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Aspergillus species in indoor environments and their possible occupational and public health hazards

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Abstract

The genus *Aspergillus*, which consists of a few hundred opportunistic mold species found in various climatic conditions, causes diseases including localized infections, fatal diseases, allergic responses, and inhaled conidia in humans. Herein, we present an overview of the most common diseases and allergic infections caused by *Aspergillus* species and their associated health hazards in various indoor environments worldwide.
Keywords: *Aspergillus*, Allergen, Indoor environments, Public health hazards

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Introduction

*A*spergillus species are filamentous fungi that are commonly found in soil, decaying vegetation, and seeds and grains, where they thrive as saprophytes. *Aspergillus* species can be occasionally harmful to humans [1-3]. Most *Aspergillus* species are found in a wide variety of environments and substrates on the Earth throughout the year [4]. Only a few well-known species are considered as important opportunistic pathogens in humans [1, 2].

Polyphasic taxonomy has had a major impact on species concepts in the genus *Aspergillus*. The genus has been subdivided into 22 distinct sections; *Aspergillus, Fumigati*, *Circumdati*, *Terrei*, *Nidulantes*, *Ornati*, *Warcupi*, *Candidi*, *Restricti*, *Usti*, *Flavipedes*, and *Versicolores* contain clinically relevant species [5]. Although there are more than 200 known species in the genus, only a small number of them are associated with infections in humans [6].

In humans, *Aspergillus fumigatus* is the most common and life-threatening airborne opportunistic fungal pathogen, which is particularly important among immunocompromised hosts [7-12]. Inhaling *A. fumigatus* spores (conidia) into the lungs may cause multiple diseases, which depend on the immunological status of the host in humans. These diseases include invasive pulmonary aspergillosis, aspergilloma, and different forms of hypersensitivity diseases such as allergic asthma, hypersensitivity, pneumonitis, and allergic bronchopulmonary aspergillosis (ABPA) [9, 13].

There is considerable concern regarding the potential health outcomes of exposure to biological materials existing in the air [14-17]. Molds constitute an important threat to human health; their effects range from moderate allergies and severe asthma to disseminated infections. Exposure to molds in indoor places is not typically considered a specific risk factor in the etiology of fungal diseases unless some special conditions are present that are essential for specific infections.

Fungal infections that are particularly aggressive to tissues are limited to immunocompromised individuals (e.g., hospitalized patients). *Aspergillus* species are a ubiquitous mold in home and hospital environments. Indoor plants represent a natural environment for the growth of these fungi [18]; however, few recommendations have been made about avoiding known sources of fungal proliferation (plants and flowers) in indoor places.

Several studies have previously revealed that exposure to indoor, air-borne fungi from moisture-damaged buildings can result in adverse health effects [19, 20]. *Aspergillus* is one of the well-documented molds known to cause health problems. Molds such as *Aspergillus* may adversely affect human health based on toxicity, allergy, and infection [21]. Some species of *Aspergillus* are known to be capable of producing secondary metabolites or mycotoxins [22]. Inhaling high concentrations of mixed organic dusts, including mycotoxins, volatile organic compounds (VOCs), and allergens (glucans), are associated with sick building syndrome [23].

The present paper is a review of studies performed on *Aspergillus* species in indoor environments; these species were shown to be occupational and public health hazards worldwide. We initiated our search by reviewing all the English references published in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), during 1965-2015, using the following keywords: "*Aspergillus*", "indoor environments", "allergy", "occupational hazard", "volatile organic compound", and "mycotoxin". After we reviewed this initial series of reports, we scanned individual references listed in each publication to find additional case reports.

