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# Molds and respiratory allergy- part I

## Abstract

Allergic reactions to molds were defined more than three hundred years ago, but the importance of mold allergy has been undervalued for a long time. Mold allergens essentially cause respiratory symptoms in sensitized individuals. Molds cultivate best in warm, damp, and humid conditions, and they spread and replicate by making spores. The genera of molds causing allergy and allergy-related problems most often are Alternaria alternate, Cladosporium herbarium, Aspergillus fumigates and Penicillium. Of the estimated number of more than 1 million different fungal species, approximately 80 species have been linked with respiratory allergy. Alternaria is the most -known and well-studied mold species associated with fungal allergy in the literature. Although the sensitization prevalence to commercial extracts is approximately 3% in epidemiologic studies, in selected allergic patients, especially with asthma, the sensitization rate increases up to 30%. Sensitization to molds is more prevalent in individuals living in damp dwellings compared to subjects living in residential properties without any sign of dampness. Alternaria alternate is the best known to be related to immunologically base respiratory tract symptoms in children and adults, although Cladosporium, Aspergillus and Penicillium have also been held responsible to varying degrees. Molds are known to cause a variety of immune effects, including diminishing Th1-type response while not diminishing or even stimulating Th2-type reactivity. Besides asthma development, several studies have also shown that severity of asthma correlates significantly with measures of total humidity and fungal growth in the house. Diagnosing mold allergy with skin prick testing is still problematical by absence of standardized allergenic extracts, possible many allergenic epitopes and fear about the poor sensitivity of the immediate coetaneous hypersensitivity reaction. However, molecular cloning techniques have allowed researchers to separate DNAs coding for fungal allergens and to produce a better panel of recombinant allergens for the diagnosis of mold allergy.

**Keywords:** mold, fungus, allergy, rhinitis, asthma

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## Introduction

In the first part of our article on mold allergy; we firstly describe molds as indoor and outdoor allergens, then mechanisms of mold allergen-induced sensitization and sensitization prevalence to mold allergens in general as well as allergic population are told. At the end of first part, characteristics and diagnosing of mold allergy in upper and lower respiratory systems are revealed.

### What is a mold?

A mold is a fungus that grows in the form of multicellular filaments called hyphae. Molds are also called filamentous fungi that can be found both indoors and outdoors.[1] Molds breed best in warm, wet, and humid conditions, and they multiply and reproduce by making spores. No one knows how many species of fungi exist in nature, but estimates range from tens of thousands to perhaps a million or more.[2] The genera of molds that cause allergy and allergy-related problems most often are Alternaria alternate, Cladosporium herbarum, Aspergillus fumigatus and Penicillium.[3,4] The most frequently involved genera in children are Cladosporium species in northern Europe and Alternaria species in the Mediterranean region and North America.[5]

### Perennial molds as indoor allergens

Perennial molds are usually Penicillium and Aspergillus species. Several studies have determined that Aspergillus- and Penicillium--type spores were the most prevalent in the indoor air of residential properties and exceeded outdoor levels. The prevalence of indoor molds has been 5–10% in cold climate and 10–30% in moderate and warm climates.[5]

**Penicillium:** Species of Penicillium are ubiquitous soil fungi preferring cool and moderate climates, commonly present wherever organic material is available. Penicillium, genus of blue or green mold fungi, exists as asexual forms. Penicillium species are present in the air and dust of indoor environments, such as homes and public buildings.[6] They are also known to be found on foodstuffs, leather and fabrics. Some species have a blue color, commonly growing on old bread and giving it a blue fuzzy texture. Some Penicillium species affect the fruits and bulbs of plants, including Penicillium expansum: apples and pears; Penicillium digitatum: citrus fruits; and Penicillium allii: garlic. They also have economic importance in the production of antibiotics (penicillin), organic acids and cheeses.[7]

**Aspergillus:** Aspergillus is a group of molds, which is found everywhere world-wide, especially in the autumn and winter in the Northern hemisphere. Aspergillus is also common in the home, including bedding. Aspergillus niger causes black mold of foodstuffs. Aspergillus oryzae is used to ferment sake, and Aspergillus wentii to process soybeans.[8] Only a few of these molds can cause illness in humans such as Aspergillus flavus, Aspergillus niger, and Aspergillus fumigatus causing aspergillosis. Most people are naturally immune and do not develop disease caused by Aspergillus. However, when disease does occur, it takes several forms. The types of diseases caused by Aspergillus are wide-ranging, varying from an allergy-type illness to life-threatening generalized infections.[9]

### Seasonal molds as outdoor allergens

Although common atmospheric molds are classified as Alternaria, Cladosporium, Penicillium, Aspergillus and Mucor; best known seasonal (outdoor) molds are Alternaria and Cladosporium species.

