

Importance of Mold Allergy in Asthma

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Fungal exposure is hypothesized (controversially) to contribute to asthma development and to trigger symptoms in patients with asthma. The ubiquity of environmental fungal exposure makes a careful review of evidence essential. Evidence that exposure to high concentrations of fungal spores, antigens, or metabolites is associated with asthma development is limited. However, because mechanisms of asthma genesis are poorly understood, so too are the mechanisms of this potential association. This association is not proof of causality. Stronger evidence supports the hypothesis that fungal exposure triggers symptoms in asthmatic individuals. Proposed mechanisms have been tested and correlations between exposure and symptoms demonstrated. Though some correlations remain speculative, controlled studies could test such hypotheses. Because asthma is common and fungal exposure is ubiquitous, it is surprising that asthmatics don't have more symptoms when exposed to fungi. Fortunately, symptoms are dose dependent, creating an opportunity to develop clinically effective interventions. Given the right guidance, even patients with severe asthma can create healthy indoor environments.

Introduction

Fungi are members of a distinct kingdom of life: eukaryotic, spore-producing, achlorophyllous organisms with absorptive nutrition that generally reproduce both sexually and asexually. They usually have filamentous branched somatic structures, known as hyphae, that typically are surrounded by cell walls [1]. *Mold* is a generic term that usually refers to anything that grows on organic media by forming mycelia and that appears fuzzy. It probably is derived from the old English “molde” as in “moldering in the grave.” Members of the scientific community disagree

somewhat about the details of fungal taxonomy. Technically, yeasts are considered to be fungi but slime molds are not part of that kingdom. Many laypersons would not consider mushrooms to be molds even though in fact they are fungi. For this review, we use the term *fungus* even though most laypersons consider molds and fungi to be nearly the same thing.

Asthma is a clinical syndrome characterized by widespread narrowing of the pulmonary airways associated with an infiltration of inflammatory cells, mucus production, and airway edema. The clinical correlates of this syndrome usually include signs and symptoms of lower airways obstruction, variability in response to bronchodilators or provocative agents, and recurrence. An estimated 8% to 12% of the US population has asthma, with a disproportionately high prevalence among minorities in urban settings. Though asthma prevalence, morbidity, and mortality rose throughout the 1990s, these trends have stabilized and have even started to decline in recent years. Even so, asthma remains one of the most common causes of missed school and work, reduced quality of life, emergency department visits, and hospitalizations.

For many years, a relationship was suspected between exposure to fungi and both the development and exacerbation of asthma. Although evidence that fungi can act as asthma triggers is fairly solid, the precise extent and mechanisms by which this occurs has been controversial. Evidence that exposure to fungi can actually contribute to the development of asthma is less clear. In the current discussion, we review the evidence for each of these possibilities and describe their likely mechanisms.

Clinical Significance of Fungi

There are thousands of known species of fungi. People often come into contact with these organisms in their roles as pathogens, saprophytes, free-living and water-borne organisms, and thermophiles [2]. All fungi derive energy from organic matter in their environment. This organic matter is converted through the use of excreted enzymes into simple bio-organic molecules, which can be absorbed from the environment to provide energy and building blocks for growth and reproduction. The natural function of most fungi is to cause decomposition of

Table 1. Fungal taxa commonly identified in environments inhabited by humans

Spore (nonviable estimation)	Prevalence indoors (1 = most prevalent)
Penicillium/Aspergillus	1
Cladosporium	2
Ascospores	3
Alternaria	4
Periconia	5
Stachybotrys	6
Basidiospores	7
Chaetomium	8
Smut	9
Torula	10
Sordaria	11
Rust	12

(Data from Portnoy et al. [5].)

organic material, thereby recycling nutrients through the ecosystem. As part of their natural competition for food and resources, fungi secrete substances, including mycotoxins and hydrolytic enzymes, into the environment. All of these largely proteinaceous materials are potentially allergenic for predisposed humans.

