

Fungal Allergy as Yet Unsolved

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Introduction

In the 1870s, Blackley [1] described allergic symptoms as a consequence of exposure to fungi. Often referred to as “molds,” fungi belong to Kingdom Mycota, a biological kingdom separate from plants and are widely distributed around the world [2]. The classification of fungal species is in flux as new genetic techniques supplement the traditional identification of fungi based on their culture characteristics and microscopic spore morphology [3–5]. Some of the more common fungi that lead to allergic disease are listed in Table 1. This chapter will discuss the relevance of fungal exposure to various health effects, particularly with regard to immunologically-mediated conditions affecting the respiratory system.

Most fungal exposure occurs outdoors [2]. A number of fungal taxa have been found in atmospheric samples, some of which can only be identified by culture techniques due to the similarity in appearance of fungal spores, such as ascospores and basidiospores [2]. Surveys conducted in the U.S. show that ascospores, basidiospores and *Cladosporium* species comprise the majority of spores observed in outdoor samples [2]. Typically during wet weather, ascospores and basidiospores predominate, while during dry weather, Deuteromycetes (e.g., *Alternaria*, *Cladosporium*) are prominent [6]. Local concentrations of allergenically important taxa such as *Alternaria*, are common in various areas of the world [7]. The most well-known group of allergenic fungi are the Deuteromycetes (an artificial grouping) or Fungi Imperfecti (hypomycetes), which represent the asexual forms of ascomycetes [2]. New genetic techniques indicate that many fungi species exist in two stages – those that reproduce sexually (e.g., Ascomycetes) and those that reproduce asexually (e.g., Deuteromyces) [3–5]. Since these are stages of a single organism, allergen exposure attributed to one fungal species may occur from other forms of the same fungus. Depending on the sampling methodology, spore counts

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Table 1 Frequently encountered allergenic fungi

<i>Deuteromycetes (hypomycetes) or Fungi imperfecti</i>
<i>Alternaria</i> esp. <i>Alternaria alternata</i>
<i>Aspergillus</i> species esp. <i>Fumigatus</i>
<i>Cladosporium</i> species esp. <i>herbarium</i> and <i>C. cladosporoides</i>
<i>Penicillium</i> species <i>P. chrysogenum</i> (notation), and <i>P. citrinum</i>
<i>Drechslera</i> species
<i>Epicoccum nigrum</i>
<i>Fusarium</i> species
<i>Curvularia lunata</i>
<i>Ulocladium</i> species
Ascomycetes
<i>Chaetomium</i> species
Zygomycetes
<i>Mucor</i> species
<i>Rhizopus nigricans</i>
Basidiomycetes
<i>Carpinus</i> species
<i>Ganoderma</i> species
<i>Psilocybe cubensis</i>
<i>Pleurotus ostreatus</i>
Yeasts
<i>Candida albicans</i>

can vary tremendously in the sample. The use of impaction samplers such as RotoRod™ (Surveillance Data, Inc., Plymouth Meeting, PA) may miss capturing smaller spores and, therefore, falsely lower the actual concentration of certain spores in the atmosphere. Suction devices such as Burkard samples (Burkard Mfg, Rickmansworth, Herdfordshire, England, Hertfordshire, United Kingdom) and Allergenco (Allergenco MK-3 [formerly Samplair], Allergenco, San Antonio, TX) capture the smaller spores and give a better understanding of the range of concentrations of microscopically identifiable fungal spores [8]. Figure 1 shows the distribution of these in the United States. The terms “low, moderate, high and very high” spore counts simply represent historical data based on the observed concentrations of spores in the atmosphere [6], and, therefore, these concentrations do not necessarily predict the clinical response of a sensitized patient.

