Allergic Fungal Airway Disease
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Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>ABPA</td>
<td>Allergic bronchopulmonary aspergillosis</td>
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<td>ABPM</td>
<td>Allergic bronchopulmonary mycosis</td>
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<td>AFAD</td>
<td>Allergic fungal airway disease</td>
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<td>AFRS</td>
<td>Allergic fungal rhinosinusitis</td>
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<td>AFTOL</td>
<td>Assembling the fungal tree of life</td>
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<td>CF</td>
<td>Cystic fibrosis</td>
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<td>CRS</td>
<td>Chronic rhinosinusitis</td>
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<td>EAACI</td>
<td>European Academy of Allergy and Clinical Immunology</td>
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<td>FDA</td>
<td>US food and drug administration</td>
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<td>FEV1</td>
<td>Forced expiratory volume in one second</td>
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<td>Ig</td>
<td>Immunoglobulin</td>
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<td>ImmunoCAP</td>
<td>Immunoassay capture</td>
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<td>IUIS</td>
<td>International Union of Immunological Societies</td>
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<td>SAFS</td>
<td>Severe asthma with fungal sensitisation</td>
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<td>SPT</td>
<td>Skin prick test</td>
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<td>Th</td>
<td>T helper</td>
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<td>Treg</td>
<td>Regulatory T cell</td>
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<td>UK</td>
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<td>US(A)</td>
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<td>WHO</td>
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Abstract

Fungi are ubiquitous and form their own kingdom. Up to 80 genera of fungi have been linked to type I allergic disease, and yet, commercial reagents to test for sensitisation are available for only a relatively small number of species. In terms of asthma it is important to distinguish between species unable to grow at body temperature and those that can (thermotolerant) thereby having the potential to colonise the respiratory tract. The former, which include the commonly studied *Alternaria* and *Cladosporium* genera, can act as aeroallergens where their clinical effects are predictably related to exposure levels. In contrast thermotolerant species, which include fungi from the *Candida, Aspergillus* and *Penicillium* genera, can cause a persistent allergenic stimulus independent of their airborne concentrations. Moreover their ability to germinate in the airways provides a more diverse allergenic stimulus, and may result in non-invasive infection which enhances inflammation. The close association between IgE sensitisation to thermotolerant filamentous fungi, and fixed airflow obstruction, bronchiectasis and lung fibrosis suggests this leads to a much more tissue damaging process than seen with aeroallergens.

This review provides an overview of fungal allergens and the patterns of clinical disease associated with exposure. It will clarify the various terminology associated with fungal allergy in asthma and make the case for a new term (allergic fungal airway disease) to capture all people with asthma at risk of developing lung damage as a result of their fungal allergy. Lastly it will discuss implications for the management of fungal related asthma.

Keywords:
Thermotolerant fungi, Allergic fungal airways disease (AFAD), Asthma, Allergic fungal rhinosinusitis (AFRS), Immune responses, Diagnosis, Treatment
Introduction

Fungi are eukaryotes, forming their own kingdom. Around 100,000 fungal species have been named [1], but estimations range from 1.5 to 3 million worldwide [2, 3]. According to the fungal tree of life project (AFTOL), the fungal kingdom can be divided into as many as 8-10 phyla. Among these the Ascomycota and Basidiomycota group together forming the Dikarya, representing approximately 98% of described fungal species [4]. These ubiquitous organisms have adapted to a variety of ecological habitats. They are involved in the degradation of decomposing organic matter in nature [5], but are also used in industry, for example in the production of food, antibiotics or enzymes [6].

Most fungi, such as the plant pathogenic *Cladosporium* and *Alternaria* species, are mesophilic; growing at an optimum temperature between 18 to 22°C. They rarely cause infection but can be encountered as allergens. Thermotolerant fungi are able to grow in the environment and at body temperature and therefore capable of acting as allergens, commensals or opportunistic pathogens [7]. Fungal pathogens have evolved independently and repeatedly throughout the kingdom [8]. They can damage their host through infection, ranging from superficial cutaneous infections to life threatening invasive mycoses, by producing toxins or by inducing allergic reactions [9]. Only a few species have been detected from the upper or lower respiratory airways [10, 11]. These include yeasts, *Candida* species in particular, *Penicillium* and *Aspergillus* species, with the latter constituting the most prominent cause of fungal lung infections.