In addition to cell division, fungi reproduce through spores formed as a result of either sexual or asexual processes. These spores typically have a tough exterior covering, and are designed to survive extreme environmental conditions. Spores are found in both outdoor and indoor air and, though the species present will vary with climate suitability, the distribution of spores in the environment is quite uniform. Because the identifiable airborne forms of fungi consist primarily of spores, much research into fungal health effects on humans has focused on exposure to spores as the main offending agent.

More than 70,000 species of fungi have been described in the literature. Because fungi may have two or more morphologic stages, commonly used names often differ from the precise systematic scientific nomenclature. Fungi that are most frequently found in surveys of human exposure have been the focus of investigation for their allergic potential. Many of these have been identified as significant causes of allergy [3].

Recent advances in species identification using both immunologic and genomic methods have only increased the number of fungal species potentially implicated in airborne exposure and the genesis of asthma. Species-specific monoclonal antibodies have been used in combination with fluorescent-confocal halogen immunoassay technique to allow speciation of morphologically indiscernible fungal fragments. Application of this method will enable the characterization of the con-

tribution of fungal fragments to adverse health effects and provide more complete patient-specific exposure and sensitization information [4•].

Exposure to Indoor Fungi

Nearly all house dust contains fungal spores and mycelial fragments, which may easily become airborne upon disturbance (eg, walking across carpet). Indoor exposures to fungi are of particular interest due to the increased tendency for people to spend time inside buildings constructed for energy efficiency and therefore with limited ventilation. Fungi commonly identified in surveys of indoor exposure are listed in Table 1 [5].

In the National Survey of Lead and Allergens in Housing, specifically looking at exposure to *Alternaria* in 831 US homes, *Alternaria* antigens were detected in 95% to 99% of dust samples [6•]. Further analysis showed that the age of the housing unit, geographic region, urbanization, poverty, family race, observed mold and moisture problems, dehumidifier use, and presence of cats and dogs all were independent predictors of elevated concentrations of *Alternaria* antigens.

Harmful Effects of Fungal Materials

Allergy to fungi

Fungal spores have been recognized as significant causes of allergy ever since Blackley suffered from bronchial distress for days after inhaling spores from *Penicillium glaucum* [7]. Spores also were identified as causes of allergy by the Dutch physician Willem Storm van Leeuwen in the early 20th century [7]. Numerous animal studies used fungal spores to induce allergic symptoms. Chronic intranasal administration of *Cladosporium herbarum* spores or *Alternaria alternata* extract caused an increase of total serum immunoglobulin (Ig) E and the appearance of specific IgE in Balb/c mice. Airway hyperreactivity subsequently was demonstrated in these animals and was maintained during the entire experiment [8•].

Fungi, like many inhaled biologic substances, have the potential to induce production of specific IgE antibodies in genetically susceptible individuals. The most common fungi reported to induce specific IgE in humans include *Cladosporium*, *Aspergillus*, *Penicillium*, *Alternaria*, *Basidiospores*, and *Epicoccum* [3,9–11]. Unfortunately, because extracts are not available to test for all clinically relevant fungi, there may be unidentified taxa that also induce significant allergic sensitization [12].

Nearly all fungal allergens identified thus far are proteins, many of which have enzyme activity. There has been much speculation that enzymes, particularly proteolytic enzymes, may serve to enhance the allergenicity of these proteins. Because proteolytic enzymes by their nature must be able to resist self-destruction, they tend to persist in the environment.

Pen ch 13, for example, is a serine protease that also is one of the major allergens produced by *Penicillium citrinum* [13]. This enzyme has been found to dose-dependently induce interleukin (IL)-8 cytokine expression in airway epithelial cells. Pen ch 13 also cleaves protease-activated receptors at their activation sites and induces intracellular Ca^{2+} mobilization. All these actions tend to steer the immune response toward a T helper (Th) 2 phenotype. Pen ch 13 also contains cross-reactive and allergen-specific IgE epitopes with another serine protease, Pen ch 18 [14]. In a recent review, several cysteine and serine protease allergens found in house dust mites, including Der p 1, Der p 3, Der p 6, and Der p 9 were found to act as Th2 adjuvants [15]. Other allergens likely also induce Th2 responses in the absence of proteolytic enzyme activity. The implication that intrinsic proteolytic activity contained in many allergens provides for the possibility of enhanced allergenicity may be correct; however, proteolytic activity is certainly not required for a protein to be an allergen [15].

