Clinical Commentary Review

Exposure and Health Effects of Fungi on Humans

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Fungi are ubiquitous microorganisms that are present in outdoor and indoor environments. Previous research has found relationships between environmental fungal exposures and human health effects. We reviewed recent articles focused on fungal exposure and dampness as risk factors for respiratory disease development, symptoms, and hypersensitivity. In particular, we reviewed the evidence suggesting that early exposure to dampness or fungi is associated with the development of asthma and increased asthma morbidity. Although outdoor exposure to high concentrations of spores can cause health effects such as asthma attacks in association with thunderstorms, most people appear to be relatively unaffected unless they are sensitized to specific genera. Indoor exposure and dampness, however, appears to be associated with an increased risk of developing asthma in young children and asthma morbidity in individuals who have asthma. These are important issues because they provide a rationale for interventions that might be considered for homes and buildings in which there is increased fungal exposure. In addition to rhinitis and asthma, fungus exposure is associated with a number of other illnesses including allergic bronchopulmonary mycoses, allergic fungal sinusitis, and hypersensitivity pneumonitis. Additional research is necessary to establish causality and evaluate interventions for fungal- and dampness-related health effects. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

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Fungi are ubiquitous microorganisms that can be found in all parts of the world. When airborne, fungi take the form of spores, mycelia, and hyphael fragments. Such bioparticulates, when inhaled, are believed to contribute to adverse health effects in individuals who are predisposed to experience disease. Such individuals include those who produce specific IgE to fungal antigens, others with respiratory conditions that are susceptible to irritant effects of exposure, and immunocompromised patients who are susceptible to infections.

Common outdoor fungi include *Alternaria*, *Cladosporium*, *Epicoccum*, as well as ascospores and basidiospores though these fungi are often found indoors because they enter through open doors and windows and can be carried indoors. Fungi more classically associated with indoor water damage or decay include *Penicillium*, *Aspergillus*, *Stachybotrys*, *and Chaetomium*. A review of these diverse fungi can be found in the accompanying article "Taxonomy of allergenic fungi" by Levetin et al.[1]

In all epidemiologic studies, exposure to mold and dampness are considered together. Dampness is a generic term that is used to communicate a range of moisture conditions. Although most people can recognize an environment that is damp, there is no consensus description or measurement that defines the term. In this article, *dampness* is defined as sufficient moisture on or in a substrate to support microbial growth. Dampness has often been associated with a combination of the following factors occurring simultaneously: visible water damage or stains, visible mold, and odors from microbial growth.[2] However, dampness also supports dust mites and sometimes the growth of actinomycetes, which can be associated with other health problems. Thus, it can be challenging to isolate the health effects of fungal exposure in damp environments.[3]

Another limitation of studies designed to identify health risks of fungal exposure is that total fungal exposure is difficult to measure. There is no criterion standard method to identify and quantify fungus. Methods vary from direct microscopy or culture-based volumetric air sampling to measurement of fungal metabolites such as beta-D-glucan or ergosterol. Fungal diversity can also be evaluated by immunoassays, PCR, and genomic sequencing.[4] Furthermore, many fungal allergens are broadly cross-reactive.[5,6] In sensitized individuals, exposure to related species can cause symptoms due to shared epitopes.

In this review, we will address the evidence linking dampness and fungal exposure and adverse health effects. In particular, we will review evidence suggesting that early exposure to dampness or fungi is associated with the development of asthma and that exposure to dampness or fungi in those with asthma increases morbidity. These are important issues because they provide a

Abbreviations used
IOM- Institute of Medicine
OR- odds ratio

rationale for interventions that might be considered for homes and buildings in which there is an increase in occupant fungal exposure. In addition to rhinitis and asthma, exposure to fungi is associated with a number of other illnesses including allergic bronchopulmonary mycoses, allergic fungal sinusitis, and hypersensitivity pneumonitis.

OUTDOOR FUNGAL EXPOSURE

Starting in the 1930s, quantitative measurements of outdoor pollen and spore concentrations have been conducted in the United States.[7] Quantitation is performed using visual or culture-based air sampling methods, which enumerate the bioaerosol composition of the atmosphere. Volumetric air sampling of fungal spores involves impaction, impingement, or filtration using various instruments. Newer techniques including immunoassays, molecular methods such as PCR, and genomic sequencing are becoming more widely used.[4]

Mean spore concentrations outdoors usually range from 50 spores/m^3 during cold, snowy weather to 50,000 or more spores/m^3 of air during warm, moist seasons.[8,9] Because spores can be transported long distances in dust clouds arising in warmer areas,[10] they can be detected in even the most remote regions of the globe.[11] Temperature and dew point appear to be important factors that determine the types of spores found in outdoor air.[12] For example, ascospores typically are associated with precipitation, whereas *Alternaria* and *Cladosporium* are associated with dry conditions.