Pathogenicity of *Aspergillus*
Mycotoxin production

Aspergillus species secrete numerous secondary metabolites known as mycotoxins into their environment [24]. Mycotoxins are produced during consecutive enzyme reactions via several biochemically simple intermediary products from the primary metabolism of acetates, mevalonates, malonites, and some amino acids. *Aspergillus* produces some of the most significant known mycotoxins including aflatoxin, gliotoxin, and ochratoxin A [1]. The secondary metabolite gliotoxin has attracted the most interest in *A. fumigatus* because of its potent immunosuppressive and cytocidal properties and the fact that it can be readily detected during experimental infection and in sera from patients with aspergillosis [25, 26]. Nevertheless, the specific roles of other toxins in the pathogenesis of aspergillosis are well-defined.

Fungal metabolites may also impair phagocytic functions that would normally destroy conidial and hyphal forms. Gliotoxin reduces adherence and phagocytosis of fungal elements; aflatoxin affects phagocytosis, intracellular killing, and spontaneous superoxide production. Complement binding and activation of bound opsonins, which normally enhance phagocytosis, are affected by aflatoxin, as well, making fungal elements less susceptible to

destruction [27]. In another study, Niyo et al. [28] using a rabbit model demonstrated that T2 toxin decreased phagocytosis of *A. fumigatus* conidia by alveolar macrophages, thereby, increasing the severity of experimental aspergillosis. Khoufache et al. [29-30] exhibited that verruculogen, another mycotoxin produced by *A. fumigatus*, modified the electrophysiological properties of human and porcine epithelial cells, which might slow ciliary beating and damage the epithelium to influence on colonization of *A. fumigatus* in the airways.

Adaptation to vertebrate hosts

Aspergillus species possess versatile features enabling them to survive in various environmental conditions; the species is a ubiquitous fungal pathogen in a wide range of hosts including humans and animals [4]. *Aspergillus fumigatus* conidia, in comparison with conidia of most other molds, are more efficiently dispersed in the air [4]. Even slight air currents can disperse conidia due to their remarkable hydrophobicity. These airborne conidia are protected from ultraviolet irradiation given the presence of melanin in their cell walls [4, 31].

Aspergillus fumigatus can be isolated from a wide range of environmental conditions at an optimal temperature of 37°C (range: 12–65°C) and pH of growth sites between 2.1 and 8.8 [4]. Thermotolerance facilitates the growth of the fungus not only in decaying organic matter (its primary ecological niche), but also within mammalian or avian respiratory tracts. *Aspergillus fumigatus* commonly resides in compost, a dynamic environment that undergoes considerable fluctuations in temperature and intense microbial activity. The ability to thrive in this habitat needs a substantial level of thermo-tolerance, which is assumed to contribute to virulence [31]. These properties might be evolved in response to competitors within the ecological niche of the organism and are unlikely to reflect specific adaptations to counter vertebrate host defense mechanisms.

In addition, the presence of various glycosylhydrolases [32], a group of extracellular proteinases in the *A. fumigatus* genome, confirms the ability of the fungus to grow by degrading polysaccharides from plant cell walls and acquiring nitrogen sources made available through degradation of proteinaceous substrates [33].

The physical characteristics of conidia enable *A. fumigatus* to reach and adhere to the epithelium of the airways and distal parts of the respiratory tract more efficiently than other fungal species with similar-sized airborne spores [4]. *Aspergillus fumigatus* conidia are globose to subglobose with a

size (2–3.5 μm) small enough to bypass mucociliary clearance and reach the lower airways. Moreover, the presence of melanin in the conidial wall and highly negatively charged sialic acid residues contribute to protection of *A. fumigatus* against host cell responses [34, 35].

Similar to many other infectious diseases, the development of *Aspergillus* infections is dependent on prolonged interactions between the pathogen and the host. To invade animal tissues, *Aspergillus* species rely on the coordinated expression of a wide range of genes involved in fungal growth including conidial germination, cell wall assembly, thermotolerance, nutrient acquisition, and resistance to adverse conditions such as oxidative stress. Various types of stress were observed to occur during *Aspergillus* pathogenesis, which cause fungal responses to overcome stress and may be associated with increased virulence and fungal persistence [36, 37].