The Cladosporium spores generally exceed all other airborne biologic particles in outdoor air.[2] Alternaria is predominantly detected in great abundance in outdoor air in areas where grain is grown. Alternaria is the most -known and well-studied mold species associated with fungal allergy in the literature.[4]

**Alternaria alternate (prototypic mold for allergy):** Alternaria alternata is a common and broad-based mold species occurring on many plants and other substrates including soils, food stuffs and textiles. Alternaria alternata is mainly an outdoor fungus whose spores disseminate in warm, dry air, so in temperate climates, their count peaks in the summers. Known habitats are soils, corn silage, rotten wood, composts, bird nests, and various forest plants. Black spots on tomatoes may be caused by Alternaria alternate.[10–12] Alternaria may also be found in damp, inadequately ventilated houses, where its allergenic characteristics might co-create the sick building syndrome. It is frequently noticed on condensed water on window frames of houses.[13]

## Some major mold allergens from alternaria and aspergillus

The allergenic extracts from Alternaria hyphae and spores still remain in use, but they are variable and insufficiently standardized as they are often a random mixture of allergenic ingredients and coincidental impurities. In contrast, contemporary biochemistry and molecular biology make it possible to obtain pure allergen molecules. To date, 16 allergens of Alternaria alternate have been discovered, many of which are enzymes such as Alt a 4 (disulfide isomerase), Alt a 6 (enolase) and Alt a MnSOD (Mn superoxide dismutase). Others have structural and regulatory functions (Alt a 5, Alt a 12, etc.) and the function of some allergenic proteins e.g. Alt a 1, Alt a 2, etc. are still unknown.[14] Many potent allergenic proteins have also been defined from Aspergillus and most of the allergens are proteases, such as Asp f 5, Asp f 10, Asp f 13, Asp f 15, and Asp f 18.[15]

## Sensitization prevalence to mold allergens

Of the estimated number of more than 1 million different fungal species, approximately 80 species have been linked with respiratory allergy.[1] Although the sensitization prevalence to commercial extracts is approximately 3% in epidemiologic studies, in selected patients, particularly with asthma, the sensitization rate raise up to 30%.[16] Sensitization to molds is more prevalent in subjects living in damp dwellings compared to subjects living in dwellings without any sign of building dampness.[17]

**In general population of the world:** The reported prevalence of Alternaria sensitivity varies significantly among different studies,[18,19] ranging from 2% in Nordic countries to more than 20% in some Mediterranean areas.[20] In the European Community Respiratory Health Survey, which included 18,102 adults screened at 35 centers, the prevalence of positive results in skin tests for Alternaria was 3.3% and ranged from 0.2% to 14.4%.[21] Sensitization to Alternaria and Cladosporium has been reported to be 3% to 30% in European countries.[16] Overall sensitization to the two molds was found to be 15%, and isolated Alternaria or Cladosporium sensitization was 3%.[19] In an epidemiology report from the French 6 cities study, the overall prevalence of Alternaria sensitization in children was 2.8%.[22]

The reported Alternaria sensitization prevalence in population samples of children ranges from less than 1% in Austria up to 50% in Arizona, USA.[23] In the general population of the USA, a large-scale epidemiological study indicated that 3.6% of the populations were sensitized to Alternaria alternate.[16] Of 1218 children born on the Isle of Wight in 1989/90, and followed for atopy at age 4 years, 981 were skin-prick tested with a battery of allergens. Of these 61/981 (6%) responded positively to Alternaria alternate and Cladosporium herbarum. At 4 years of age, Alternaria and Cladosporium were the third most common causes of sensitization, after dust mite and grass pollen. Allergic asthma was the most common disease in children sensitized to molds.[24]

