mepolizumab treatment in patients with sensitization to *Aspergillus* and/or *Penicillium* but not to other fungi. Overall, the studies of biologics in asthma are limited by lack of prospective, randomized studies specifically examining their effects in patients with asthma and fungal sensitization.

FUTURE DIRECTIONS

Though a spectrum of disease exists, fungal asthma may represent a unique asthma phenotype. More precise definitions are needed to describe the association between fungal sensitization and asthma, as not all patients with fungal sensitization have severe asthma or ABPM. Given the link between fungal sensitization and asthma severity, testing for fungal sensitization should be considered in patients with severe or difficult-to-control asthma. Currently, the role of azoles in the treatment of asthma with fungal sensitization is unclear due to conflicting data. The detection of fungal colonization in addition to fungal sensitization may help identify patients more likely to benefit from azole therapy. Preliminary data suggest that fungal sensitization does not negatively affect response to biologics. Therefore, patients with severe or uncontrolled asthma with indication for biologic therapy should receive it, regardless of fungal sensitization. However, more information is needed on the impact of fungal sensitization on the efficacy of biologic therapy. There are planned and ongoing clinical trials to study the efficacy of dupilumab (ClinicalTrials.gov NCT04442269) and benralizumab (ClinicalTrials.gov NCT04108962) on patients with severe asthma and ABPA.

CONCLUSION

Fungal sensitization is being increasingly recognized as an important contributor to the development, clinical course and control, and severity of asthma. However, better characterization of the spectrum of fungal lung disease in asthma is needed as presently not all patients with fungal sensitization can be classified as having SAFS or ABMA, and other phenotypes need to be characterized to describe the role of fungi in asthma (e.g., the role of fungal colonization in patients with asthma). Conflicting data exist regarding the efficacy of azoles in SAFS. Data on the role of biologics in patients with asthma and fungal sensitization are limited, and randomized controlled trials targeting this population are needed.

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Conflicts of interest

There are no conflicts of interest.

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