The incidence of allergic disease, which affects around one in three people in the UK [12], has increased in modern economic societies over the last 50 years and now, and represents a considerable challenge to the healthcare industry [13]. Everybody inhales a complex mixture of hyphal fragments, fungal spores and yeasts daily [14]. The species’ composition varies between days and seasons with the highest concentrations in late summer and early autumn, where > 50,000 fungal spores per cubic meter of air per day can be present [14]. They frequently exceed the concentration of pollen grains by 100-1000 fold [9]. Numbers also vary between the outdoor and indoor environment, with indoor fungal spore concentration comprising around 16% of the outdoor concentration in non-contaminated housing [15]. The majority of airborne spores are produced by members of the Ascomycota and Basidiomycota, with asexually produced conidia comprising 30 to 60% of total airborne spores [9]. Larger spores (> 10 μm) are usually deposited in the nasopharynx and associated with hay fever symptoms, however, the majority of fungal spores are smaller ranging from 2-10 μm, including those from *Aspergillus* and *Penicillium* species [9, 16]. Small spores and fragments of larger spores can reach the lower airways [9, 17]. The quantity of fragments of some fungi can exceed their respective number of spores [18] [19].

Both the upper and lower airways try to remove the fungi by mechanical means such as the sinus turbulence or the mucociliary escalator, and by immunological means such as engulfment and digestion by alveolar phagocytes. The immune response thereby represents a balance between pro-inflammatory reduction of fungal burden and anti-inflammatory reduction of host tissue damage [20]. Most fungal allergens are released after spores germinate [21] as they are covered by a protective hydrophobin layer which enables evasion.
from the immune system [22]. Symptoms triggered by fungal allergens range from rhinitis to allergic bronchopulmonary aspergillosis (ABPA), a complication usually accompanying other lung diseases such as asthma. Thermotolerant fungi play a special role as they are able to colonise the lower airways, thereby representing a persistent allergen source. Although a few studies highlight the importance of sensitisation to fungi to human health, their contribution to allergic airway diseases is still understudied [23, 24].
Allergic immune responses to fungi

The defence against pathogens in humans is based on a combination of innate and adaptive immune responses. Traditionally, the latter discriminates T-helper cell (Th)1, Th2, Th17 and regulatory T cell responses, dependent on the pathogens and cytokines involved. Th2 responses are usually directed against parasites, whilst the antifungal response is predominantly mediated by Th1 and Th17 cells [25]. Allergic reactions represent a deranged Th2 immune response against normally harmless molecules [26]. This response is commonly associated with the production of allergen-specific immunoglobulin (Ig)E antibodies. This humoral type I immune response represents one of four classified hypersensitivity responses [27]. IgE antibodies are produced after first contact with the allergen, which renders the affected person in an asymptomatic stage called atopy. After re-exposure to the allergenic source, allergen-specific IgE antibodies bound on high-affinity receptor FcεRI of innate effector cells such as basophils and mast cells are crosslinked. This leads to the immediate release of anaphylactogenic mediators [26] and peripheral blood eosinophilia [28]. These cells reside mostly near skin and mucosal surfaces such as the respiratory or gastrointestinal tract, where the subsequent allergic reactions occur. They can manifest as IgE-associated atopic dermatitis [29], allergic rhinitis or rhinosinusitis, allergic asthma or food allergy [23]. A sensitised individual does not have to experience symptoms, which may depend on the level of exposure, or other contributing factors during exposure, such as the individuals’ health condition and their immune system [30, 31].

Type I hypersensitivity reactions have been observed to about 80 fungi, predominantly to species from the Ascomycota [24]. The prevalence of sensitisation to fungi is unclear, although estimates suggest 3 to 10% of the general population, 12 to 42% of atopic patients and up to 66% of patients with severe asthma may be sensitised to fungi [9, 10, 32]; yet, not all of those sensitised will develop allergic symptoms [5]. Prevalence varies with age [33, 34] and can differ between countries [35]. Surveys based on skin prick testing (SPT), which is relatively insensitive for some fungal allergens, may underestimate prevalence of IgE sensitisation.