Irritant effects

An irritant is defined by the US Occupational Safety and Health Administration as “a noncorrosive chemical which causes a reversible inflammatory effect on living tissue by chemical action at the site of contact.” As a more general definition, an irritant is a substance that on immediate, prolonged, or repeated contact with normal living tissue will induce a local inflammatory reaction.

The effect of irritants is temporary. Examples of primary irritants include capsaicin, which is the source of the “hotness” of hot peppers of the genus *Capsicum* (eg, chili, cayenne, and jalapeno); gingerol, which causes the hotness of ginger; piperin and piperine derived from pepper (especially black pepper); and isothiocyanate, which is derived from horseradish, radishes, onions, and mustards.

The amount of inflammation associated with irritants depends on their degree of irritation, duration of exposure, and sensitivity of the target organ. People with asthma tend to be more sensitive to the irritant effects of airborne substances such as perfumes, ozone, and smoke than those with normal lung function. The amount of exposure to a substance that is capable of causing an irritant reaction often is orders of magnitude less than the amount causing toxicity. Therefore, estimates of exposure to fungal materials that are necessary to cause toxicity are not relevant to irritant reactions.

Fungi produce several potentially irritating substances. These include microbially derived volatile organic compounds (VOCs), glucans (which are related to endotoxins), and ergosterols, although the full spectrum of fungal irritants has not been fully enumerated. As with other irritants, the health effects of exposure to these substances is directly related to the amount and duration of exposure. That is why well-ventilated buildings are

considered to be healthier than those in which airborne potentially respirable irritants can accumulate.

Because many substances in buildings are volatile and potentially irritating, it often is difficult to determine whether a particular inflammatory reaction is due to irritants derived from fungi or from other sources. Therefore, to document that a fungally derived substance is responsible for a symptom, it is necessary to demonstrate that the substance is present in the environment, exposure is of sufficient magnitude and duration to trigger the observed reaction in the affected individual, and other substances that could account for the symptoms are not present.

Microbially derived volatile organic compounds

In buildings, VOCs come from a variety of sources, including paints, plastics, and cleaners. Some VOCs, particularly household scents and perfumes, can serve as mucous membrane irritants when present at high concentrations. They also may affect the central nervous system, producing such symptoms as headache, nausea, attention deficit, inability to concentrate, or dizziness [16].

Microbially derived VOCs (MVOCs) are produced as byproducts of fungal metabolism. Therefore, it is often difficult to determine what portion of total VOCs are the product of fungal growth. They have been used as marker compounds for selectively detecting fungal species in indoor domestic environments. Their likely impact on human health currently is the subject of much investigation.

Because MVOCs are simple organic molecules, they are potential asthma triggers and therefore may cause irritation of the membranes of the eyes, nose, and throat. Some individuals can detect extremely low concentrations of MVOCs and may be adversely affected by the odor. As with any smell, once a compound reaches a person's odor threshold concentration, it may trigger psychological responses possibly leading to headaches, lethargy, and nausea or vomiting. It is not known whether such responses are learned or if they represent time-dependent sensitization of portions of the brain, perhaps mediated through the olfactory sense. Such responses may even serve a protective function [17].

Ergosterol and glucans

Ergosterol and glucans are fungal-derived substances that correlate with total fungal biomass [18]. The β (1-3) D glucan from fungal cell walls is suspected to produce nonspecific inflammation due to its attachment to lipopolysaccharide binding protein, CD14 cell surface protein, and Toll-like receptor (TLR)-4. This binding leads to production of local inflammatory cytokines that result in the migration of inflammatory cells into the lung. These cytokines may also penetrate into the blood and attract additional inflammatory cells. Airway challenges in animals and field studies in humans have identified a relationship between glucans

and airway inflammation [19]. Several epidemiologic studies link exposure to glucans with health effects in humans [20,21]; however, these studies have numerous confounding factors, including the possibility that the fungi themselves could account for symptoms. Although glucans have been shown to trigger inflammation in culture and animal studies, clinical evidence in humans remains circumstantial until controlled challenge studies are performed.