**In patients with respiratory allergic diseases such as asthma and allergic rhinitis:** The first case of mold allergic respiratory disease recorded in English literature consisting of deterioration of asthma on mold exposure in 1698. Then in 1870s, Charles Bleckley induced hoarseness, aphonia and an attack of ‘‘bronchial catarrh’’ by inhaling fungi from straw.[4] In 1924, asthma attributed to wheat rust fungus exposure was reported by Cad ham.[25] Currently, molds are considered the third most frequent cause of allergic respiratory disease after mites and pollens.[4] The National Health and Nutrition Examination Survey in the USA found a 3-fold increase in the frequency of mold sensitivity between 1980 and 1994.[16] Similarly; a study of mold allergy was performed in extrinsic asthmatic children living in an urban environment from 1977 to 1988 in Hungary. According to the skin prick test, 11% of those were positive to the molds studied in 1977, the proportion being 30% in 1985 and 39% in 1988.[26]

Surveys conducted in various parts of the world indicate that fungal sensitivity is common, particularly among asthmatic individuals. In a large-scale epidemiological study of children with asthma residing in inner cities of the USA, the most common sensitizer was Alternaria; 38% of 1286 asthmatic children had positive skin test to this allergen.[20] Approximately 3% of the patients in Portugal reacted positively to either Alternaria or Cladosporium in a study by D Amato G et al.,[19] while in Spain 20% showed positive skin tests to these molds.[5] In a Turkish study, most of the 614 respiratory allergic patients had extrinsic asthma (73%) while 27% having allergic rhinitis. Aspergillus fumigatus was the most important fungus causing skin test positivity at the rate of 26%.[27] A retrospective study was performed on 2,342 patients treated in the allergy department from 1985 to 1996. Mean age of the patients was 26, 55% were males and 45% females. 40% of them had asthma and 60% had allergic rhinitis. Sensitization to molds was 2%. The mold sensitization increased in parallel with age and it was the highest between 60 to 69 age group. House dust and molds were more common causes of allergic asthma than pollens.[28] In 1995, a study was carried out sponsored by the Societal Espanola de Alergologiae Immunologic Clinical in which 10% of all patients with suspected respiratory allergy were demonstrated to be positive to Alternaria and/or Cladosporium.[29,30] According to a multicenter European study sponsored by the Aerobiology Subcommittee of the European Academy of Allergology in 1997, 10% of all patients suspected of having respiratory allergy responded positively to Alternaria, Cladosporium, or both.[5,19] In the Alergológica 2006 study, 13% of the pediatric patients with allergic rhinitis and 15% of those diagnosed with childhood asthma were sensitized to fungi.[31]

## Pathogenesis of airway inflammation and respiratory allergic diseases by mold allergens

Molds are known to cause a variety of immune effects, including diminishing Th1 type reactivity while not diminishing or even stimulating Th2-type reactivity. For instance, many fungal allergens contain intrinsic protease activity, resulting in an adjuvant effect leading to a prolonged Th2 type of response. Alternaria was shown to possess potent Th2 adjuvant effects in vivo by inducing airway sensitization to an experimental antigen such as OVA, and a common aeroaller-

gen, short ragweed pollen.[32] When Dendritic cells were exposed to Alternaria in vitro, they demonstrated distinct inflammatory responses. These Alternaria-exposed Dendritic cells facilitated Th2-skewed humoral and cellular immune responses when transferred into the airways of naive animals. The exclusive and effective Th2 adjuvant characteristics of Alternaria, which were thought to be partially mediated through Dendritic cells, might explain the strong association between Alternaria and human allergic airway disorders.[32]

Furthermore, recent studies in animal models demonstrated that fungal proteases might play an important role in the development of allergic airway inflammation. Kheradmand et al.[33] showed that intrinsic protease activity of the fungal allergens from Aspergillus fumigates promoted chronic eosinophilic inflammation in the airways of mice exposed to these allergens.[34] Protease activity of fungal extracts was demonstrated to be capable of inducing morphologic changes and cytokine production in airway epithelial cells. Kauffman et al.[35] demonstrated that Alternaria extracts induced cell shrinkage and desquamation when applied to cultured airway epithelial cells in vitro. This was accompanied by enhanced production of IL-6 and IL-18 at high concentrations of the Alternaria extract. These effects were demonstrated to be due to intrinsic protease activity in the extracts because they were abrogated by the addition of protease inhibitors. Potentially, fungal proteases were also to be able to activate epithelial cells through protease-activated receptor (PAR) type-2 mechanisms. This might lead to airway epithelial desquamation and heightened airway responsiveness as a result of the exposure of airway irritant receptors.[36]