Type IV hypersensitivity reactions, also called delayed-type hypersensitivity reactions, may also play a role in allergic fungal airways disease. The type IV responses are T cell-mediated, inducing apoptosis of target cells [27]. Both type I and IV hypersensitivity responses are observed in ABPA [36, 37].

Fungal allergens can be secreted, cytoplasmic or structural proteins [24, 38]. Based on known allergens, predicted allergens and the results of IgE binding to phage libraries it has been suggested that 0.5 to 1% of the proteins within a fungus may be allergens [39]. Although more than 80 fungal genera have been associated with allergy [9], the World Health Organization (WHO) and International Union of Immunological Societies (IUIS; www.allergen.org, October 2016) list only 111 allergens from 29 fungal species. The majority of allergenic proteins are from the classes of proteases, glycosidases, protein synthesis/secretion, stress response proteins and gluconeogenesis [40]. The allergen profile can differ between fungal spores and germinated hyphae, and germination increases the amount of detectable allergens [21].
A person can be co-sensitised to multiple allergens [41]. Fungi most associated with fungal polysensitisation are *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium chrysogenum* and *Saccharomyces cerevisiae*, whilst monosensitisation occurs most commonly in individuals sensitised to *Alternaria alternata* [42]. The extent to which polysensitisation is due to cross-sensitisation between fungal allergens as opposed to primary sensitisation is unclear [43]. An argument for the latter would be that fungal sensitisation is often associated with sensitisation to other airborne allergens [42]. While a few allergens are unique, such as the major allergens from *A. fumigatus* (Asp f 1) and *A. alternata* (Alt a 1) [38], the same or very similar epitopes can be shared between different organisms, which can include self-antigens [38, 44]. These epitopes often derive from proteins with similar functions, produced by different species, so-called orthologues [39]. This has been observed between closely-related species such as *P. chrysogenum* and *P. citrinum* and distantly related species such as *Candida boidiini* and *A. fumigatus* [45-47]. Cross-reactivity among fungal allergens may result in false-positive sensitisation tests and may contribute to exacerbation of allergic symptoms in conditions like ABPA. However, the clinical significance of cross-reactivity among fungal allergens requires further investigation [38].

Another factor to consider with fungal polysensitisation is genetic predisposition as suggested by an Italian study, where 82.9% of fungal-sensitised children had a family history of fungal sensitisation [48]. However, there are few studies that have explored the genetic basis of fungal lung disease other than some work linking human leukocyte antigen genotypes with ABPA [49, 50].

### Diagnosis of fungal allergy

It is unclear how much exposure to fungi over which time frame is necessary to trigger sensitisation, or how much genetic factors or immunoregulatory elements play a role, since not everyone becomes sensitised. In general, until a person is known to be allergic to a certain component, that individual has to go through a process of anamnesis and allergen-reactivity tests. The SPT is most commonly used for the diagnosis of sensitisation. The SPT is not as sensitive as intradermal tests [51], but has a lower rate of false positives [31]. In addition, blood tests for specific IgE are available with the immunoassay capture (ImmunoCAP) system being the preferred platform [23].

In 2004, extracts for 75 fungal species were available between 7 different US manufacturers [52], however, none of these have been approved by the FDA [23]. Fungi are usually not included in a standard SPT or specific IgE test panel because of a low index of suspicion that they are clinically relevant. Individuals suffering from fungal allergies are often not aware of fungi as a potential allergen source since they are frequently co-sensitised to other aeroallergens such as grass pollens, peak at similar times. If included, the most commonly fungi tested are *A. alternata* and *C. herbarum*, which are recommended by the European community health survey [35]. However, for a more encompassing understanding of fungal sensitisation, the panel should also include *A. fumigatus*, *P. chrysogenum*, *Candida albicans*, *Malassezia* and *Trichophyton* species and *Saccharomyces cerevisiae* [7, 10]. Most
sensitisation assays test against fungi within the Ascomycota, in particular conidia-producing anamorphs (asexual forms) or yeasts [9]. The prevalence of sensitisation to basidiospores (sexual spores from the Basidiomycota) is thought to be similar but not often tested for, and allergic reactions to ascospores (sexual spores from the Ascomycota) are understudied [9]. Non-Dikarya fungi such as *Rhizopus* and *Mucor* species have also been implicated in asthma [10]. However, the number of described species is far higher and many potential allergens are not well characterised.