Toxicity

Mycotoxins are organic compounds of small molecular weight that, although generally not volatile, often attach to small particles that can become airborne. Therefore, enumeration of airborne spores may not account for total mycotoxin exposure any more than cat hair or dust mite fecal pellet counts would accurately describe cat or dust mite allergen exposure. Many but not all fungi species produce mycotoxins. Toxigenic fungi vary in the amount and types of mycotoxins produced, depending on the substrate on which they grow and other environmental conditions [22].

Because most damp indoor environments contain a mixture of fungal species, it is likely that multiple mycotoxins are present. Health effects caused by exposure to such mixtures may differ from the effects of a single mycotoxin, as would occur in a controlled laboratory exposure. The effect of such multiple exposures may differ from that of any single toxin or particular species of mold. Because indoor samples usually consist of a mixture of fungi and their spores, tests for total cytotoxicity may be necessary to assess the total potential for toxicity of indoor samples [23].

The toxic effects of airborne mycotoxins and other irritants as they relate to asthma are poorly understood. Toxic secondary metabolites have been documented to be present in airborne spores and in airborne dust and bioaerosols [24]. However, the amount, duration, and route of exposure (other than by ingestion) that is necessary to cause adverse health effects have not been determined for mycotoxins. Airborne toxic exposures in indoor environments related to fungi and mycotoxins have recently been nominated for study by the National Toxicology Program. This reflects public and media concern about potential noninfectious adverse health effects related to fungal exposures caused by recent natural disasters. Although still in the planning stages, the fact that such studies are being planned is significant.

Sensitivity and Exposure to Fungi and Asthma

Numerous articles have documented a strong association between exposure to damp housing and asthma, although it is not clear whether the dampness itself is involved in the genesis of respiratory problems or is merely a marker for the presence of other conditions

promoted by dampness [9,25–30]. In 2004 the Institute of Medicine (IOM) published a report entitled *Damp Indoor Spaces and Health* [31]. This evidence-based document listed several health conditions for which various degrees of scientific evidence seemed to exist, ranging from insufficient evidence up to causality, between the condition and exposure to mold in a damp environment. The IOM report found sufficient evidence of an association between exposures to fungi in a damp environment and development of upper respiratory tract (nasal and throat) symptoms and asthma (eg, wheeze and cough) symptoms in already sensitized asthmatic persons. The report did not find evidence of an association between fungal exposure and the initial development of asthma or its symptoms in otherwise healthy children.

Garrett et al. [9] studied associations between house dampness, airborne fungal spore levels, and health outcomes in 149 children from 80 households. These investigators found an association between several conditions of damp housing including musty odor, water intrusion, high humidity, limited ventilation, and indoor fungal growth along with high spore concentrations. They also found associations between exposure to *Penicillium* and the presence of asthma as well as between the development of specific IgE and exposure to *Cladosporium* or *Penicillium*. They concluded that indoor exposure to certain fungal genera was a risk factor for asthma, atopy, and respiratory symptoms in children and that actual measurement of spore concentrations were better predictors of health outcomes than reported dampness.

Allergy to fungi also has been found to correspond with asthma. In the first US National Health and Nutrition Examination Survey, 4295 participants underwent allergy skin testing for eight allergens. Persons with asthma were 5.1 times more likely to react to *Alternaria* than were nonasthmatics. When both asthma and allergic rhinitis were considered, *Alternaria* remained strongly associated with these disorders [32]. This observation was further confirmed by results from the National Inner City Asthma Study in which fungus-sensitive children with asthma in urban communities across the United States were found to be exposed to substantial amounts of airborne fungi in both indoor and outdoor air [33]. Exposure to fungi was greater in homes that also had dampness problems, cockroach infestation, and cats. In another study of 499 homes tested for the presence of 13 different fungal species, *Cladosporium*, *Penicillium*, and *Zygomycetes* were most commonly associated with asthma.