Aspergillus allergens and allergies

Fungi are one of the most important and widespread producers of allergens. It has been estimated that nearly 50% of people develop allergic symptoms to fungi during their lifetime [38]. However, it must be noted that molds are not predominant allergens and that outdoor fungi are more important than the indoor ones. The allergic responses of most people are limited to rhinitis and asthma. To reduce the risk of progression or intensification of an allergy, fungi must not be allowed to grow in indoor environments. Fungal colonization in homes, schools, or offices must be detected and wiped out before moisture facilitates the growth of such fungi [39, 40].

In asthma etiology, fungal allergens are believed to be less significant than dust existing in homes; nevertheless, eliminating fungi from residential environments can improve asthma. Studies have shown that there is an association between asthma exacerbation in adults and high concentrations of indoor *Aspergillus* spp. and their allergens [40, 41]. According to the existing literature, the number of fungal colonies in homes that provide healthcare for asthmatic children is higher, especially in children's beds and the rooms in which children spend most of their time [42].

According to the official website of allergens (www.allergen.org), several species of *Aspergillus,* including *A. fumigatus*, *A. niger*, *A. flavus*, and *A. oryzae*, are allergic. To date, 21 known and 25 predicted allergens of *A. fumigatus* have been identified [43]. Two allergens, *Asp fl18* and *Asp fl 13*, have been detected in *A. flavus*, and four

allergens have been identified for *A. oryzae*: *Asp lipase*, *Asp o lactase*, *Asp o 21,* and *Asp o 13* [44].

Sensitivity to *Aspergillus* is related to allergic diseases [45, 46]. *Aspergillus* might be a significant source of internal allergens [47]. In a study by Jaakkola et al., specific IgE to *A. fumigatus* was significantly related to asthma in adults [48]. Several studies demonstrated how moisture and the observable growth of fungi in houses might harm healthy human respiratory systems (49–51).

The above-mentioned studies revealed a significant relationship between the humidity of residential environments and the growth of fungi in indoor environments, breathing difficulties, asthma, and respiratory symptoms. The severity of asthma and the average number of symptoms confirm its association with moisture content and fungal growth.

In adolescents, sensitivity to inhaled allergens has revealed higher rates of IgE compared with environmentally inhaled allergens during the first years of life (50). After sensitivity to cat and dog hair, sensitivity to dust in homes during childhood is an important condition in Western countries [51]. The distribution and medical importance of sensitivity to fungi is still unknown among young patients.

Sensitivity to house dust, childhood respiratory symptoms, and possible fungal allergens may result from living in humid homes [52]. Recently, researchers have investigated the relationship between the concentration of airborne fungal spores and health outcomes in children. Exposure to particular types of fungi in indoor environments in winter is shown to be a risk factor for asthma, atopy, and respiratory symptoms in children [43, 53–55].

Abnormal allergic syndromes, such as ABPA and allergic fungal rhinosinusitis, and allergic responses to fungi in indoor environments might be due to IgE or IgG, both of which are associated with exposure to fungi in indoor environments, although fungi in indoor environments are not considered as risk factors for these conditions [56–58].

Fungi might contain allergens, toxins, and occasionally infectious components. β-D-Glucans, which constitute the structural compounds of most fungal cell walls, are known to stimulate macrophages and neutrophils. These compounds are effective markers of surfaces containing fungal clusters on dusty surfaces [59]. Fungal glucans, especially (1→3)-ß-D-glucans, have been reported to play an essential role as inducers of chronic pulmonary diseases [60]. Glucans may be associated with signs of non-specific inflammation, as well. The water-insoluble form of glucan causes a delayed

response in terms of reduced levels of macrophages and lymphocytes in the lung wall [61].

Glucan levels above 1 ng/m³ cause symptoms such as chronic bronchitis, joint pain, itchy nose, chest tightness, and heaviness in the head [62]. Thorn and Rylander proposed that glucan could be used as a marker for identifying airway inflammation risk [63]. Beijer et al. [64] found that a respiratory challenge to β-D-glucans might affect the inflammation of respiratory cells, which could be related to prolonged exposure to fungi inside of houses. Fungi are ubiquitous, and exposure to them is unavoidable; therefore, exposure to fungi might directly or indirectly influence human well-being.