Discrepancies between SPT and specific IgE make it difficult to ascertain the fungal sensitisation of an individual. Studies comparing SPT and specific IgE are often discordant in both asthma [32] and rhinitis [53]. The SPT has a high negative predictive value whilst the ImmunoCAP is more sensitive, so some authors suggest using both [32].

It is important to note, that sensitisation pattern changes with age [54-56], suggesting that measurement of sensitisation has to be repeated over time.

A possible reason for the problem of discordance is the fact that fungal extracts are not standardised and differ between SPT and IgE. Extracts vary between companies, and even between batches from the same company. The choice of the fungal strain, culture conditions, protein source (spores, hyphae or secreted proteins) and extraction protocols used can all influence the allergen content and antigenicity of fungal extracts [9, 52].

**Conditions related to fungal allergy**

*Allergic fungal rhinitis and allergic fungal rhinosinusitis (AFRS)*

One entrance point for fungi to the respiratory system is the nose, which is reflected in high culture rates from nasal mucus [57]. Up to 40% of the population suffers from allergic rhinitis with symptoms such as sneezing or clear rhinorrhea, which results in sleeping problems and decreased quality of life.

AFRS represents 5-10% of chronic rhinosinusitis (CRS) in immunocompetent patients and is caused by fungal colonisation of a sinus with impaired mucociliary clearance [40]. AFRS represents 6-9% of CRS requiring surgery [58]. Only around 50% of AFRS patients are asthmatic [59]. AFRS is mostly associated with *Aspergillus* species, followed by *Bipolaris, Curvularia* and *Alternaria*. Other fungi such as *Rhizomucor* and *Fusarium* have been rarely implicated [60, 61]. AFRS was first observed in a patient diagnosed with ABPA in 1976, who had ABPA-typical fungal mucus plugs within the paranasal sinuses, which is a thick eosinophilic secretion [62]. This is why AFRS is sometimes described as the upper airway version of ABPA, even though they rarely coincide [63, 64]. AFRS causes nasal airway obstruction, unilateral chronic sinus infection, thick dark mucus rhinorrhea, impaired postnasal drainage, facial pain and pressure, as well as orbital or facial distortion in advanced disease [65, 66]. The major diagnostic criteria for AFRS are: sensitisation to several fungi and other allergens, nasal polyposis, abnormalities seen by computed tomography, eosinophilic mucous, fungal presence without tissue invasion and positive fungal stain of sinus contents [40, 65, 67]. Other characteristics include paranasal sinus mucoceles, high
attenuation sinus contents, bone remodelling of sinuses, orbit and skull base [68], higher total IgE [59] and T-cell mediated eosinophilic inflammation [40]. The underlying immune response of AFRS are type I, IgG-mediated type III and type IV hypersensitivity responses. This subsequently leads to impaired draining of the mucus through the sinonasal passages, which promotes fungal growth and inflammation.

Asthma

Asthma is a chronic disease, which affects > 300 million people worldwide [69]. The disease is a huge burden on health systems with £500 billion per year being spent in the UK alone [70]. Patients suffer from variable airflow obstruction and a range of symptoms including breathlessness, airway inflammation, and reduced expiratory volume in one second (FEV1) [69]. The symptoms are the result of pathophysiological abnormalities, including changes in the resistance to airflow and airway hypersensitivity responses of the airway smooth muscle cells, leading to contraction [71]; increased cough reflex, mucus hypersecretion and lung damage, expressed as fixed airflow obstruction, bronchiectasis, lung fibrosis [7, 72], subepithelial membrane thickening, smooth muscle hypertrophy and hyperplasia [73-75]. These abnormalities are independent of each other, resulting in a high heterogeneity of the disease. Consequently, various endotypes have been defined, including allergic asthma [76, 77].

There have been several studies amongst both paediatric and adult populations that have associated outdoor and indoor fungal exposure with symptoms of asthma including hospital admissions [78-81], decreased lung function, increased use of asthma medication and greater risk of cough [82-86] or as causative agents of asthma [87-89].