Certain genera of fungi, such as *Aspergillus* and *Penicillium*, often account for indoor exposures, although these may also be encountered in outdoor environments as well [9]. Sampling techniques in the indoor environment involve more than just airborne spore counts, but include culturing of materials with evident fungal growth [10]. Cellophane tape lifts of growing fungi may reveal spores that can be identified directly by microscopy [10]. Newer advances include measurement of fungal allergen concentrations from airborne or settled house dust samples [8, 11, 12]. One can also measure ergosterol, which is found in cell walls of fungi, but it is also found in other microbes [8]. Glucans found in fungal cell walls can be assayed, and they have been investigated in terms of their potential to create inflammatory airway changes [13, 14]) (as well as therapeutically altering Th2 responses)

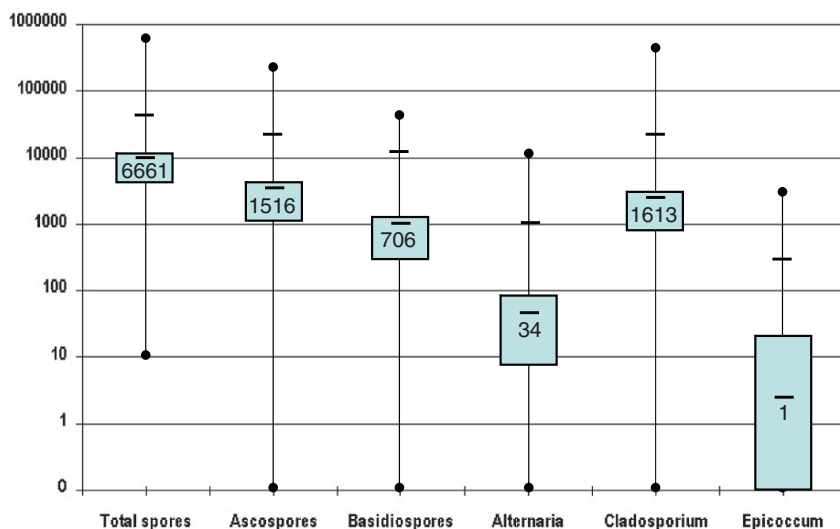


Fig. 1 Box plots of total spores, acrospores, bascidiospores, and three genera form National Allergy Bureau station as measured by Burkard samplers in the United Stated based on the 2000 Pollen and Spore Report (Used with permission from the National Allergy Bureau and all of its station American Academy of Allergy, Asthma and Immunology, November 2005)

[15, 16]. Mycotoxins can also be assayed which have particular relevance in the current climate of concern regarding their effect on health in individuals exposed to indoor fungi [17, 18].

Fungal Allergens

The advent of molecular biology approaches to identify and purify allergens has led to tremendous improvements in our understanding of biological role and relationship of allergens from a variety of sources. This has proven especially valuable in understanding fungal allergy [19–21]. Clearly, highly conserved functional protein in fungi can act as allergens and are distributed over a variety of fungal species (e.g., enolase, dehydrogenases, P₂ ribosomal proteins).

Table 2 lists some of the more important allergens that have been identified either by protein purification techniques or the newer molecular biological techniques. An extensive listing of reported fungal allergens can be obtained via the Allergome website (www.allergome.org). This valuable source of information lists purified fungal allergens, their biological characteristics, and studies on their use as diagnostic or therapeutic agents. The Allergenome database is updated monthly and, therefore, gives current information on virtually all purified and characterized fungal allergens. The molecular biology of fungal allergens has

Table 2 Some characterized fungal allergens

Species	IUIS description	Function
<i>Alternaria alternata</i>	Alt a 1	Unknown
	Alt a 11	Enolase
<i>Aspergillus fumigatus</i>	Asp f 1	Mitogillium (Ribotoxin)
	Asp f 13	Alkaline
		Serine protease
<i>Penicillium chrysogenum</i>	Pen ch 13	Alkaline
		Serine protease
<i>Cladosporium herbarium</i>	Cla h 1	Unknown
	Cla h 6	Enolase

opened up new horizons for research and classification of fungal species. Since fungi exist in more than one recognized form, genetic studies on fungi show that often there are similar proteins in other fungal and nonfungal sources [3, 4]. The full genomic sequencing of *Aspergillus fumigatus* has led to a better understanding of *Aspergillus* allergen gene sequences in the revision of gene databanks and fungal allergen nomenclature [4].