According to a study by Skoner [65], exposure to fungi in sensitive people might lead to IgE-mediated nose-mucosa inflammation and the release of histamine. Prolonged exposure to fungi might result in rhino chronic symptoms that are not principally allergic but cause irritation [66, 67].

The symptoms of allergic rhinitis, which resemble chronic symptoms of the nose, are largely associated with sick building syndrome. Furthermore, fungi may play a role in disease development, but this distinction might be difficult to prove. Although there is a general perception that molds produce an array of ill-defined allergens and antigens, there has been significant improvement in identifying important allergens from several mold species; over 25 allergens have been reported from *A. fumigatus* alone [43].

The cloned allergens of *Aspergillus*, including heat shock proteins, serine and ribosomal proteases, enolases, and cytotoxins *Asp f1*, have a wide range of biological functions. *Asp f1*, which is homologous to mitogillin and a-sarcinis, is a major allergen of *A. fumigatus* with a molecular weight of 18 kDa; cytotoxic and ribonuclease effects are expressed by *A. fumigatus* and *A. restrictus*. This allergen is not found in spores and is secreted profusely as *A. fumigatus* germinates. Approximately 85% of *A. Fumigatus*-sensitive patients produce the IgE antibody to *Asp f1*. Measurement of the IgG anti-*Asp f1* antibody can be used as a marker of *A. fumigatus* colonization in patients with cystic fibrosis, ABPA, and aspergilloma [44]. *Asp f1* has also been applied to assess T-cell reactivity in ABPA patients.

Volatile organic compounds

Microorganisms produce large amounts of volatile microbial organic compounds (MVOCs) including alcohols, aldehydes, ketones, esters, as well as sulfur and nitric compounds. MVOCs, in principle, are considered as products of primary metabolism during synthesis of DNAs, amino acids,

and fatty acids. Although the distinction between primary and secondary metabolism is not clear, MVOCs might form during both stages. The products of MVOCs depend strongly on the substrate and environmental conditions; various compounds that define MVOCs might have a non-microbial origin [68].

It is believed that fungal VOCs (FVOCs) may cause headaches, lack of concentration, inattentiveness, and dizziness. *Aspergillus versicolor* is one of the main producers of these compounds. Some other common species of *Aspergillus* that grow in indoor environments, including *A. fumigatus*, *A. sydowii*, *A. flavus,* and *A. niger*, produce FVOCs, as well [69]. Some people such as asthmatics may respond to lower concentrations of MVOCs compared to other individuals.

Epidemiologic studies on FVOCs reported a positive relationship between FVOCs in indoor environments and asthma or allergies [22, 70]. Former studies demonstrated that volatile metabolites found in fungi cultures, such as *A. fumigates,* are detectable in the breath of patients colonized or infected by fungi [71, 72]. As of yet, little scientific attention has been focused on the diagnostic potential of VOCs produced by microorganisms, although these microorganisms are widely used in nature for communication and as chemo-attractants by plants and insects; however, the smell of bacteria has been well documented by human observers.

There might be other volatile metabolites produced by *A. fumigatus* that can be clinically useful. According to the current results, MVOCs may be the best markers of excess moisture and possible fungal contamination; however, their effects on health remain unclear.

Conclusion

Exposure to *Aspergillus* species that produce secondary or primary metabolites in the environment can promote health risks, and even small amounts of fungal contamination may lead to fatal outcomes in predisposed individuals. Thus, developing new techniques to determine the nature of these components is necessary. To obtain a better understanding of the health implications of fungal exposure in indoor environments and to improve future diagnosis, performing further studies is mandatory.

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Author's contribution

B.M. wrote the draft. M.T.H. designed the study and edited the final manuscript. N.H. collected the data. M.I and S.S. helped with data analysis and editing of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Financial disclosure

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