IgE-mediated fungal sensitisation is frequently present in early onset atopic eosinophilic asthma [7]. Sensitisation to fungi, particularly to Alternaria, has been associated with life-threatening acute asthma attacks [90], asthma-related deaths [91] and as causal agents of asthma [92-94].

Severe asthma is present in 5-10% of asthmatics, which means they require high doses of medication to treat their symptoms or experience symptoms despite optimal treatment [95]. Fungal exposure has been associated with asthma severity [96]. Almost 40% of children with asthma are fungal sensitised, but prevalence is as high as 60% in children with severe asthma [97], which may persist into adulthood. The prevalence of fungal sensitisation in adults with severe asthma is up to 70% [98], but can be as high as 76% of those requiring multiple hospital admissions [96]. Patients suffering from severe asthma are also more commonly co-sensitised to multiple fungi [32]. People with moderate to severe asthma who are sensitised to Aspergillus have impaired lung function as shown by reduced FEV1, increased severity of airway obstruction and require higher corticosteroid doses [99, 100]. A 22% drop in lung function was associated with fungal sensitisation and fungal-positive sputum culture in moderate to severe asthmatics [101]. The majority of recovered fungi were isolates of A. fumigatus, however, more than 20 other taxa were also detected [101]. There are also indications of a higher rate of tissue damage and inflammation in Aspergillus-sensitised asthmatics as more cases of bronchiectasis, higher eosinophil counts and IgE levels have been
Patients suffering from moderate-to-severe asthma, who were IgE-sensitised to *A. fumigatus* had significantly higher culture rates of this fungus (63%) compared to non-sensitised asthmatics (31%) and healthy controls (7%) [100]. These studies indicate that fungal colonisation seems to play a role as a continuous allergic stimulus. It is important to distinguish between fungal allergy due to non-thermotolerant species such as *C. herbarum* and *A. alternata*, which act as aeroallergens where clinical effects are predictable based on the spore count, and thermotolerant species such as many from the *Aspergillus* and *Penicillium* genera that can colonise the airways and cause a persistent chronic allergic stimulus which is likely to have more troublesome and unpredictable consequences.

*A. fumigatus* is by far the most common fungus associated with all forms of fungal lung disease although other *Aspergillus* species such as *A. niger*, *A. flavus*, and *A. nidulans* can also play a role [102]. Besides *Aspergillus* species, *C. albicans*, *Bipolaris* species, *Schizophyllum commune*, *Curvularia* species and *Pseudallescheria boydii* species have been listed as involved in asthma although these are usually case reports where there has been an occurrence of culture with disease. A convincing case for a causal association is not always made. Clinically relevant fungal allergy is usually present alongside other respiratory diseases such as cystic fibrosis (CF) and asthma, but can occur in absence thereof [31].

Evidence of fungal allergy complicating airway disease is found in about 7-9% of CF patients [10] and 0.7%-3.5% of patients with asthma [103] but this does depend on the criteria used as discussed below. In severe asthma there is a case that over a quarter of subjects have significant involvement from fungal allergy. Fungal allergy was defined as an endotype of asthma by an EAACI Task Force [77].