In temperate regions, spores in outdoor air tend to peak in the mid to late summer and decrease with the first hard frost in regions that experience cold winter seasons. Xerophilic spores (eg, *Alternaria*, *Cladosporium*, and *Epicoccum*) tend to peak in the afternoon during periods of low humidity, whereas hydrophilic spores tend to peak during predawn hours when there is high humidity. These include ascospores and basidiospores (mushrooms, puffballs). *Alternaria* is the most prevalent fungus in dry, warm climates.[13-15]

Cladosporium is the most commonly identified outdoor fungus.[16] It is found on dead plants or vegetable matter. *Aspergillus* is often isolated from house dust. It is also found in compost heaps and dead vegetation.[17] *Penicillium* is found in soil, food and grains, and house dust. It grows in water-damaged buildings, wallpaper, and decaying fabrics, often giving a green "mildew" color.

INDOOR FUNGAL EXPOSURE

Indoor fungal taxa are likely to vary depending on building construction and climate. The most common taxa are a combination of fungi classically associated with dampness as well as outdoor fungi that enter through openings in the building such as doors and windows.

In a study of 23 buildings, water leakage through roofs, dampness, and defective plumbing were the main reasons for damage leading to fungal contamination.[18] In a study of damp buildings, the genera most frequently encountered indoors included *Penicillium* (68%), *Aspergillus* (56%), *Chaetomium* (an ascospore) (22%), *Ulocladium* (which is related to *Alternaria*) (21%), *Stachybotrys* (19%), and *Cladosporium* (15%).[18] One study of 21 offices in 4 office buildings showed that concentrations of dustborne fungi positively related to carbon dioxide and were highest at temperatures between 20°C and 22.5°C. In addition, fungal concentrations were highest in September and lowest in March.[19]

In a survey of 190 homes in Paris, the most common indoor isolates were *Cladosporium* and *Penicillium* species. *Aspergillus* was recovered in 60% of homes and *Alternaria* in less than 20%. The best predictors for indoor fungal concentrations were their outdoor concentrations when windows were open and the overall dampness in the house when windows were closed.[20] In recent studies exploring the fungal species spectrum in 173 homes in the Midwest region of the United States, *Cladosporium*, *Penicillium*, *Aspergillus*, *Basidiospores*, *Epicoccum*, and *Pithomyces* were more frequently present and in higher concentrations in homes with a child who has asthma than in homes without a child with asthma even after adjusting outdoor spore concentration.[21]

Building products most vulnerable to mold attacks include organic materials containing cellulose, wood, jute, wallpaper, drywall, and cardboard.[18] *Penicillium* can use various nutrients such as decaying vegetation with relatively little dampness for short periods of time, whereas *Stachybotrys* requires sustained wetness and easily digestible cellulose such as drywall or paper. Despite these variations in growth requirements, there is a surprising overall consistency in the types of indoor spores.

One study demonstrated that rankings by prevalence and abundance of the types of airborne and dustborne fungi did not differ from winter to summer, nor did their indoor to outdoor ratios differ.[22] During the winter when infiltration of spores from outdoors was minimal, mean indoor levels of airborne spores in one study ranged from less than 10 spores/m^3 to more than 20,000 spores/m^3.[23]

INDOOR FUNGAL EXPOSURE AND THE RISK OF DEVELOPING ASTHMA

Studies of the possible association between early fungal exposure and subsequent development of asthma or rhinitis have been performed. Such studies are necessarily observational because it is not feasible to randomly assign children to live in environments with various amounts of fungal exposure and to then monitor their health over time. Although observational studies provide information about associations, they cannot be used to infer causality because other factors that correlate with fungal exposure may also influence any observed health effects.

A systematic review by Mendell et al[2] evaluated various types of fungal exposure and the risk of developing asthma. The authors identified 17 studies of fungal exposure and subsequent asthma (8 that had been included in an earlier Institute of Medicine [IOM] report[24] and 9 new studies) that met their inclusion criteria. Of these studies, 6 were prospective, 8 were retrospective, and 3 were cross-sectional. The odds ratios (ORs) for the development of asthma in these studies ranged from 0.63 to 7.08 in both retrospective and prospective studies; however, only the cross-sectional studies included OR ranges that were consistently greater than 1. They concluded that evidence showed indoor dampness or mold to be associated with asthma development. The limitation of this review is that the studies were not quantitatively