The identification, purification and characterization of allergens also allow for the production of monoclonal antibodies to these allergens, which are subsequently utilized to ascertain the concentration of allergens in diagnostic and therapeutic vaccines [22, 23]. Further, the development of immunoassays to quantitate allergen exposure either in air or dust samples from indoors have greatly expanded our knowledge about a variety of allergens, e.g., house dust mites, cat, cockroach, and mouse [24–27]. These techniques are utilized in assessing the concentration of fungal allergens from environmental samples as well [12]. However, work in this area has lagged behind that of other allergen sources. Studies from the U.S. utilizing rabbit antisera, instead of monoclonal antibodies, in immunoassays detected the presence of *Alternaria* allergens in the indoor environment in settled dust samples [11]. The detection of indoor *Alternaria* antigens in the samples correlated with the presence of asthma symptoms in individuals residing in such homes [28]. Of note is the fact that fungal allergens may not be detectable in nonviable spores. However, upon germination, major allergens such as Asp f 1 are readily secreted into the environment and detectable by these immunoassays [29]. Similar results have been demonstrated with *Alternaria* [30].

Health Effects of Fungal Exposure

The health effects related to fungal exposure include IgE-mediated sensitivity, which can elicit the symptoms of allergic rhinitis and allergic asthma [17]. Allergic fungal sinusitis (AFS) and allergic bronchopulmonary aspergillosis (ABPA) represent diseases in which fungi colonize (particularly *Aspergillus*) either in the sinuses or the bronchi where they produce allergens that induce both T and B cell responses [5]. Hypersensitivity pneumonitis may result from fungal exposure that induces

T-cell and B-cell pathogenic mechanisms that do not involve IgE [17]. Fungal infections primarily occur in immune-compromised individuals, but some organisms can infect normal, healthy individuals as well (e.g., blastomycosis).

Toxic effects of fungi may occur with high-level exposure to mycotoxin. (e.g., mycotoxicosis in silage workers). While a variety of health effects have been attributed to indoor fungal exposure (toxins), many are poorly characterized and represent a highly controversial area [31]. Idiopathic pulmonary hemorrhage/hemosiderosis occurring in infants has been attributed to exposure to *Stachybotrys*, although this also remains a controversial area [32, 33].

Fungi produce volatile organic compounds that are easily detected by their distinct odor. These compounds include alcohols and aldehydes that may produce irritant effects in the eyes and respiratory tract [34, 35]. Since fungi typically inhabit very moist environments, the musty smell of fungi also indicates that unseen, ubiquitous house dust mites may also be present.

The role of fungi sensitivity in allergic rhinitis is not as well investigated as it has been in asthma [7]. Clearly, in many patients who exhibit positive fungal allergen skin tests and experience rhinitis symptoms that persist past time of the first frost (in climates with distinct seasons), which may be in part due to exposure to fungal spores that prevail in the air until there is snow cover on the ground. Perennial symptoms may occur from indoor fungal exposure.

Allergic fungal sinusitis (AFS) represents a distinct entity (the diagnostic criteria are found in Table 3) [5]. Individuals with AFS develop sinus colonization with fungi frequently after being exposed to repeated courses of antibiotics. They are immunocompetent and often manifest nasal polyposis. The characteristic pathologic finding is "allergic" or eosinophilic mucin, which, with appropriate staining (Giemsa-Gomori silver staining) may reveal the presence of fungal hyphae. On computerized tomography, very radiodense areas (due to ferrous compound leposition) with the sinus cavity and bony erosions (due to the expansion of inspissated secretions) may be seen. Affected individuals may exhibit immediate positive skin tests to the responsible fungus (e.g., *Aspergillus*, *Bipolaris*). Treatment of AFS involves surgical drainage and courses of oral corticosteroids. It is not clear if oral antifungal therapy plays a significant role in the management of these patients [36, 37]. While subcutaneous immunotherapy has been touted to be beneficial [38], this modality has not been subjected to double-blind, placebo-controlled trials.