The semantics of fungal allergy associated airway disease

The term allergic bronchopulmonary aspergillosis (ABPA), or mycosis (ABPM) when another fungal genera was involved, has dominated both the literature and conceptual approaches to fungal allergy in relation to asthma and CF. The term was first coined in the 1950s in a small case series describing a pattern of severe lung damage associated with fungal sensitisation [104]. Further case series were published, mainly from the UK and USA, in subsequent decades culminating in the 1970s in a description of the immunological and radiological features that characterised these patients, such as eosinophilia, fixed airflow obstruction, and bronchiectasis. This became established in the literature as a firm set of diagnostic criteria although it was based on a relatively small number of patients and was anecdotal without any of the statistical underpinning that would be expected in modern practice. The problem with the criteria is that they are largely based on a florid immunological response to fungal sensitisation characterised by high levels of total IgE and specific IgG. An IgE of >417 IU/L (or 1000 IU/L in some reports), is given great prominence [7, 105]. However the total IgE is not a very specific or sensitive marker of fungal associated lung disease. While levels of IgE of >1000 IU/L almost invariably denote the presence of IgE sensitisation to thermotolerant fungi, this can be due to yeasts such as *Candida* or skin commensals such as *Malassezia* or *Trichophyton*; IgE sensitisation to which is common, particularly if there is a history of
eczema which often accompanies asthma. Even where the raised IgE is due to *Aspergillus* or *Penicillium* sensitisation, patients may have normal lung function with little evidence of the lung damage, which is the hallmark of allergy to thermotolerant fungi. In addition many patients with an IgE of $<417$ IU/L sensitised to fungi do have evidence of lung damage. The restrictive nature of the criteria for ABPA has meant that they do not make much sense to the practising clinician and as a result the term ABPA has tended to be used rather loosely to describe asthma where the clinician believes fungal allergy may be playing a part, and as a result the term has lost credibility. A number of attempts have been made to revise the criteria over subsequent decades but the problem is that there has often been an element of circularity where the criteria for ABPA have been used as the gold standard starting point for the revision [105]. An alternative approach was taken by the group in Manchester who recognised the problem with total IgE and got around this be using the term severe asthma with fungal sensitisation (SAFS) to refer to anyone with severe asthma and IgE sensitisation to any fungi with an IgE of less than 1000 IU/L. However again this definition was based on the arbitrary cut off of 1000 IU/L which is problematic in a condition where the total IgE varies considerably over time. In addition it includes people who are sensitised to non-thermotolerant fungi and yeasts which are not obviously associated with lung damage in the same way as thermotolerant filamentous fungi. In addition many patients with fungal lung disease do not necessarily have asthma as usually defined (fungal allergy has a heterogeneous presentation), and if they do have asthma this may not fit the criteria for severe asthma. The starting point for any discussion about the clinical relevance of fungal allergy should be what distinguishes it from asthma without fungal allergy. The evidence points towards lung damage with fixed airflow obstruction, bronchiectasis and other radiological abnormalities such as fleeting shadows, mucus plugging and lung fibrosis as being particular features of AFAD. The question then should be, what are the best biomarkers of the presence of lung damage? We have studied a population of 431 patients with generally severe asthma (broadly defined) enriched for those with fungal allergy to determine the relationship between immunological markers of sensitisation, lung function and radiological abnormalities [106]. The best biomarker was a positive specific IgE to *A. fumigatus* or *P. chrysogenum*. This was independent of atopy. The total IgE was associated with fleeting lung shadows (present in a fraction of patients), but no other features of lung damage. We concluded that total IgE was not helpful in determining who was at risk from developing lung damage due to fungal allergy. However an unbiased cluster analysis picked out a small (~10%) population, who had a florid immunological response to fungi with a very high total IgE, poor lung function (post-bronchodilator FEV$_1$ 63% predicted) and high rates of bronchiectasis (80%). This group all met the criteria for ABPA and presumably represents those patients from where the concept of ABPA was derived. However equal numbers of patients who fitted the criteria for ABPA were found in the other clusters emphasising the difficulty of separating ABPA from the general population of people with allergic sensitisation to fungi in any statistically meaningful way. The conclusion from this study was that the only useful biomarker to predict risk of developing lung damage in asthma from fungal allergy is a positive IgE to thermotolerant filamentous fungi [106]. While a small subgroup of patients with a florid immunological response are at higher risk of developing lung damage, separating them out from the much larger body of patients with fungal allergy by using the term ABPA gets in the
way of appreciating the full spectrum of fungal allergy related lung disease. To describe
patients with airway disease who are IgE sensitised to thermotolerant fungi mainly of the
*Aspergillus* and *Penicillium* genera we prefer the inclusive term **allergic fungal airways
disease (AFAD)** which can be qualified in terms of severity and also the underlying
condition (e.g asthma, CF) if appropriate [7].

**Treatment of AFAD**

Therapeutic strategies against AFAD include allergen avoidance, antifungal medications,
surgery and immunotherapy.