Another study of the relationship between production of fungal-specific IgE and development of asthma in 485 adults with newly diagnosed asthma found that the risk of developing asthma increased in a dose-dependent manner as the total and fungus-specific IgE increased. In particular, an increased risk of having asthma was found in individuals with elevated IgE to *Aspergillus fumigatus* and *C. herbarum* [34].

Fungi as triggers of asthma

Two types of evidence have been used to support the hypothesis that exposure to fungi can trigger asthma symptoms in persons already known to have asthma. These include demonstration of a direct correlation between the development of asthma symptoms and exposure to fungi, and observations that high exposure to fungi (eg, during thunderstorms) corresponds to emergency department visits and hospitalization for treatment of asthma episodes.

Many studies have shown that exposure to indoor fungi can trigger allergic symptoms [9,27,35]. In particular, species of *Alternaria*, *Aspergillus*, *Penicillium*, and *Trichoderma* have been reported to trigger asthma symptoms in previously sensitive individuals [36,37]. Many other species of fungi (eg, *Aureobasidium* and *Helminthosporium*) have been associated with asthma. Sensitivity to *Aureobasidium pullulans* was significantly associated with more severe asthma, and sensitization to *Helminthosporium* was associated with an increased number of asthma exacerbations requiring hospitalization [38].

Stark et al. [11] studied 499 newborn infants to determine whether fungal exposures contribute to an association between home dampness and respiratory symptoms. They found a relationship between development of lower respiratory symptoms and exposure to airborne *Penicillium*, dust-borne *Cladosporium*, *Zygomycetes*, and *Alternaria* after controlling for gender, presence of water damage or visible mold, season, breastfeeding, and exposure to other children. Zock et al. [39] examined associations between fungal exposure and adult asthma and concluded that exposure to indoor fungal growth has an adverse effect on adult asthma.

Zureik et al. [30], as part of the European Community respiratory health survey, assessed the relationship between severity of asthma and sensitization to airborne fungi. They evaluated 1132 adults with current asthma and found that frequency of sensitization to *A. alternata* or *C. herbarum*, or both, increased significantly with increasing asthma severity in an association that was present in all of 38 regional study areas. These authors concluded that sensitization to fungi was a significant risk factor for development of severe asthma in adults.

Newson et al. [40] studied admissions for asthma from 1987 to 1994 in children and adults in the Trent region of England. Spore counts were elevated on four of the six epidemic days, but epidemics occurred only on four of 343 days with high total spore counts. The relationship between asthma severity and development of specific IgE to fungal allergens in asthmatic subjects was more common in individuals with multiple asthma admissions. In addition, the number of asthma admissions was related to the number and size of positive fungal skin tests. This suggests that fungal sensitization is associated with asthma episodes leading to hospital admission [40].

Several studies have indicated that overall sensitivity to fungi is a risk factor for severe and fatal asthma attacks [12,30,41]. This is supported by several observations that asthma-related deaths and hospital emergency admissions are markedly increased on days with high fungal spore counts [40,42,43]. *Alternaria* is one of the most frequently studied fungi associated with exacerbations of asthma. In a landmark study, elevated concentrations of *Alternaria* spores in outdoor air were strongly associated with asthma deaths [44]. This finding was supported recently in the United Kingdom, where elevated concentrations of *Alternaria*, due to thunderstorms, were associated with an increase in asthma attacks [45•]. Because *Cladosporium*, *Epicoccum*, and *Stemphylium* have epitopes that cross react with *Alternaria* [46–48], each likely has a similar, but perhaps less well documented, association with asthmatic episodes.

Development of asthma

Though it is reasonable to expect that exposure to fungi in sensitized individuals with asthma is likely to lead to symptoms, it is less clear that exposure to fungi is likely to increase the risk of developing asthma. The problem is that the cause of asthma itself is not known. Until this question is resolved, the best we can expect from studies of fungi and asthma is circumstantial evidence of increased exposure in individuals who develop asthma.