A syndrome termed "chronic rhinosinusitis" has been used to describe patients with typical chronic sinusitis (often associated with nasal polyposis) and have culturable fungi (e.g., *Alternaria*) in surgical specimens [39]. It has been postulated that the fungus induces mucosal inflammation by activating eosinophils

Table 3 Diagnostic criteria for Allergic fungal sinusitis

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- Normal immune status (e.g., no HIV, B- or T-cell deficiency)
 - Presence of nasal polyposis
 - Characteristic computerized tomographic findings (e.g., bony erosions, radiodense areas in sinus)
 - Eosinophilic mucin with fungal hyphae
 - Demonstrable IgE sensitivity to implicated fungus (e.g., positive skin-prick test or *in vitro* test)
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(via PAR-2 receptors) [39, 40] and that treatment with sinus-nasal irrigations continuing antifungal agents may be beneficial [41]. However, scrutiny of the controlled trials of the antifungal irrigations demonstrates limited benefit, and it is questionable whether such approaches can be generalized to all patients who have chronic sinusitis [42].

The Role of Fungi in Asthma

Recently, epidemiologic studies suggest that fungal sensitivity plays an important role in the development, persistence and severity of allergic asthma [7]. Many individuals throughout the world are sensitive to various fungi, particularly *Deudermomyces* species [5]. Testing for basidiomycete sensitivity has proved problematic since commercially-available extracts are not available, but research studies that employed basidiomycete skin test extracts demonstrated a significant rate of sensitization among individuals with allergic respiratory diseases [43]. Depending on the locale, approximately 25% of individuals appearing for evaluation of rhinitis or asthma have a positive skin test to one or more fungal species [43].

Sensitivity to *Alternaria alternate*, especially, appears to be associated with asthma [7]. Several studies indicate that it is a major sensitizer in children with asthma [7, 44–46]. Children who are sensitized early in life continue to have persistent asthma [44]. More importantly, several studies have shown near-fatal attacks of asthma being associated with sensitivity and exposure to this fungus [44, 47]. Urgent visits for acute asthma episodes have been correlated with *Alternaria* sensitivity and exposure to its spores in the atmosphere [48], and a recent publication demonstrated that fragmented *Alternaria* spores in the air and the presence of *Alternaria* sensitivity were highly correlated with acute emergency room visits for asthma during period of thunderstorms [49, 50]. Furthermore, other studies have linked the number of fungal spores in the atmosphere to asthma deaths [51]. Clearly, fungal sensitivity is a significant factor in asthma in many areas of the world.

The mechanisms by which fungi induce asthma are often IgE related. However, other mechanisms may also be important. There is evidence that proteases in fungal extracts are capable of causing direct effects on airway epithelium which generate production of inflammatory cytokines, such as IL-8 [52, 53]. Furthermore, proteases contained in many allergens (not limited to fungi) can activate eosinophils via the PAR-2 receptor [40]. Proteases have also been shown to act as Th-2-type adjuvants leading to enhanced eosinophilic inflammation and prolonged IgE responses in animal models [54]. This is a fertile area for further investigation.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis affects individuals with underlying cystic fibrosis or chronic asthma [55–57]. The exact etiology is not entirely clear; however, spores of *Aspergillus fumigatus* are felt to be trapped within the mucus

secretions of the airways in these individuals where they germinate resulting in the secretion of *Aspergillus* allergens. There is a marked Th2-type response with elevations not only in serum-specific IgE to *Aspergillus fumigatus*, but in the total serum IgE level as well. Production of serum-specific IgG antibodies to *Aspergillus* also occurs. Serum *Aspergillus fumigatus* antibody titers can be measured by enzyme-linked immunoassays. Some individuals may have precipitating (IgG) antibodies to *Aspergillus* that is detected by radial immunodiffusion assays (Ouchterlony technique). Other fungi (e.g., *Dreschlera*) may produce a similar picture on occasion [55].