**Allergen avoidance**

Allergen avoidance is difficult as fungi are ubiquitous in nature. This is further complicated
by a lack of allergenic thresholds for most fungi. The exception being *Alternaria* and
*Cladosporium* were 100 spores for *Alternaria* and 3,000 spores for *Cladosporium* per cubic
metre of air is known to evoke allergic symptoms [107], with these thresholds frequently
exceeded outdoors during the late summer and autumn. Gardening, particularly involving the
making of compost and collection of dead and rotting vegetation, is a potentially important
source of high levels of fungal spores and gardeners with fungal allergy should wear masks
during these tasks. Various occupations such as industrial composting and farming also bring
people into contact with high levels of fungal spores, and many such industries have
avoidance strategies in place. The risk of fungal exposure within buildings can be avoided by
moving from the building [108] or decreased by active interventions such as removing visible
mould or water damaged materials and application of fungicides [109-113]. The effectiveness
of these strategies remains controversial and as a result, general guidelines for mould
avoidance are still not established.

**Asthma treatment**

Many patients with AFAD have severe asthma which requires intensive treatment, usually at
the top stages of the British Thoracic Society guidelines. Sometimes this involves frequent
courses of high dose oral corticosteroids or continuous oral steroids. However as a group
acute severe exacerbations are not a particularly prominent feature of AFAD and periods of
poor control tend to be more chronic coming on over days and weeks rather than hours and
often lasting for months. Because of the frequency of bronchiectasis exacerbations may be
caused by a bacterial bronchitis which can be stubborn to treat. Omalizumab has been used
anecdotally with success in patients with ABPA [114-116], but there are no clinical trials of
this treatment specifically in patients with AFAD. In patients with severe fixed airflow
obstruction pulmonary rehabilitation, a program of exercise, education and support provided
by clinically trained staff, is appropriate.

**Antifungal therapy**

The key difference between the management of asthma with and without fungal
complications is the potential role of antifungal therapy. Since fungal airway colonisation is
thought to be the underlying trigger for AFAD there is a strong rationale for treatment with
antifungal agents. However both clinically, and in the small number of well randomised clinical trials that have addressed this question, the outcome or treatment is often disappointing. Four randomized-controlled trials have assessed antifungal treatment in asthma associated with AFAD. Three used itraconazole [117-119], the fourth used voriconazole [120]. Although the disease names and inclusion criteria were slightly different in each study they were all treating essentially the same population of patients. There was a modest benefit at best in the three itraconazole studies and no improvement with voriconazole. The benefits seen with itraconazole may well have been due to its corticosteroid enhancing effects [121] which are less prominent with voriconazole. The reason for the minor benefit of triazole antifungal agents may be due in part to the difficulty in eradicating the fungi from the airways due to lack of penetration of the drug into the bronchial lumen [122, 123]. In our study [120] 40% of subjects still had at least one positive culture while taking voriconazole. In addition rates of positive sputum culture returned to baseline within 2 months of stopping the intervention. Triazoles are more likely to be effective when there is active infection. In AFAD this is usually manifested as a fungal bronchitis in which there is production of large amounts of mucopurulent sputum which contains a heavy growth of filamentous fungi. Relatively few patients with AFAD suffer from this problem, but it is these patients who anecdotally do well with antifungal therapy. Selection for treatment with antifungals therefore needs to be based on carefully selecting those patients with an active bronchitis reflecting heavy fungal colonisation as shown by culture of airway secretions. As culture methods for sputum fungal culture are not standardised or quantified and often insensitive [124] fungal bronchitis is not well recognised or characterised. Fungal bronchitis is however a common problem in all airways disease irrespective of IgE sensitisation and often involves yeast as well as filamentous fungi.

Treatment strategies for AFRS were extensively reviewed by Ryan et al. [65]. AFRS is usually treated by surgery in order to remove the polyps and eosinophilic mucin, clear the affected sinuses and create access for topical intranasal medication. If the sinuses are not completely cleared, inflammation will continue and resistance to anti-inflammatory drugs occurs. Patients can take nasal irrigations and intranasal steroids to reduce inflammation and maintain sinus drainage. AFRS patients, who were followed-up for 7 seven years, had to undergo two more surgeries and repeated courses of oral steroids on average per year, thereby showing persistent polypoid mucosal edema and increased total IgE. The advantage of antifungal treatment with itraconazole has not been unambiguously demonstrated. While itraconazole intervention improved endoscopic appearance and reduced the use of oral steroids as well as the relapse phase (30%) in some studies, it was non-effective or even worsened the conditions in 63% of AFRS patients elsewhere. In contrast to oral itraconazole treatment, local treatment with fluconazole nasal spray was beneficial, resulting in the lowest recurrence rate (10%), whilst 66.7% recurrence was shown with itraconazole. However, the clinical benefit of antifungal treatment requires further investigation [65].