### What is the importance of mold exposure on the development of respiratory allergic diseases?

As mentioned, mold-induced respiratory allergies and research on Alternaria both have a long-term history: the first was described as early as 1698 and the second dates back to 1817. However, in 1930 when Alternaria spores were demonstrated to cause allergic asthma. The relationship to the development of asthma was firstly suggested by Cantani and Ciaschi in a study of more than 6.000 atopic children in Italy.[14,37] Nowadays, mold exposure during infancy was demonstrated to be a predictor of potential asthma development.[38] In a birth cohort study, a sub study of the prospective Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), exposure during infancy to three mold species (Aspergillus ochraceus, Aspergillus unguis and Penicillium variable) common to water-damaged buildings was observed to be associated with childhood asthma at age 7.[39] Halonen et al.[40] provided prospective evidence that Alternaria sensitization at age 6 was the only aeroallergen associated with new asthma at age 6 and 11 years in a semiarid environment. This study suggested that sensitization to Alternaria was potentially responsible for the development of asthma. Besides asthma development, several studies have also shown that severity of asthma correlates significantly with measures of total dampness and mold growth in the dwelling.[41] Living in damp dwellings was found to be associated with current asthma, lower FEV1 and higher PEF variability.[42] Concomitantly, mold exposure and recent water damage has been reported to be associated with asthma symptoms and bronchial hyper responsiveness in adult asthmatics.[43]

### Distinctive characteristics of mold (alternaria) -induced asthma and allergic diseases

Alternaria alternata is the best known to be related to immunologically base respiratory symptoms in children and adults, although Cladosporium, Aspergillus and Penicillium have also been implicated to varying degrees.[4] Alternaria species sensitization also might predict polysensitization to a variety of molds, some that are not customarily tested.[16] Alternaria spores, which range between 2 and 8 μm in diameter, are small enough to be inhaled and, under laboratory conditions, provoke respiratory symptoms and airway responsiveness in asthmatics.[44] Alternaria sensitization is independently associated with asthma and responsible for asthma exacerbations and airway hyper responsiveness in sensitized asthmatic subjects.[4,40] Prevalence of current symptomatic asthma and use of asthma medications increase significantly with higher Alternaria alternate allergen levels indoor.[45] Alternaria has been increasingly recognized as a risk factor for the development and persistence of asthma, asthma severity, and potentially fatal asthma exacerbations.[18,19] Alternaria sensitivity and exposure to airborne fungal spores have been associated with severe episodes of potentially fatal asthma**.** The risk of death from asthma has also been correlated with the presence of fungal spores in the atmosphere.[20] Therefore, patients having severe acute asthma attacks should be evaluated for Alternaria sensitivity.[16] Alternaria species sensitization in asthmatic subjects with grass pollen sensitivity predicts susceptibility to thunderstorm-associated asthma.[5] Mold allergy was shown to result in a more severe course of rhino-conjunctivitis as well.[20]

### Difficulties in diagnosing of mold allergy

Mold allergy is usually diagnosed with clinical symptoms and findings in addition to positive laboratory evaluations by specific IgE to mold species and/or skin prick testing. Mold allergy is difficult to diagnose for a number of reasons: Molds generally may present no seasonal variation in outdoor environment, making the patient's history less reliable in clinic. Also, there have been almost a million species of mold identified, and a single fungal species can produce more than 40 different proteins stimulating IgE production; consequently, distinguishing clinically major mold antigens is problematic.

Additionally, standardization of mold extracts was observed to be most difficult one. In contrast to other aeroallergens, mold extracts tend to have low allergenic activity and fluctuate considerably from batch to batch. Several factors are responsible for the poor quality of natural fungal extracts, among which the influence of culture conditions on allergen contents. Consequently, diagnosing mold allergy with prick testing is still problematical by absence of standardized allergenic extracts, many possible antigenic epitopes and concern about the poor sensitivity of the cutaneous immediate hypersensitivity response.[46] However, molecular cloning techniques have allowed researchers to separate DNAs coding for fungal allergens and to create a better panel of recombinant allergens for the diagnosis of mold allergy.[47]

## Conclusion

Even though mold allergy is difficult to diagnose and to manage, it is one of the major risk factors for the development and persistence of upper and lower respiratory allergic disease such as asthma, asthma severity, and potentially fatal asthma exacerbations. More definitive methods / technologies should be developed more and available in routine use for an effective diagnostic approach and management of fungal allergy.

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## Conflicts on interest

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