ABPA patients experience chronic wheezing but may also develop symptoms that include chest discomfort, cough with production of brown mucus plugs (containing fungal hyphae) and low-grade fever accompanied by peripheral blood eosinophilia. It is the presence of pulmonary infiltrates along with peripheral blood eosinophils that distinguishes this condition from the underlying asthma or CF. The differential diagnosis includes other syndromes known collectively as PIE (pulmonary infiltrates with eosinophilia) syndromes [55].

The diagnosis of ABPA is established in those individuals who have experienced pulmonary eosinophilia with infiltrates by the demonstration of sensitivity to *Aspergillus fumigatus* via a positive skin test and/or elevated serum-specific *Aspergillus fumigatus* IgE antibody titers (two times greater than that of an *Aspergillus* allergic and non-ABPA asthmatic) (Table 4). A subset of ABPA patients manifest proximal central saccular bronchiectasis (ABPA-CB) on chest computerized tomography (chest CT scanning), which is often considered a hallmark of the illness. However, some individuals with severe persistent asthma may also exhibit the serological manifestations of ABPA, yet do not have bronchiectasis (ABPA-S) [55]. A disease-staging system has been developed, e.g., stage 1, defined as the initial development of pulmonary infiltrates with eosinophilia to stage 5, defined by pulmonary fibrosis, a sequellae of repeat bouts of pulmonary infiltrates [57].

Table 4 Criteria for diagnosis of ABPA

Major

- Underlying asthma or cystic fibrosis
- Pulmonary infiltrates with peripheral blood eosinophilia
- Immediate hypersensitivity to *Aspergillus fumigatus* (elevated specific IgE to *A. fumigatus*, positive *A. fumigatus* skin test)

Minor

- Elevated total serum IgE
- Specific IgG to *Aspergillus fumigatus* (or presence of precipitating antibodies to *Aspergillus fumigatus*)

Subcategories of ABPA

- ABPA-CB
 - Presence of central (proximal) saccular bronchiectasis
 - ABPA-S
 - Positive serologic assays without central bronchiectasis
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Adapted from the Criteria of Greenberger PA. Allergic Bronchopulmonary Aspergillosis. In Adkinson NF Jr., Yunginger JW, Busse WW, Bochner BS, Simons FER, Holgate ST (eds.) Middleton's Allergy, Principles and Practices, 6th edition, Mosby, Philadelphia; 2003, p. 1355

Treatment of ABPA involves prolonged courses of oral corticosteroids and management of persistent asthma with appropriate therapy [56, 57]. Antifungals may be of some value in selected cases [58]. Allergen immunotherapy with *Aspergillus fumigatus* vaccines is generally avoided because of concerns regarding the potential development of immune complex disease [56]. However, this has not been systematically studied [55]. Omalizumab may be a treatment adjunct in the near future but has not been extensively studied.

Over the past several years, there has been growing concern about the health effects of indoor fungal exposure in public buildings and homes (references to go here). Indoor fungal growth is often the consequence of high-humidity levels due to leakage of moisture into the environment. Indoor fungal growth may potentially cause respiratory symptoms in individuals residing in these environments. Numerous epidemiological studies link home dampness to indoor fungal growth and, as a consequence, respiratory symptoms including cough and wheeze especially in children [59, 60]. Both pro and con studies have been reported [61–64].

Clearly, individuals with IgE-mediated sensitivity to the so-called “indoor fungi,” *Aspergillus* and *Penicillium* species, among others, may experience rhinitis or asthma when these fungi are present in the environment [17, 65]. However, it should be noted that unless indoor airborne fungal spore levels exceed outdoor levels, exposure is typically far greater in the outdoor environment [2, 10]. Airborne samples containing levels of spores (esp. *Aspergillus*, *Penicillium*, or even *Cladosporium*) that exceed the simultaneously sampled outdoor level suggests an indoor “point” source.