**Immunotherapy**

Immunotherapy can cure allergic diseases or reduce symptoms and medication usage. The WHO guidelines for safe and effective immunotherapy recommend the use of well-defined
vaccines for carefully selected patients [125]. However, fungal extracts are not standardised [9, 52] and immunotherapy is not recommended for patients with asthma, showing high frequencies of adverse reactions [30]. As reviewed by Twaroch et al. [30], only a limited number of controlled immunotherapy trials exist, showing inconsistent results and a small clinical benefit of *A. alternata* and *C. herbarum* extracts in subjects suffering from rhinoconjunctivitis and/or mold-induced asthma. Subcutaneous immunotherapy with *C. herbarum* extract resulted in decreased bronchial, conjunctival and skin reactivity, increased peak expiratory flow and decreased medication score, however, symptoms were not significantly different between treatment and placebo group. Similar results were obtained with subcutaneous or sublingual immunotherapy using extracts from *Alternaria* species. An increase in IgG levels, including IgG4, was frequently observed [30], which is generally considered favourable in immunotherapy. Its production probably derives from the activation of regulatory T cell (Treg) activation, which is crucial for tolerance. The non-inflammatory isotope is thought to prevent antigen-binding of IgE and therefore subsequent mast cell and basophil activation. Due to its poor binding property, serum levels itself are not an indicator of its protective function, and neither is a decrease of IgE an indicator of a decreased response to allergens. Instead, it is more likely that the IgE/IgG ratio in serum shows a predominance of Tregs over Th2 cells [126].

The use of recombinant fungal allergens in immunotherapy has not been assessed yet, although it was demonstrated that a hypoallergenic derivative of Asp f 2 [127] and Alt a 1 efficiently blocked IgE-binding in sera of fungal-sensitised patients [128]. Similar results were obtained with mutated Alt a 13 allergen, which also resulted in reduced IL-4 production by T cells by Alt a 13-treated peripheral blood mononuclear cells [129]. These studies are a good basis for further clinical trials using recombinant allergens, although more clinically relevant allergens need to be determined in the population before a widespread vaccine can be used [30].

**Conclusion**

IgE sensitisation to fungi is common in asthma, particularly in its more severe manifestations, affecting both children and adults. The clinical outcomes from allergy to aeroallergens such as *Alternaria* and *Cladosporium* are predictable from their spore levels and cause short-term allergic manifestations similar to grass pollen. The clinical impact is relatively modest considering the very high levels of spores in the summer and autumn, possibly because the spore envelope is relatively non-allergenic and the spores in some cases are too large to access the lower airways. Certain climatic conditions such as summer thunderstorms disrupt spores causing them to be more potent. In contrast thermotolerant fungi such as *Aspergillus* and *Penicillium* species can colonise the lung where they create more persistent allergenic stimuli and, when there is heavy colonisation, an infective component. This leads to progressive lung damage due in part to chronic obstruction of the airways with viscid mucus. All asthmatics who are IgE sensitised to these fungi are at risk of developing lung damage, but there is a subset with a florid immunological response who are at the greatest risk. However, under present knowledge, there are no criteria other than IgE sensitisation to thermotolerant filamentous fungi that can select this or any other sub-group in a clinically
useful way, so we prefer an inclusive term such as allergic fungal airway disease (AFAD) to identify asthmatics at risk from fungal allergy as opposed to exclusive terms such as ABPA or SAFS which exclude significant numbers of relevant patients from consideration.

Treatment of AFAD is similar to severe asthma with the exception that triazole antifungals have a place in the treatment of an accompanying fungal bronchitis.


111. Shortt N, Rugkasa J. "The walls were so damp and cold" fuel poverty and ill health in Northern Ireland: results from a housing intervention. Health Place. 2007;13(1):99-110.


