

Clinical Commentary Review

Clinical Evaluation and Management of Patients With Suspected Fungus Sensitivity

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives

Learning objectives:

1. To ask appropriate questions to identify patients who are likely to be sensitive to mold.
2. To determine whether a patient is likely to be experiencing harm from fungus exposure and if so by what mechanism.
3. To perform appropriate tests for IgE sensitization to fungi.
4. To recommend appropriate immunotherapy, when indicated, to mold-sensitive patients.

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Fungus-sensitized patients usually present with symptoms that are similar to symptoms presented by those who are sensitized to other aeroallergens. Therefore, diagnosis and management should follow the same pathways used for patients with allergic conditions in general. The physician should consider that a relationship between fungal exposure and symptoms is not necessarily caused by an IgE-mediated mechanism, even when

specific fungal IgE is detected. Until recently, IgE-mediated allergy has been documented only for a limited number of fungi. We propose a series of questions to be used to identify symptoms that occur in situations with high fungal exposure and a limited skin-prick-test panel (*Alternaria*, *Cladosporium*, *Penicillium*, *Aspergillus*, *Candida*) that can be amplified only in cases of high suspicion of other fungal exposure (eg, postfloods). We also review *in vitro* testing for fungi-specific IgE. Treatment includes environmental control, medical management, and, when appropriate, specific immunotherapy. Low-quality evidence exists supporting the use of subcutaneous immunotherapy for *Alternaria* to treat allergic rhinitis and asthma, and very low quality evidence supports the use of subcutaneous immunotherapy for *Cladosporium* and sublingual immunotherapy for *Alternaria*. As is the case for many allergens, evidence for immunotherapy with other fungal extracts is lacking. The so-called toxic mold syndrome is also briefly discussed. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

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Abbreviations used

LR- likelihood ratio (given that a test is either positive or negative, the *LR* is the ratio of the pretest odds that the patient has a given condition divided by the posttest odds that the patient has that condition)

SCIT- subcutaneous immunotherapy

SLIT- sublingual immunotherapy

SPT- skin prick test

Patients with concerns about mold allergy are commonly seen by allergists in clinical practice. Such individuals might be specifically concerned about possible adverse health effects from exposure to mold that they have observed in their house, or they may be seeking care for medical conditions that subsequently turn out to be triggered, at least in part, by fungi. There is a clear relationship between exposure to fungi and asthma (and rhinitis) symptom exacerbations,¹ but part of these reactions might be due to mechanisms other than fungal allergy,² even if T_H2-skewed reactions are found in these individuals and even if fungus-specific IgE is reported. Thus, the presence of IgE to fungus in a patient with asthma does not necessarily mean that fungal allergy is the cause. Even when we take into account the fact that not all IgE-sensitized patients have allergy, mold allergy does appear to be a relatively common condition, because the prevalence of sensitization to fungi, as determined by skin prick test (SPT), is estimated to be as high as 19% of the allergic population.³ In addition, because the prevalence of sensitization among various fungal genera is highly variable, with some taxa eliciting an IgE response more frequently than do others, the spectrum of mold allergy is also likely to be variable depending on the genera to which the patient is exposed.

Fungus-sensitized patients usually present with symptoms that are similar to symptoms presented by those who are sensitized to other aeroallergens. Clear links have been reported between sensitization to *Alternaria* and *Cladosporium* and seasonal respiratory allergy symptoms. As outdoor allergens these fungi behave similarly to pollen allergens, with particular seasons/conditions that elevate their concentration in air (end-summer/autumn, thunderstorms, etc) eliciting at that particular moment symptom exacerbations. Alternatively, *Penicillium* sensitization has been linked to indoor allergen exposure, especially in humid moldy environments and after floods.¹ There are data related to *Aspergillus* and *Candida* that suggest a possible role as allergens.³ Thus, some fungi do seem to cause direct allergy with respiratory allergic symptoms. Convincing data for other allergy-causing fungi apart from these 5 (*Alternaria*, *Cladosporium*, *Penicillium*, *Aspergillus* and *Candida*) are lacking, which does not mean that they do not exist. Therefore, methods for the diagnosis and management of fungus-allergic patients should follow the same clinical pathways that are used for patients with allergic conditions in general. This includes eliciting a history consistent with respiratory diseases that are likely to be triggered by exposure to fungi, identifying plausible mechanisms for the observed adverse health effects given the history of exposure, detecting the presence of fungus-specific IgE, and treatment with appropriate environmental controls, medical management, and, when appropriate, specific immunotherapy. This review will consider each of these components as they pertain to identifying and treating patients who have fungal allergy.

MECHANISMS OF ADVERSE HEALTH EFFECTS

Fungal contaminants (allergens and irritants) are produced by actively growing fungi and become incorporated into a building's reservoirs over time. Reservoirs then periodically release these contaminants back into the environment when disturbed, which can lead to long-term intermittent or continuous exposure to a building's occupants. The presence of dampness (defined as sufficient moisture to support fungal growth on available substrates) tends to augment the production of fungal and other microbial contaminants, which is why dampness has been associated with adverse health effects.⁴

The specific adverse health effects triggered by fungal exposure depend on the fungal products to which the patient is exposed. An extensive discussion of fungal products that are capable of triggering health effects and their mechanisms appears elsewhere in this issue.² For the current discussion, primary exposures include fungal allergens, volatile organic compounds, and various other substances that serve as either proinflammatory molecules or irritants. The possible effect of other substances on health, such as mycotoxins, will be addressed later. The mechanisms of adverse health effects from fungal exposure therefore are as follows: (1) the patient could be allergic to the fungus; (2) the patient could be experiencing an irritant effect from exposure; (3) the patient could be infected by the fungus; (4) the patient could be allergic to other allergens, and coexposure to fungi acts as an adjuvant stimulating a T_H2 response via nonspecific routes of the innate immune system; and (5) there could be other mechanisms that are unknown.

CLINICAL EVALUATION

Fungal exposure has been associated with increased symptoms in patients with allergic rhinitis, asthma, and atopic dermatitis.⁵ The clinical evaluation of a patient with one of these conditions, therefore, is the same regardless of the patient's fungus sensitivity status. It begins by eliciting a history consistent with increased symptoms that are triggered by exposure to the suspected allergen.⁶

Indoor environments with high fungal exposure generally include those with increased moisture content as is found in a basement or other damp environment. Old buildings often experience moisture problems that result in fungal growth. It therefore helps to ask whether symptoms increase in the presence of dampness, visible mold in the home, and a moldy odor. This type of question necessarily is nonspecific because old buildings often have multiple air quality issues such as rodent or cockroach infestations, lack of ventilation, and increased particle counts due to decaying organic material that can trigger symptoms. Questions that have been shown to correspond to health effects from fungi are whether there is visible mold and whether there is a moldy smell.⁵

Outdoor situations in which increased moisture may be associated with fungal exposure include storms or prolonged periods of damp weather, cut grass, raking leaves, which stirs up fungal spores, and work with organic materials such as compost. The sexual state of *Alternaria* produces ascospores for a brief period in the late spring followed by increasing concentrations as the growing season progresses into early fall. *Alternaria conidia* tends to peak on dry days at midday with increasing concentration as a function of wind turbulence. Table I includes specific questions the physician might ask to determine whether there is

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