Evidence for an association between the presence of fungi and the genesis of asthma is more tentative than the evidence for fungal spores as asthma triggers. A linear relationship has been found between exposure to indoor fungi and development of lower respiratory illnesses in children during the first year of life [11]. Recently, Belanger et al. [49] studied 849 newborn infants with an asthmatic sibling during their first year of life, and found that persistent exposure to fungi increased the risk of wheezing both in infants of mothers who had asthma and in infants of mothers without asthma. Using European data, Gent et al. [50] examined 880 infants at high risk for developing asthma, and concluded that infants who were exposed to high levels of *Penicillium* were at significant risk for subsequent wheezing and persistent cough.

Environmental remediation of fungi to reduce asthma symptoms

If increased fungal exposure is associated with asthma either as a causative agent or simply as a trigger, then measures to reduce such exposure in asthmatic populations should improve health outcomes. Several comprehensive cleaning studies using environmental control coupled with fungus remediation, home repair, and education have been successful. Eggleston [51] reviewed the allergen intervention research and concluded that avoidance is appropriate for allergic patients with asthma and that reduction in multiple exposures must be considered.

Kercsmar et al. [52] reduced asthma morbidity in children by employing remediation for moisture sources. Families of asthmatic children in 62 moldy homes were provided with home-cleaning education, an asthma action plan, individualized household repairs, reduction of water infiltration, removal of water-damaged building materials, and repair of heating/ventilation/air-conditioning. The remediation group had a significant decrease in symptom days when compared with a control group that received only cleaning information. The remediation group also had fewer exacerbations. As part of the inner-city asthma study, Morgan et al. [53•] studied 937 children with asthma for 1 year. Interventions included cleaning education, allergen exposure remediation, and environmental tobacco smoke avoidance. The intervention group experienced declines in exposure to multiple home allergens and significantly reduced asthma-associated morbidity during the intervention year and the year afterward.

General home cleaning and cleaning with hypochlorite (bleach) has proved effective in reducing in-home allergen exposure. Hypochlorite treatment serves to denature allergens in hard-to-clean areas (eg, carpet, upholstery). Matsui et al. [54] reported that the allergic potency of recombinant Fel d 1 was reduced by low concentrations of chlorine bleach. Nickmilder et al. [55•] found regular house cleaning with bleach reduced risks of respiratory and allergic diseases in school-age children. In work recently completed in 90 asthmatic children, quality-of-life scores for groups using hypochlorite-based cleaning products improved through the study [56]. Dust allergen levels were decreased 14% overall, and both viable and nonviable airborne spore levels were decreased 18% and 42%, respectively. Significant improvement occurred in quality-of-life scores for participants provided with a hypochlorite-based cleaning product specifically for reduction of allergen levels [56].

Conclusions

Limited evidence supports the hypothesis that exposure to high concentrations of fungal spores, fungal antigens, and possibly fungal metabolites is associated with an increased risk of developing asthma. The mechanisms for this hypothesis are not understood because the mechanisms of asthma genesis are not understood. Therefore, this evidence is merely an association and not proof of causality.

The hypothesis that exposure to fungi can trigger symptoms of asthma in sensitized individuals is supported by much stronger evidence. Mechanisms for this occurrence have been proposed and tested, and direct correlations between exposure and symptoms have been demonstrated. Though certain mechanisms (eg, toxic reactions to mycotoxins, psychological reactions to MVOCs) remain somewhat speculative, these hypotheses could be tested in controlled studies in the future.

Finally, because asthma is common and fungal exposure is almost universal, it is surprising that people with asthma don't have more symptoms when they come into contact with fungi. Fortunately, symptoms tend to occur in a dose-dependent manner, creating an opportunity for the development of clinically effective remedial interventions. Because certain household products (eg, dilute bleach) can reduce fungal exposure, given the right guidance, individuals likely can create indoor environments with healthy air quality for people with even the most severe asthma. Now we need to train doctors to provide this expert guidance.

Disclosures

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