Beyond their role as allergens, fungi produce volatile organic compounds (VOC) that are responsible for the “musty” smell associated with mold growth and can induce ocular and respiratory irritation as previously mentioned. The (1→3)-beta-D-glucans, a component of fungal cell walls have been researched for a number of years. The effect of the (1→3)-beta-D-glucans on respiratory health is somewhat controversial [14]. Some reports suggest they may elicit airway inflammation (through non-IgE-dependent mechanism, while other reports suggest that they may abrogate Th2 responses [15, 16].

Controversial Areas

The role of fungi in “illnesses” which does not involve infection or allergic reactions is controversial [17, 31]. The “Yeast Connection” or “Candidiasis Syndrome” is one example [66]. A variety of symptoms such as listless, headache, gastrointestinal and other nonspecific symptoms have been ascribed to “sensitivity” to *Candida albicans*, a ubiquitous, commensurate organism. Individuals diagnosed with this “condition” report exposures to antibiotics, mucosal yeast infections, and demonstrate delayed hypersensitivity to *Candida albicans*. Since delayed hypersensitivity to *Candida albicans* is a normal immune response, it is doubtful that the symptoms of the “Candidiasis Syndrome” can be attributed to an immune response to the organism.

Table 5 Some mycotoxins produced by fungi

Aflatoxin	<i>Aspergillus flavus</i> , <i>Aspergillus parastiticus</i>
Altenuic acid	<i>Alternaria alternata</i>
Alternariol	<i>Alternaria alternate</i>
Chaetoglobosin	<i>Chaetomium globosum</i>
Citrinin	<i>Aspergillus</i> spp., <i>Penicillium</i> spp.
Citreoviridin	<i>Aspergillus terreus</i> , <i>Penicillium citreoviride</i>
Cochliodinol	<i>Chaetomium cochliodes</i>
Cytochalasin E	<i>Aspergillus clavatus</i>
Deoxynivalenol (vomitoxin)	<i>Fusarium</i> spp.
Gliotoxin	<i>Alternaria</i> , <i>Penicillium</i> , <i>Aspergillus</i> spp.
Moniliformin	<i>Fusarium</i> spp.
Ochratoxin	<i>Aspergillus ochraceus</i> , <i>Penicillium viridictum</i>
Oxalic acid	<i>Aspergillus niger</i>
Patulin	<i>Aspergillus clavatus</i> , <i>Penicillium</i> spp.
Roridin E	<i>Myrothecium</i> spp., <i>Stachybotrys</i> spp.
Rubratoxin	<i>Pennicillium rubra</i>
Satratoxins F, G, H	<i>Stachybotrys chartarum</i>
Slaframine	<i>Rhizoctonia leguminicola</i>
Sterigmatocystin	<i>Aspergillus</i> spp., <i>Penicillium rugulosum</i>
T-1, T-2 toxins	<i>Fusarium</i> spp.
Tremorgens	<i>Aspergillus</i> , <i>Mucor</i> , <i>Rhizopus</i> , <i>Penicillium</i>
Tricothecenes	<i>Fusarium</i> , <i>Aspergillus</i> , <i>Stachybotrys</i> spp.
Trichoverrins, trichoverrols	<i>Stachybotrys chartarum</i>
Zearalenon	<i>Fusarium</i> spp.

Individuals with this diagnosis are often treated with nonabsorbed oral antifungal agents (nystatin), but no controlled trials have ever been conducted [66].

A list of potential mycotoxins produced by fungi is listed in Table 5. It is known that high-level exposure to mycotoxins can occur and may lead to the recognized “mycotoxicosis syndrome,” chills, fever and pulmonary infiltrates, and the typical immunologic findings of hypersensitivity pneumonitis (HP) are not usually present in HP [67]. It should be noted that precipitating (IgG) antibodies to fungi in individuals is not specific for the diagnosis of HP, but reflects exposure to the fungus.

Another controversial “condition” is the “toxic mold syndrome” [68]. Individuals report living in environments where there is significant fungal growth that leads to headache, impaired cognition and “immune dysregulation” [17]. Many of these reports are anecdotal and do not employ case-controlled methodologies. The detection of the fungus, *Stachybotrys* (“black or toxic”) which can produce mycotoxins under certain conditions does not necessarily indicate that the organism is indeed secreting mycotoxins into the environment [68–70]. It is questionable that the concentration of mycotoxins is sufficient to induce illness by the respiratory route [17] (ACOEM 2002). Position statements released by the American College of Occupational and Environmental Medicine (ACOEM 2002) and the American Academy of Allergy, Asthma and Immunology [17] recommend further research in

this area will be necessary to fully understand whether indoor fungal exposure poses a significant health risk. Recent studies from flooded homes in the U.S. show that there is little effect of fungal exposure on respiratory function in children [71].

Diagnosis and Treatment of Fungal-Related Allergic Disease

Diagnostic Testing for Fungal Allergy

One of the limitations encountered by clinicians is the lack of standardized fungal allergenic extracts for diagnostic testing and therapy [22, 72, 73]. While a number of fungal allergens have been isolated, purified, and characterized, the standardization of diagnostic and therapeutic reagents for fungal allergy has not yet occurred. Commercially available fungal allergenic products for diagnostic and therapeutic testing vary in their allergenic composition and concentrations [23]. Unfortunately, attempts to develop an international reference of *Alternaria alternata* extract did not meet with success due to instability of the candidate reagent [74, 75].

Monoclonal antibody-based assays for quantifying fungi may lead to improved reagents for the clinician and researcher [22]. As newer technologies are developed, it is hoped that significant improvements can be made in *in vivo* and *in vitro* diagnostic tools

Treatment of Fungal Allergic Diseases

As with any allergen exposure, avoidance is the first principle of treatment. Exposure to fungal spores chiefly occurs in the outdoor environment [17]. Therefore, exposure avoidance is difficult at best. Individuals with fungal sensitivity can wear a dust-mite mask when performing activities in the outdoors, such as leaf-raking or working in composted materials to reduce high levels of exposure. Closing windows and using air conditioning may also reduce exposure to fungi from the outdoors [7].

Indoor exposure to fungi, which may be responsible for symptoms, is managed best by controlling the intrusion of moisture [17, 76]. Active fungal growth in materials can be mitigated by chlorine-containing bleach solutions with a detergent. Fungal growth that invades fabrics, wallpaper, woodwork may require removal and replacement. Air cleaners have been shown to remove fungal spores from circulating in the environment [77]. Ionic air cleaners are not recommended, since they may generate ozone, a respiratory irritant. There has been no data demonstrating whether the reduction in airborne spore levels in the indoor environment by air cleaners has any clinical benefit.

Immunotherapy for fungal allergens has had limited study [78]. However, it has been shown to reduce both allergic rhinitis and asthma symptoms in selected patients [79–81]. Subcutaneous immunotherapy has been the traditional method although

more recently the employment of sublingual immunotherapy has gained interest, but there have been no well-controlled studies of its use in fungal allergy [82].

One would anticipate that the use of anti-IgE (omalizumab) during seasonal exposure to fungi may be helpful in reducing the risk of severe and fatal asthma, particularly in older children and young adults sensitive to *Alternaria*. No published papers have appeared at this time. In addition, anti-IgE therapy is being studied as an adjuvant in the treatment of ABPA, and a few preliminary reports have appeared [55]. Because the serum IgE level in ABPA by far exceeds the recommended level for therapy with anti-IgE, the use of this treatment will require further investigation.

Summary

It has been difficult to link fungal exposure with symptoms even in sensitized individuals [83]. Fungal-spore count is one marker that is utilized but since intact spores may not be actively producing allergen, the association between spore counts and allergic symptoms is problematic. Refined methods that include actual allergen exposure to the respiratory tract [30] may be more relevant. There are a number of controversial areas regarding fungal exposure and its health effects particularly as it relates to the indoor environment [17]. Advances in the identification of fungal allergens will lead to improvements in the diagnosis and treatment of fungal allergic disease. As the title of the chapter, "Fungal Allergies: As Yet Unsolved," indicates, the study of fungal exposure and its consequences on human health, including allergic respiratory diseases and their therapies, deserves further investigation.

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